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-dibromo-3-chloropropane 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-dibromo-3-chloropropane.

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-dibromo-3-chloropropane 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-dibromo-3-chloropropane. 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-dibromo-3-chloropropane come from inhalation or oral studies in animals. The most commonly examined endpoints were body weight, liver, kidney, and reproductive effects. Most human data come from assessments of the male reproductive system in cohorts of occupationally exposed factory workers or cohorts of farmers or pesticide applicators. A limited number of studies evaluated the effects of dermal exposure to 1,2-dibromo-3-chloropropane.
Figure 6-1. Summary of Existing Health Effects Studies on 1,2-Dibromo-3-Chloropropane By Route and Endpoint*

The majority of the studies examined inhalation or oral exposure in animals (versus humans). Potential reproductive, body weight, renal, and hepatic effects were the most studied endpoints.*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Inhalation Studies</th>
<th>Oral Studies</th>
<th>Dermal Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>9</td>
<td>11</td>
<td>—</td>
</tr>
<tr>
<td>Respiratory</td>
<td>10</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>Hematological</td>
<td>1</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Hepatic</td>
<td>9</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>Renal</td>
<td>11</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>Dermal</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Ocular</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Endocrine</td>
<td>2</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Immunological</td>
<td>4</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Neurological</td>
<td>4</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Reproductive</td>
<td>29</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Developmental</td>
<td>1</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Other Noncancer</td>
<td>1</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*Includes studies discussed in Chapter 2; the numbers of studies include those finding no effect. Occupational exposures are assumed to have been predominantly via inhalation.
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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.** Sufficient information was not available on the health effects of 1,2-dibromo-3-chloropropane to derive an MRL for acute-duration inhalation exposure. In one study, reproductive effects were noted in rats following acute inhalation exposure to 1,2-dibromo-3-chloropropane (Saegusa et al. 1982). Although this is the most sensitive endpoint for 1,2-dibromo-3-chloropropane toxicity, the data are only available for rats. Intermediate-duration studies indicate that rabbits are more sensitive than rats to reproductive effects of 1,2-dibromo-3-chloropropane. Therefore, reproductive toxicity data are needed for acute inhalation exposures in rabbits and humans.

There are insufficient data for derivation of an acute-duration oral MRL. Several studies provided information on LD₅₀ values and sublethal effects following acute oral exposure to 1,2-dibromo-3-chloropropane. However, among the available acute-duration oral studies, dominant lethality was observed at the lowest dose tested (10 mg/kg/day) (Teramoto et al. 1980). Additional acute-duration oral studies in the most sensitive animal species are needed to identify NOAELs and LOAELs for the most sensitive endpoint of oral 1,2-dibromo-3-chloropropane toxicity.

**Intermediate-Duration MRLs.** There are no data needs for intermediate-duration animal studies to serve as a basis for MRLs.

**Chronic-Duration MRLs.** Information regarding effects following chronic-duration exposure to 1,2-dibromo-3-chloropropane is available for rats and mice exposed by inhalation (NTP 1982) or from the diet (Hazleton 1977, 1978a; NCI 1978). The data were not suitable for MRL development because rabbits appear to be more sensitive than rats or mice to male reproductive effects (as demonstrated from intermediate-duration oral studies) and chronic-duration inhalation and oral toxicity studies are not available for rabbits. Additional chronic-duration inhalation and oral studies could be designed to establish the threshold for reproductive effects in rabbits in order to derive chronic-duration MRLs for 1,2-dibromo-3-chloropropane.
Health Effects. The toxicity of inhaled and ingested 1,2-dibromo-3-chloropropane has been assessed in laboratory animals. Although the primary use of 1,2-dibromo-3-chloropropane as a fumigant and nematocide has been cancelled, residues may still be found in soil and contaminated drinking water sources. Populations living in areas where 1,2-dibromo-3-chloropropane is found in soil and/or drinking water should be monitored for potential exposure-related health effects. Since 1,2-dibromo-3-chloropropane may still be used as an intermediate in the production of other substances, workers who may be exposed should be monitored as well. Limited information was located regarding systemic effects following dermal exposure.

Respiratory. No studies were located regarding respiratory effects in humans after exposure to 1,2-dibromo-3-chloropropane by any route. Inhalation exposure of laboratory animals resulted in adverse effects in the nasal cavity, trachea, and bronchi that included inflammatory and proliferative changes and epithelial necrosis (NTP 1982; Saegusa et al. 1982; Torkelson et al. 1961). Chronic exposure of rats and mice resulted in tumors of the respiratory tract (NTP 1982). 1,2-Dibromo-3-chloropropane can volatilize from contaminated soil or surface water. Therefore, people living in areas where 1,2-dibromo-3-chloropropane may be detected in air should be monitored for possible exposure-related effects on the respiratory system.

Gastrointestinal. Available human data are limited to a single study that examined the correlation between ingestion of drinking water containing 0.004–5.75 ppb 1,2-dibromo-3-chloropropane and gastric cancer and found no correlation (Wong et al. 1989). Acute-, intermediate-, and chronic-duration oral exposure of laboratory animals to 1,2-dibromo-3-chloropropane resulted in inflammatory, proliferative, and degenerative effects in the gastrointestinal tract (Ghanayem et al. 1986; Hazleton 1977, 1978a, 1978b; NCI 1978; Torkelson et al. 1961); chronic-duration oral exposure also resulted in stomach cancer (Hazleton 1977, 1978a, 1978b; NCI 1978). Substantial oral exposure to 1,2-dibromo-3-chloropropane (from contaminated drinking water or food sources) is not likely among the general population. However, in areas where 1,2-dibromo-3-chloropropane was used as a fumigant and nematocide, food grown in the formerly-treated soil and nearby drinking water sources should be monitored and people living in such areas should be monitored for possible exposure-related effects on the gastrointestinal system.
Renal. No studies were located regarding renal effects in humans after exposure to 1,2-dibromo-3-chloropropane by the oral route. No renal effects were detected from the urinalysis of workers occupationally exposed to 1,2-dibromo-3-chloropropane (Whorton et al. 1977). Inhalation and oral exposure of laboratory animals resulted in renal effects that included nephritis and nephrosis, necrotic effects in kidney proximal tubules, and proliferative changes (Kato et al. 1980; NTP 1982; Saegusa et al. 1982; Torkelson et al. 1961). Substantial oral exposure to 1,2-dibromo-3-chloropropane (from contaminated drinking water or food sources) is not likely among the general population. However, in areas where 1,2-dibromo-3-chloropropane was used as a fumigant and nematocide, food grown in the formerly-treated soil and nearby drinking water sources should be monitored and people living in such areas should be monitored for possible exposure-related effects on the renal system. 1,2-Dibromo-3-chloropropane can volatilize from contaminated soil or surface water. Therefore, people living in areas where 1,2-dibromo-3-chloropropane may be detected in air should be monitored for possible exposure-related effects on the renal system.

Reproductive. The toxicity of 1,2-dibromo-3-chloropropane to the male reproductive system has been assessed in workers who were exposed primarily by inhalation (Biava et al. 1978; Lanham 1987; Potashnik et al. 1978, 1984; Slutsky et al. 1999). The only information on reproductive effects in low-dose orally exposed humans is that no changes in birth rates were observed in populations that were exposed to drinking water contaminated with 1,2-dibromo-3-chloropropane (Wong et al. 1988). Therefore, more studies regarding reproductive effects in humans after oral exposure from contaminated water would be useful. No data were located regarding the reproductive toxicity of 1,2-dibromo-3-chloropropane after dermal exposure. The testicular toxicity of 1,2-dibromo-3-chloropropane after inhalation and oral exposure was demonstrated in rats and rabbits, but not in mice. More information for reproductive effects (including reproductive function) from all routes of exposure and different exposure durations, and on interspecies differences would be useful. Mostly negative results were obtained for reproductive effects in experimental animals after inhalation and oral exposure of females; however, ovarian cysts were reported in rats after inhalation exposure (Rao et al. 1983). More data about 1,2-dibromo-3-chloropropane toxicity to the female reproductive system would be useful. More data about 1,2-dibromo-3-chloropropane reproductive toxicity in human males might be helpful to correlate exposure levels with effects.
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**Developmental.** No developmental effects were observed among workers occupationally-exposed to 1,2-dibromo-3-chloropropene (presumably by inhalation), but the cohort was not big enough to give reliable information (Goldsmith et al. 1984; Potashnik and Abeliovich 1985; Potashnik and Phillip 1988). Negative results were obtained after examination of the offspring in a population exposed to 1,2-dibromo-3-chloropropene through drinking water (Whorton et al. 1989). Reduced litter weight and size were found in rats at oral doses that caused maternal toxicity (Johnston et al. 1986; Ruddick and Newsome 1979). There is no information regarding developmental effects after dermal exposure. Additional data on developmental toxicity in experimental animals would be useful to identify possible risks for humans.

**Immunotoxicity.** No data were located regarding immunological effects of 1,2-dibromo-3-chloropropene in humans after inhalation, oral, or dermal exposure of any duration. Results of animal studies suggest that the spleen (NTP 1982; Reznik et al. 1980a; Saegusa et al. 1982), lymph (NTP 1982; Reznik et al. 1980a), and thymus (NTP 1982) may be targets following inhalation exposure. Hazleton (1977, 1978a) evaluated immunological endpoints in animals exposed to 1,2-dibromo-3-chloropropene in the diet. The apparent greater susceptibility of 1,2-dibromo-3-chloropropene-exposed animals to pulmonary infections also suggests a possible immunologic effect. A battery of immune function tests has not been performed in humans or in animals, but would provide valuable information to confirm or refute the suggestive evidence. Studies regarding skin sensitization with 1,2-dibromo-3-chloropropene have not been performed.

**Neurotoxicity.** No data were located regarding neurological effects in humans known to have been orally or dermally exposed to 1,2-dibromo-3-chloropropene. Workers occupationally exposed to 1,2-dibromo-3-chloropropene reported subjective neurological symptoms (Whorton et al. 1977). Neurological effects (e.g., meningoencephalitis, cerebral mineralization, cerebral necrosis) were observed in laboratory animals repeatedly exposed to 1,2-dibromo-3-chloropropene by inhalation (NTP 1982; Rao et al. 1983). Reduced activity was reported in rats receiving 1,2-dibromo-3-chloropropene from the diet at 67.5 mg/kg/day (Torkelson et al. 1961). Reel et al. (1984) reported depression of the central nervous system in rats receiving 1,2-dibromo-3-chloropropene from the diet, but did not indicate doses at which this effect was elicited. No data were located regarding neurotoxicity of 1,2-dibromo-3-chloropropene after dermal exposure in animals. Additional neurological and neurobehavioral tests in experimental animals would help to identify possible subtle neurological effects and the exposures associated with them.
Cancer. Well-conducted chronic inhalation, oral, and dermal exposure studies in animals demonstrate the carcinogenicity of 1,2-dibromo-3-chloropropane (NCI 1978; NTP 1982; Van Duuren et al. 1979). This is supported by the genotoxicity studies on prokaryotic and eukaryotic organisms. Further epidemiological studies of exposed workers would be useful to determine the possible risk in humans.

Genotoxicity. 1,2-Dibromo-3-chloropropane was positive for genotoxicity in most in vivo and in vitro assays (see Section 2.20). Depending on species, age, and exposure route or test system, generally negative results were observed for sperm gene crossover and heritable cross mutations (Kale and Baum 1982a), specific-locus gene mutations (Russell et al. 1986), bone marrow chromosomal aberrations (Shelby and Witt 1995) and bone marrow micronuclei (Albanese et al. 1988; Shelby and Witt 1995), human testicular DNA damage (Bjorge et al. 1996), and rat liver unscheduled DNA synthesis (Soderlund et al. 1991). Additional genotoxicity studies for 1,2-dibromo-3-chloropropane do not appear necessary.

Epidemiology and Human Dosimetry Studies. Several epidemiological studies have been conducted in humans exposed to 1,2-dibromo-3-chloropropane. Some dealt with the occurrence of cardiovascular disease and cancer in the exposed workers or in a population exposed to contaminated drinking water (Hearn et al. 1984; Wong et al. 1984, 1989). The limitations of occupational studies are coexposure to other chemicals and uncertainty about actual 1,2-dibromo-3-chloropropane concentrations in the workplace. More retrospective studies would be useful to determine possible 1,2-dibromo-3-chloropropane-induced mortality from cancer.

Other epidemiologic studies dealt with 1,2-dibromo-3-chloropropane toxicity on the reproductive system after occupational exposure or exposure via contaminated drinking water. 1,2-Dibromo-3-chloropropane-induced toxicity to the human male reproductive system was well established in several cross-sectional studies. Reliable dosimetry data on the exposed population and correlation with early signs of mild oligospermia would be useful. Follow-up studies of exposed workers would be of value to further determine the reversibility of testicular effects. The determination of 1,2-dibromo-3-chloropropane toxicity to the female reproductive system would be valuable. More data about the reproductive outcome in exposed populations and the possibility of spontaneous abortions after exposure would be useful. The inhalation and dermal routes of exposure are important for occupationally exposed individuals; inhalation, oral, and dermal exposure might be of concern to populations living near hazardous waste sites as
1,2-dibromo-3-chloropropylane might get into soil and then contaminate the source of water used for bathing or drinking.

**Biomarkers of Exposure and Effect.** No biomarkers of exposure were identified for 1,2-dibromo-3-chloropropylane. Further studies regarding possible biochemical changes after 1,2-dibromo-3-chloropropylane exposure would be useful. The identification of urinary metabolites specific to 1,2-dibromo-3-chloropropylane and their correlation with levels of exposure would also be useful.

No biomarkers of effect that would be specific to 1,2-dibromo-3-chloropropylane have been identified. Several studies indicated that 1,2-dibromo-3-chloropropylane induced DNA damage and changes in the activity of microsomal enzymes (Kluve 1983; Suzuki and Lee 1981) or alterations in sperm parameters (Biava et al. 1978; Potashnik et al. 1978, 1984; Slutsky et al. 1999); however, these changes are not specific for 1,2-dibromo-3-chloropropylane exposure and cannot be used as biomarkers. It is not likely that specific biomarkers of effect exist for 1,2-dibromo-3-chloropropylane. No studies are suggested because toxicologically significant exposure to 1,2-dibromo-3-chloropropylane is not likely since it was banned for use as a pesticide in the United States in 1985.

**Absorption, Distribution, Metabolism, and Excretion.** 1,2-Dibromo-3-chloropropylane can be absorbed through the lungs, gastrointestinal tract, and skin, as indicated by toxicity studies (Gingell et al. 1987a; Kato et al. 1979a). Absorption has been studied specifically only after oral exposure (Gingell et al. 1987a; Kato et al. 1979a). The absorption followed first-order kinetics, and no saturation has been observed with concentrations tested thus far. In animals, 1,2-dibromo-3-chloropropylane is quickly distributed to tissues throughout the body, with highest concentrations accumulating in adipose tissue (Kato et al. 1979a, 1980). The metabolic pathway has been well-studied in rats (e.g., Jones et al. 1979; Pearson et al. 1990; Soderlund et al. 1995). Excretion occurs mainly via urinary metabolites in exposed animals, and smaller amounts are excreted in breath and bile (Gingell et al. 1987b; Kato et al. 1979a). No comparisons have been made regarding absorption, distribution, metabolism, and excretion via different routes of exposure. Additional studies using inhalation and dermal exposure routes would be useful.

**Comparative Toxicokinetics.** The differences between reproductive toxicity in mice and rats were demonstrated in several studies. Similar differences were observed in toxicokinetics between rats and hamsters (with high testicular toxicity) and mice and guinea pigs (with low testicular toxicity) (Lag et al. 1989a; MacFarland et al. 1984). Also, rabbits were found to be more susceptible to reproductive effects than rats (Rao et al. 1982, 1983). The fact that reproductive toxicity of 1,2-dibromo-3-chloropropylane was
also observed in humans might suggest that rabbits, and possibly rats, could serve as a model for 1,2-dibromo-3-chloropropane toxicity. Further investigation of toxicokinetics in different species and the comparison of detected metabolites with those detected in humans would be useful.

**Children's Susceptibility.** No information was located regarding potential age-related differences in susceptibility to 1,2-dibromo-3-chloropropane toxicity. Animals studies could be designed to evaluate potential age-related differences. Most human exposure to 1,2-dibromo-3-chloropropane in the past has involved occupational exposure via production of the pesticide, its use as an intermediate in the production of other pesticides, or exposure during mixing and application when it was registered for agricultural use. The most likely source of information regarding potential age-related differences in susceptibility among humans would be from dermal contact with contaminated soil, ingestion of contaminated water, or inhalation following volatilization from contaminated soil or water. If such populations could be identified, they should be monitored for possible age-related differences in susceptibility.

**Physical and Chemical Properties.** Physical and chemical property data are essential for estimating the transport and partitioning of a chemical in the environment. Most of the essential physical and chemical properties needed to estimate the environmental fate and transport of 1,2-dibromo-3-chloropropane are available (see Table 4-2).

**Production, Import/Export, Use, Release, and Disposal.** Data regarding the production methods for 1,2-dibromo-3-chloropropane are available; however, comprehensive data regarding current production volumes, release, and use patterns are lacking. Current levels of production, release, and use are considered relatively low due to the banning of the chemical's major use as a soil fumigant. Use, release, and disposal data can be useful for determining areas where environmental exposure to 1,2-dibromo-3-chloropropane may be high. Based upon relatively outdated data, significant concentrations are expected to be found mainly in the groundwater and drinking water near areas where 1,2-dibromo-3-chloropropane was used extensively as a soil fumigant (Burmaster 1982; Carter and Riley 1981; Cohen 1986; Kloos 1983; Kutz and Carey 1986; Nelson et al. 1981; Oki and Giambelluca 1987; Peoples et al. 1980; Westrick et al. 1984). Only general data are available on the methods of disposal of 1,2-dibromo-3-chloropropane (HSDB 1989). Specific disposal information would be useful for determining the effectiveness of the disposal methods. Regulations are available pertaining to the restrictions upon the land disposal of 1,2-dibromo-3-chloropropane.
Environmental Fate. The ultimate environmental fate of 1,2-dibromo-3-chloropropane remains unclear due to a lack of data. The chemical partitions to water and the atmosphere, volatilizes from water and soil, leaches through soil, degrades in the atmosphere, and via hydrolysis in water, and is persistent in soils (see Chapter 5). Additional experimental data concerning biodegradation in soil would aid in assessing the ultimate environmental fate of 1,2-dibromo-3-chloropropane.

Bioavailability from Environmental Media. 1,2-Dibromo-3-chloropropane can be present in water and food and it is absorbed through the gastrointestinal tract (see Section 3.1.1). This suggests that exposure to 1,2-dibromo-3-chloropropane may occur as the result of ingestion of soil by children playing near hazardous waste sites. No data were found concerning absorption through the lungs or through dermal contact. Knowledge of the bioavailability through the various exposure routes is essential in assessing the potential body burdens that may occur as a result of exposure to known environmental concentrations.

Food Chain Bioaccumulation. Experimental data regarding the bioconcentration of 1,2-dibromo-3-chloropropane in plants, aquatic organisms, and animals were not located in the literature. However, based on an estimated BCF of 11.2, 1,2-dibromo-3-chloropropane is not expected to bioconcentrate in fish and other aquatic organisms (Bysshe 1982; Munnecke and VanGundy 1979); thus, biomagnification in aquatic food chains is unlikely. Additional information on bioconcentration in plants and animals and biomagnification in terrestrial food chains would be helpful in assessing the potential for exposure of terrestrial animals at higher trophic levels.

Exposure Levels in Environmental Media. The data concerning the detection of 1,2-dibromo-3-chloropropane in the environment are limited and outdated. Current and comprehensive monitoring data, especially in areas where the chemical has been used in the past, are needed to estimate human intake. Food survey analyses are needed since it is difficult to ascertain whether previous surveys tested for the presence of 1,2-dibromo-3-chloropropane.

Exposure Levels in Humans. No monitoring data were found indicating that 1,2-dibromo-3-chloropropane has been found in human tissues or blood. Data concerning the level of 1,2-dibromo-3-chloropropane in human tissue samples would be helpful in assessing the extent of human exposure to the chemical and in estimating its body burden.
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**Exposures of Children.** No studies are available to assess whether children are at a higher exposure risk than adults. Studies examining potential exposure sources for children would be useful.

6.3 Ongoing Studies

No ongoing studies were identified for 1,2-dibromo-3-chloropropane.