DRAFT OF
PRIORITY DATA NEEDS FOR DICHLOROPROPENES

Prepared by:

Syracuse Research Corporation
Under Contract No. 200-2004-09793

Prepared for:

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Services
Agency for Toxic Substances and Disease Registry

NOTE TO THE READER

The Priority Data Needs documents are intended to characterize substance-specific priority data needs determined via the ATSDR Decision guide for identifying substance-specific data needs related to toxicological profiles (54 Federal Register 37618, September 11, 1989). The identified priority data needs reflect the opinion of the Agency, in consultation with other federal programs, of the research necessary for fulfilling its statutory mandate under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (Superfund) or CERCLA. They are not intended to represent the priority data needs for any other program.

We plan to revise these documents in response to public comments and as additional data becomes available. Therefore, we encourage comments that will make these documents of the greatest use.

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The document has been reviewed by Annette Ashizawa, Ph.D., ATSDR's Chemical Manager for the Toxicological Profile for Dichloropropenes. In addition, it was forwarded to the U.S. Environmental Protection Agency and the National Institute of Environmental Health Sciences for review.

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Dichloropropenes

Prepared by: Agency for Toxic Substances and Disease Registry/
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Date prepared: September, 2007

I. Executive Summary

Dichloropropenes are included in the priority list of hazardous substances identified by ATSDR and the Environmental Protection Agency (EPA) (ATSDR 2005a). This list contains substances that have been identified at National Priorities List (NPL) sites and determined to pose a human health risk based on (1) known or suspected human toxicity, (2) frequency of occurrence at NPL sites or other facilities, and (3) the potential for human exposure to the substance. An updated Toxicological Profile for Dichloropropenes (Draft for Public Comment) was published by ATSDR in September 2006. Currently, the updated toxicological profile is being finalized.

Dichloropropenes are a chemical class comprised of the five structural isomers 1,1-, 1,2-, 1,3-, 2,3-, and 3,3-dichloropropene. The vast majority of the available exposure and toxicity information is for the 1,3-dichloropropene isomer, which is used as a pre-plant soil fumigant. Exposure to 1,1-, 1,2-, 2,3-, and 3,3-dichloropropene is expected to be unlikely and insignificant because these isomers are not produced or used in high amounts and are not commonly found at measurable concentrations in the environment. Consequently, there is little need to identify and prioritize data needs for these isomers and this document addresses 1,3-dichloropropene, which is widely detected in the environment and has a higher potential for human exposure.

1,3-Dichloropropene is a colorless liquid with a sweet smell. It dissolves in water based on a water solubility of 2.0×10^3 mg/L and evaporates easily based on a vapor pressure of 30 mm Hg at 20 °C. 1,3-Dichloropropene is used mainly as a fumigant nematocide in farming. Based on available data, between 1 and 10 million pounds (450–4,500 metric tons) of 1,3-dichloropropene were produced during 2002.

A significant proportion of the 1,3-dichloropropene released into soil or surface waters is expected to volatize into the atmosphere where it is degraded by photooxidation with hydroxyl radicals or reaction with ozone. The half-life of 1,3-dichloropropene in ambient air is expected to range between 7 and 50 hours. 1,3-Dichloropropene may also undergo biodegradation or hydrolysis in natural waters and in soil. Experimental data indicate increased rates of hydrolysis with higher temperature, the hydrolysis half-life in deionized water being about 10 days at 20 °C.

Possible routes of human exposure to 1,3-dichloropropene include inhalation of contaminated air, ingestion of contaminated drinking water, and dermal contact with pesticides containing 1,3-dichloropropene. Due to the volatility of 1,3-dichloropropene, inhalation exposure, particularly in regions where the pesticide is used commercially to fumigate soil, appears to be the major route of exposure for the general population. Children residing in regions of pesticide use are likely to be exposed to 1,3-dichloropropene by the same routes that affect adults. Occupational exposure or accidental exposure resulting from a spill is likely to occur through inhalation and dermal contact. Individuals who live near hazardous waste sites containing 1,3-dichloropropene may be exposed via inhalation or ingestion of contaminated drinking water.

Human and animal studies indicate that the primary target of 1,3-dichloropropene toxicity following inhalation, oral, and dermal exposure is the tissue at the site of contact, as shown by irritant effects in the respiratory tract (particularly nasal epithelium), gastrointestinal tract (particularly stomach), eyes, and skin. Systemic effects observed in animal inhalation and oral studies were essentially minor, not clearly toxicologically significant, and/or occurred at exposure levels similar to or higher than those causing respiratory or gastrointestinal irritation; effects mainly included urinary bladder hyperplasia and microcytic anemia. Dermal exposure induced delayed-type hypersensitivity in humans and animals. Inhalation studies in animals showed no reproductive toxicity, although developmental toxicity testing found fetotoxic effects at exposure levels that were maternally toxic. It is not known if children are more susceptible to the toxicity of 1,3-dichloropropene than adults. Evidence for the carcinogenicity of 1,3-dichloropropene is inadequate in humans but sufficient in animals.

On the basis of the available data, ATSDR has identified the following priority data needs:

Exposure

- No priority data needs have been identified.

Toxicity

- Dose-response data for acute-duration via inhalation exposure
- Immunotoxicity battery via inhalation exposure

II. Introduction: ATSDR's Substance-Specific Applied Research Program

A. Legislative

Section 104(i)(5) of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) 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 1,3-dichloropropene is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects. Such program shall include, to the extent necessary to supplement existing information, but shall not be limited to--

- laboratory and other studies to determine short, intermediate, and long-term health effects;
- laboratory and other studies to determine organ-specific, site-specific, and system-specific acute and chronic toxicity;
- laboratory and other studies to determine the manner in which such substances are metabolized or to otherwise develop an understanding of the biokinetics of such substances; and
- where there is a possibility of obtaining human data, the collection of such information.

Section 104(i)(5)(C): In the development and implementation of the research program ATSDR is required to coordinate with EPA and NTP to avoid duplication of research being conducted in other programs and under other authorities.

Section 104(i)(5)(D): It is the sense of Congress that the costs for conducting this research program be borne by private industry, either under the Toxic Substances Control Act (TSCA), the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), or cost recovery under CERCLA.

B. Impact on Public Health

The major purpose of this research program is to supplement the substance-specific informational needs of the public and the scientific community. More specifically for ATSDR, this program will supply necessary information to improve the database to conduct public health assessments. This is more fully described in the ATSDR Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (54 Federal Register 37618) [henceforth referred to as the ATSDR Decision Guide].

Experience from ATSDR health assessments shows the need for more information for select substances, on both exposure and toxicity, so the Agency can more completely assess human health effects. Exposure data collected from this substance-specific research will complement data being collected on a site-specific basis by ATSDR's Division of Health Studies and the Division of Health Assessment and Consultation. More specifically, the Agency will use the exposure data to help identify populations that need follow-up exposure or health-outcome studies.

Regarding substance toxicity, the collected data will be used to characterize the toxicity of the substance for public and scientific community. For ATSDR, the data are necessary and essential to improve the design and conduct of follow-up health studies.

C. Procedures

Section 104(i)(2) of CERCLA, as amended, requires that ATSDR (1) with EPA develop a list of hazardous substances found at NPL sites (in order of priority), (2) prepare toxicological profiles of those substances, and (3) assure the initiation of a research program to fill identified data needs associated with the substances.

The first step in implementing the ATSDR substance-specific research program for 1,3-dichloropropene occurred when the data needs for dichloropropenes were determined in the ATSDR Toxicological Profile for Dichloropropenes. Considered a subset of all information gaps on 1,3-dichloropropene, these data needs were reviewed by scientists from ATSDR and other federal agencies. They were peer reviewed by an external review panel and made available for public comment. All comments received by ATSDR on the identification of data needs for 1,3-dichloropropene were addressed before the toxicological profile was finalized. In preparing the priority data needs document, a literature search was conducted to provide updated information on 1,3-dichloropropene.

The purpose of this paper is to take the data needs identified in the Toxicological Profile for Dichloropropenes and subject them to further scientific evaluation. This will lead to priorities and ultimately to ATSDR's substance-specific research agenda. To effect this step, ATSDR developed and presented a logical scientific approach to priority setting in its Decision Guide.

Briefly, data needs are categorized as exposure or toxicity and are then subcategorized across three levels (Tables 1 and 2). Level I research is a base set of exposure and toxicity information to identify basic characteristics of each substance. Level II research is conducted to confirm the toxicity and exposure indicated by Level I data. Level III research will improve the application of the results of Level II research to people.

The Decision Guide recognized three general principles for setting priorities:

- Not all information gaps identified in toxicological profiles are data needs.
- All data needs are not the same priority.
- Substances should be considered individually, but may be grouped, because of structural similarity or other relevant factors.

Other considerations spelled out in the Decision Guide include:

- All levels of data should be considered in selecting priority data needs.
- Level I gaps are not automatically in the priority grouping. In general, Level I data have priority when there are no higher level data for the same category, and when data are insufficient to make higher level priority testing decisions. For example, priority would generally not be assigned multigenerational animal studies (Level II) if an adequate

subchronic study (Level I) had not been conducted that evaluated reproductive organ histopathology.

- Priority for either exposure or toxicity data requires thorough evaluation of research needs in other areas to help achieve a balanced research program for each substance.

The Decision Guide listed the following eight tenets to determine research priorities:

- Development and/or confirmation of appropriate analytical methods.
- Determination of environmental and human exposure levels when analytical methods are available.
- Bioavailability studies for substances of known significant toxicity and exposure.
- Studies available to characterize target organs and dose response.
- Disposition studies and comparative physiologically-based pharmacokinetics when a toxic end point has been determined and differences in species response have been noted.
- Mechanistic studies on substances with significant toxicity and substantial human exposure.
- Investigation of methods to mitigate toxicity for substances when enough is known about mode of action to guide research.
- Epidemiologic studies designed to link human disease with a substance of known significant toxicity.

These last three "prioritizing" tenets address Level III research. When Level III research is identified as priority, ATSDR will not develop detailed methods to successfully fulfill the data needs. Because there are no standard "testing guidelines" for Level III research, we expect considerable discussion between ATSDR and parties interested in conducting this research. Thus, ATSDR will only announce that its scientists believe that the accumulation of Level III research is appropriate, and it is a priority at this time. ATSDR will state the reasons why this is so.

D. Selection Criteria

ATSDR prepares toxicological profiles on substances that are most commonly found at facilities on the NPL sites and which, in its sole discretion, pose the most significant threat to human health because of their known or suspected toxicity and potential for human exposure.

Briefly, the rationale is as follows:

Dichloropropenes are a chemical class comprised of the five structural isomers 1,1-, 1,2- 1,3-, 2,3-, and 3,3-dichloropropene. The vast majority of the available information on exposure and toxicity of dichloropropenes is for the 1,3-dichloropropene isomer, which is used as a pre-plant soil fumigant. 2,3-Dichloropropene has use as a chemical intermediate; however, based on available data, this isomer is no longer produced on a commercial level and had an annual production of less than 100 kg in 1989 (IUR 2002; NTP 2006). No production and use data are available for 1,1-, 1,2-, and 3,3-dichlororpropene, and very little environmental fate, monitoring, and exposure data exist for 1,1-, 1,2-, 2,3-, and 3,3-dichloropropene. Because these four isomers are not produced or used in high amounts and are not commonly found at measurable concentrations in the environment, human exposure to 1,1-, 1,2-, 2,3-, and 3,3-dichloropropene is expected to be unlikely and insignificant. Consequently, there is little need to identify and prioritize data needs for these isomers and this document will focus on 1,3-dichloropropene, which is widely detected in the environment and has a higher potential for human exposure.

1. Frequency of Occurrence

***Finding*:** 1,3-Dichloropropene is included in the priority list of hazardous substances identified by ATSDR and EPA (ATSDR 2005a).

1,3-Dichloropropene has been found in at least 108 of the 1,684 National Priorities List (NPL) hazardous waste sites in the United States (HazDat 2006). Exposure to 1,3-dichloropropene at these sites may occur by contacting contaminated air, water, soil, or sediment. ATSDR is presently evaluating the extent of media-specific contamination at these and other sites.

2. Potential for Human Exposure

***Finding*:** ATSDR scientists have determined that there has been significant past human exposure and that the potential exists for current human exposure to 1,3-dichloropropene via inhalation, ingestion, and skin contact.

The following is a brief summary of the potential for human exposure to 1,3-dichloropropene. For a more detailed discussion of available information, refer to the ATSDR Toxicological Profile for Dichloropropenes, Chapter 6, on Potential for Human Exposure (ATSDR 2006).

1,3-Dichloropropene is a mixture of volatile cis and trans isomers and is used primarily as a nematocide to fumigate soil before planting (Harwid et al. 2005; Krijgsheld and Van der Gen 1986). It is a colorless liquid with a sweet smell (Lewis 2001; Tomlin 2003). It dissolves in water based on a water solubility of $2.0x10^3$ mg/L and evaporates easily based on a vapor pressure of 30 mm Hg at 20 °C (Dilling 1977; EPA 1981b; Tomlin 2003).

1,3-Dichloropropene is an important substance for research because of its widespread environmental contamination.

According to data obtained from EPA's Toxic Release Inventory (TRI), estimated releases of 1,3-dichloropropene in 2004 were 4,129 pounds (1.9 metric tons) to the atmosphere, 2 pounds (0.001 metric tons) to surface water, and 342 pounds (0.2 metric tons) to soil from 15, 5, and 15 domestic manufacturing and processing facilities, respectively. These releases accounted for about 92, <1, and 8%, respectively, of the estimated total environmental releases of 1,3-dichloropropene from facilities required to report to the TRI (TRI04 2006).

1,3-Dichloropropene is produced synthetically and may be released to the atmosphere in fugitive or accidental emissions during its manufacture, storage, and transport. 1,3-Dichloropropene's use as a soil fumigant for the control of nematodes in various crops results in its direct release to the environment (EPA 1978; Lao et al. 1982). 1,3-Dichloropropene is typically applied to soils prior to planting by underground injection at a depth of 12–18 inches (EPA 1998). Due to its volatile nature, it may migrate to the soil surface where it volatilizes to air. In order to reduce potential emissions to air and increase the effectiveness of 1,3-dichloropropene as a fumigant, soil sealing techniques such as immediate irrigation, soil compacting, and covering the treated fields with tarps are common agricultural practices when using 1,3-dichloropropene and other fumigants (EPA 1998).

1,3-Dichloropropene may leach into groundwater and soil from landfills and hazardous waste sites (Hauser and Bromberg 1982; Sabel and Clark 1984). The most common release of 1,3-dichloropropene to soil occurs during the application of the chemical to agricultural fields

when used as a soil fumigant (CEPA 1982; Cohen 1986; Krijgsheld and Van der Gen 1986; Maddy et al. 1982). Accidental spills may also release 1,3-dichloropropene to the environment (Markovitz and Crosby 1984; Sterrett et al. 1986).

A significant proportion of the 1,3-dichloropropene released into soil or surface waters is expected to volatize into the atmosphere where it is degraded by photooxidation with hydroxyl radicals or reaction with ozone (Atkinson et al. 1979; Thomas 1982; Tuazon et al. 1984). The half-life of 1,3-dichloropropene in ambient air is expected to range between 7 and 50 hours, depending on the concentrations of cis- and trans- isomers and reactive hydroxyl radicals (Atkinson et al. 1979). 1,3-Dichloropropene may also undergo biodegradation or hydrolysis in natural waters and in soil (Castro and Belser 1966; EPA 1998; Guo et al. 2004; McCall 1987; Roberts and Stoydin 1976; Tabak et al. 1981a, 1981b; Tu 1988; van der Pas and Liestra 1987; Yon et al. 1991). Experimental data indicate increased rates of hydrolysis with higher temperature, the hydrolysis half-life in deionized water being about 10 days at 20 °C (McCall 1987).

1,3-Dichloropropene has been identified in air, groundwater, surface water, soil, and sediment samples collected at 6, 70, 10, 28, and 6 of the 1,678 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2006).

Possible routes of human exposure to 1,3-dichloropropene include inhalation, ingestion of contaminated drinking waters, and dermal contact. 1,3-Dichloropropene is rarely detected in foods due to its relatively short environmental persistence; therefore, exposure to the general population through the consumption of food is considered to be low. High levels of exposure to 1,3-dichloropropene are most likely to occur in occupational settings where 1,3-dichloropropene is either produced or used as a soil fumigant (Albrecht 1987b; Albrecht et al. 1986; Markovitz and Crosby 1984; Nater and Gooskens 1976; Osterloh et al. 1984, 1989a, 1989b; van Joost and de Jong 1988; Wang 1984). Children who live or play near fields where 1,3-dichloropropene has been applied may be exposed to this substance through inhalation. Intake by inhalation or dermal contact is the most probable route of workplace exposure to 1,3-dichloropropene. 1,3-Dichloro-propene is a volatile compound and, after soil application as a fumigant, a fraction of the compound will volatilize and escape into the atmosphere (Krijgsheld and Van der Gen 1986). Inhalation and dermal contact are probably the major sources of exposure to individuals who work in fields where 1,3-dichloropropene is applied.

According to the National Occupational Exposure Survey (NOES) conducted by NIOSH between 1981 and 1983, it has been estimated that 2,162 workers were potentially exposed to 1,3-dichloropropene (NIOSH 2006). The NOES database does not contain information on the frequency, concentration, or duration of workers' exposure to any of the chemicals listed therein. The survey provides only estimates on the number of workers potentially exposed to chemicals in the workplace.

3. Toxicity

***Finding*:** ATSDR considers that short, intermediate, and long-term health effects can result from inhalation, ingestion, and dermal contact of 1,3-dichloropropene. Target organs or systems know to be affected include the respiratory tract, gastrointestinal tract, skin, eyes, urinary bladder, and erythrocytes.

The following is a brief summary of the toxicology of 1,3-dichloropropene. Refer to the ATSDR Toxicological Profile for Dichloropropenes chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2006).

1,3-Dichloropropene is a reactive chemical that mainly causes effects at the point of contact with tissues, particularly the nasal epithelium following inhalation exposure, stomach following oral exposure, and skin and eyes following dermal or ocular exposure. Other targets of 1,3-dichloropropene toxicity include the urinary bladder and erythrocytes.

Experimental studies of 1,3-dichloropropene in animals have been conducted using various commercial formulations. The formulations tested in many of the early studies contained chloropicrin (e.g., Telone C-17 containing 19–21% chloropicrin) or epichlorohydrin (e.g., Telone II®a containing 1% epichlorohydrin) as stabilizers, or significant amounts of 1,2-dichloropropane (e.g., DD containing 25–29% 1,2-dichloropropane). Because early investigations of 1,3-dichloropropene may have been confounded by toxic components in a formulation, most recent studies tested Telone II®b, a relatively pure formulation (≥90% 1,3-dichloropropene) in which epichlorohydrin was replaced with epoxidized soybean oil as a stabilizer (Haut et al. 1996; Lomax et al. 1989; Stebbins et al. 1999, 2000).

Irritant effects on the respiratory tract have been observed in humans and animals following inhalation exposure to 1,3-dichloropropene. In cases of humans accidentally exposed to presumably high concentrations, respiratory effects included mucous membrane irritation, chest pain, and cough (Flessel et al. 1978; Markovitz and Crosby 1984). No data are available for effects in humans following single or repeated exposures to lower levels. Respiratory effects in rats exposed to 1,3-dichloropropene vapor at high concentrations in acute lethality studies included atelectasis, lung edema, congestion, and hemorrhage (Cracknell et al. 1987; Streeter et al. 1987). Nasal turbinates were not examined for histopathology in these acute-duration studies. In intermediate- and chronic-duration inhalation studies using sublethal exposures to Telone II®b or Telone II®a vapor, effects in rats and mice included hyperplasia/hypertrophy of the nasal respiratory epithelium and degeneration of the nasal olfactory epithelium (Breslin et al. 1989; Lomax et al. 1989; Stott et al. 1988). Lung effects (congestion, hemorrhage) were observed in rats during acute lethality studies by the oral or dermal routes, but may have resulted from inhalation of 1,3-dichloropropene vapor during administration of high doses of the test material (Jones 1988a; Jones and Collier 1986a, 1986b).

Irritant effects on the gastrointestinal tract have been observed in humans and animals following oral exposure to 1,3-dichloropropene. Gastrointestinal effects observed in a case of fatal ingestion included initial acute gastroenteritis, subsequent bloody diarrhea, and hemorrhagic exudate and mucosal erosions of the stomach at autopsy (Hernandez et al. 1994). No data are available for gastrointestinal effects in humans exposed to lower single or repeated doses. Gastrointestinal effects observed in rats following oral exposure to 1,3-dichloropropene as high single gavage doses of various pesticide formulations included hyperkeratosis of the forestomach and hemorrhaging of the small intestine (Jones 1988a; Jones and Collier 1986a; Mizell et al. 1988a). Intermediate- and chronic-duration oral exposure to lower doses of Telone II®b caused basal cell hyperplasia of the nonglandular stomach in rats and mice(Haut et al. 1996; NTP 1985; Stebbins et al. 2000). Mice chronically exposed to Telone II®b by inhalation developed hyperplasia and hyperkeratosis of the forestomach (Lomax et al. 1989).

Dermal exposure to liquid 1,3-dichloropropene caused contact dermatitis and sensitization in humans (Bousema et al. 1991; Corazza et al. 2003; van Joost and de Jong 1988; Vozza et al. 1996) and guinea pigs (Mizell et al. 1988b). Dermal exposure to liquid 1,3-dichloropropene also caused skin effects ranging from erythema and edema to necrosis in rats, rabbits, and guinea pigs (Carreon and Wall 1983; Jeffrey 1987a, 1987b). Liquid 1,3-dichloropropene was irritating to the

eyes of rabbits, causing erythema, lacrimation, and palpbral closure (Jeffrey 1987a; Lichy and Olson 1975).

Non-portal-of-entry effects of 1,3-dichloropropene, observed in intermediate- and chronic-duration studies in animals, mainly included urinary bladder hyperplasia in mice exposed to Telone II®b by inhalation (Lomax et al. 1989; Stott et al. 1988), and reductions in hemoglobin and hematocrit counts consistent with microcytic anemia in dogs orally exposed to Telone II®b via diet (Stebbins et al. 1999). Urinary bladder hyperplasia also occurred in mice chronically exposed to Telone II®a by gavage (NTP 1985), but not in mice exposed to similar doses of Telone II®b in the diet; the degree to which oral bolus dosing and/or epichlorohydrin contributed to the different results in these mouse studies is not known. Clinical signs of neurotoxicity (e.g., ataxia, loss of righting reflex, salivation, and lethargy) developed in rats and rabbits following high-level acute inhalation, oral, and dermal exposure to 1,3-dichloropropene (Dietz et al. 1985; Jeffrey et al. 1987a; Jones 1988a, 1988b; Jones and Collier 1986b; Kloes et al. 1983; Mizell et al. 1988b). Developmental toxicity was evaluated in rats and rabbits gestationally exposed to Telone II®a and Telone II®b by inhalation; effects included fetotoxicity in rats exposed to Telone II®a (increased resorptions and decreased litter size) and rabbits exposed to Telone II®b (delayed ossification of vertebral centra) at concentrations that were maternally toxic (Hanley et al. 1987; Kloes et al. 1983). There was no reproductive toxicity in a two-generation inhalation study of Telone II®b in rats (Breslin et al. 1989). No histopathological effects were found in reproductive and endocrine tissues of rats, mice, or dogs following intermediate- or chronic-duration inhalation or oral exposure to Telone II®a or Telone II®b (Lomax et al. 1989; NTP 1985; Stebbins et al. 1999, 2000; Stott et al. 1988). Considering these findings and the negative results of an *in vitro* estrogen receptor binding assay (Nishihara et al. 2000), the available data do not suggest that 1,3-dichloropropene has endocrine disrupting activity.

The genotoxicity of 1,3-dichloropropene has been tested *in vitro* and *in vivo*. *In vitro* findings included mutagenicity in bacteria and mammalian cells and chromosomal and DNA damage in mammalian cells (Creedy et al. 1984; De Lorenzo et al. 1977; Eder et al. 1982a, 1982b, 1987; Haworth et al. 1983; Kevekordes et al. 1996; Loveday et al. 1989; Martelli 1997; Matsuoka et al. 1998; Myhr and Caspary 1991; Neudecker and Henschler 1986; Neudecker et al. 1977, 1980; Sasaki et al. 1988; Schiffmann et al. 1983; Stolzenberg and Hine 1980; Talcott and King 1984; Vithayathil et al. 1983; von der Hude et al. 1987; Watson et al. 1987). *In vivo* findings included DNA fragmentation, but no micronuclei or dominant lethal mutations, in rats and/or mice (Ghia

et al. 1993; Gollapudi et al. 1998; Kevekordes et al. 1996; Kitchin and Brown 1994; Morita et al. 1997; Sasaki et al. 1998; Valencia et al. 1985). The available information indicates that impurities or other confounding factors likely contributed to many of the observed effects.

Evidence for the carcinogenicity of 1,3-dichloropropene is inadequate in humans but sufficient in animals. Several human case reports of histiocytic lymphoma and acute myelomonocytic leukemia suggested a possible association between inhalation exposure to high concentrations of 1,3-dichloropropene and hematological malignancies (Markovitz and Crosby 1984). A case-control study provided suggestive evidence of increased risk for death from pancreatic cancer in people living for 20 years in areas with high usage of 1,3-dichloropropene as a soil fumigant (Clary and Ritz 2003). In chronic animal bioassays using Telone II®b, increased tumor incidences were observed for bronchioalveolar adenomas in mice exposed by inhalation (Lomax et al. 1989) and hepatocellular adenomas and carcinomas (combined) in rats orally exposed via diet (Stebbins et al. 2000). In a chronic oral gavage bioassay of Telone II®a, increased incidences were observed for forestomach squamous cell papillomas and carcinomas in rats, and forestomach squamous cell papillomas and carcinomas, bronchioalveolar adenomas, and transitional cell carcinomas of the urinary bladder in mice (NTP 1985). The bolus dosing and/or presence of epichlorohydrin in the Telone II®a could have contributed to the induction of these tumors; additionally, aspiration of Telone II®a might have contributed to the bronchioalveolar adenomas. Chronic subcutaneous administration of cis-1,3-dichloropropene induced injection site papillomas and sarcomas and lung papillomas in mice (Van Duuren et al. 1979). The Department of Health and Human Services (DHHS) has determined that 1,3-dichloropropene may reasonably be anticipated to be a human carcinogen (NTP 2005). The International Agency for Research on Cancer (IARC) has determined that 1,3-dichloropropene is possibly carcinogenic to humans (IARC 1999). The EPA has classified 1,3-dichloropropene as a probable human carcinogen (IRIS 2006).

No data are available on health effects resulting from interactions of 1,3-dichloropropene with other chemicals, or on populations that are unusually susceptible to the toxicity of 1,3-dichloro-propene. 1,3-Dichloropropene is rapidly and extensively metabolized and eliminated, mainly via glutathione conjugation and excretion of the mercapturic acid conjugate in the urine (Climie et al. 1979; Fisher and Kilgore 1989; Hutson et al. 1971; Osterloh and Feldman 1993; Osterloh et al. 1984; Stott and Kastl 1986; Stott et al. 1998; Van Welie et al. 1989; Waechter and Kastl 1988). A minor metabolic pathway involves reaction with cytochrome P-450 to form mutagenic cis- and

trans-epoxides that convert to the mutagen 3-chloro-2-hydroxy-propanal (Schneider et al. 1998a). Simultaneous exposure to other chemicals that are metabolized in whole or in part by glutathione-dependent pathways would tend to enhance the toxicity of 1,3-dichloropropene through depletion of glutathione stores and increased metabolism via the epoxide-generating pathway (Schneider et al. 1998a). People taking drugs such as acetominophen that are detoxified by glutathione also may be more susceptible to the effects of glutathione depletion from exposure to 1,3-dichloro-propene. Kidney disease or deficiencies in the mercapturic acid transport system could also enhance the toxicity of 1,3-dichloropropene.

III. Identification of Data Needs

In evaluating the exposure and toxicity testing needs for 1,3-dichloropropene, ATSDR considered all available published and unpublished information that has been peer-reviewed. From its evaluation of these data, ATSDR is recommending the conduct of specific research or testing.

A. Exposure Data Needs (Table 1)

Three of the eight "prioritizing" tenets presented in the Decision Guide directly address exposure data needs:

- Development and/or confirmation of appropriate analytical method;
- Determination of environmental and human exposure levels when analytical methods are available; and
- Bioavailability studies for substances of known significant toxicity and exposure.

The progressive accumulation of exposure information begins with developing suitable analytical methods to analyze the compound in all relevant biological and environmental media, followed by confirmation of exposure information, before the conduct of any Level III research. However, in order to know what analytes are available to monitor, some basic environmental fate information is generally required and becomes a priority if it is lacking.

Bioavailability and food chain bioaccumulation studies are appropriately placed in Level II, and should be undertaken after analytical methods are developed and the substance has been confirmed at many hazardous waste sites and in environmental media.

1. Levels I & II Data Needs

a. Analytical Methods

***Purpose*:** To determine if available methods are adequate to detect and quantify levels of 1,3-dichloropropene in environmental and biological matrices. The methods should be sufficiently specific and sensitive to measure (1) background levels in the environment and the population; and (2) levels at which biological effects might occur.

***Finding*:** A data need has been identified. A limited number of methods is available to determine 1,3-dichloropropene in biological materials (Daft 1989; Kastl and Hermann 1983), and none of the methods have been standardized. It is difficult to monitor for exposure to 1,3-dichloropropene in humans because the biological half-life of 1,3-dichloropropene is <2 days (Bond et al. 1985; Climie et al. 1979; Dutcher et al. 1985; Hutson et al. 1971; Medinsky et al. 1984). Van Welie et al. (1989) described a method for determining the mercapturic acid metabolites, N-acetyl-S-(cis-3-chloropropenyl-2)-L-cysteine (or cis-DCP-MA) and N-acetyl-S-(trans-3-chloropropenyl-2)-L-cysteine (or trans-DCP-MA) in the urine. However, a standard level of these metabolites in urine has not been established that corresponds to a level of human exposure of 1,3-dichloropropene. Additional study and the development of standardized methods regarding the detection of dichloropropene and its metabolites in human biological materials (urine, blood, and tissue) are needed.

Methods for determining of 1,3-dichloropropene in environmental matrices have appeared in the literature. Of these, standardized methods exist for the analysis of 1,3-dichloropropene in air (EPA 1996b), water (EPA 1986, 1995, 1996a, 1996b, 2001; NEMI 1997a, 1997b, 2001; USGS 1998), soil (EPA 1999), and solid waste samples (EPA 1996a, 1996b). These methods are sufficiently sensitive to measure levels in the environment that approach ATSDR's Environmental Media Evaluation Guides (EMEGs) calculated from ATSDR's Minimal Risk Levels (MRLs). For soils, the levels of accuracy have not been reported. For air, both accuracy and precision data are lacking. The accuracy and precision at which the trans-isomer can be measured in water is questionable. Therefore, refinement of the current standardized procedures will aid in determining levels of human exposure to 1,3-dichloropropene.

***Priority Recommendation*:** The identified data need is not considered priority. Although, a data need exists for the development of reliable, sensitive, and specific methods to quantify levels of 1,3-dichloropropene in human blood and tissue, this is not considered a priority because it may not be practical to measure a chemical with such a short biological half-life.

b. Physical/Chemical Properties

***Purpose*:** To determine whether adequate data on the chemical and physical properties of 1,3-dichloropropene are available to permit estimation of its environmental fate under various conditions of release, and evaluation of its pharmacokinetics under different exposure durations and routes.

***Finding*:** A data need has not been identified. The physical and chemical properties of both cis- and trans-1,3-dichloropropene have been described and are readily available in the literature (Dilling 1977; EPA 1981a; Kenaga 1980; Leistra 1970; Lewis 2001; Lide 2005; O'Neil et al. 2001; Verschueren 2001). Some of these physical properties were required for assessing the fate and transport of 1,3-dichloropropene in the environment where experimental data were not available.

***Priority Recommendation*:** A data need has not been identified.

c. Exposure Levels

(1) Environmental Media

***Purpose*:** To determine whether adequate data are available on the levels of 1,3-dichloropropene in the ambient and contaminated environments for purposes of conducting meaningful follow-up exposure and health studies.

Finding: A need to obtain reliable and current data on concentrations of 1,3-dichloropropene in contaminated environmental media at hazardous waste sites has been identified.

Air and water monitoring data are available for 1,3-dichloropropene. 1,3-Dichloropropene was positively detected in air in generally <5% of urban air samples collected across the United States

(EPA 1991; Pankow et al. 2003; Pratt et al. 2000; Spicer et al. 1996). Mean concentrations among the positive samples from both urban and rural locations across the United States ranged from 0.088 to 0.33 ppb. 1,3-Dichloropropene air concentrations as high as 35.2 ppb have been measured at high-use locations (Baker et al. 1996). A few nationwide surveys have been conducted in which 1,3-dichloropropene was analyzed for in water; however, only the STORET database lists positive detections of this substance (EPA 2006; Kolpin et al. 2000; Moran et al. 2004). 1,3-Dichloropropene was detected in approximately 40% of 12,673 water samples listed in STORET (EPA 2006). However, only 6% of the samples contained 1,3-dichloropropene above the quantitation limit (unspecified). The range, mean, and median of quantifiable 1,3-dichloropropene concentrations were 0.002–25, 0.5, and 0.5 ppb, respectively. 1,3-Dichloropropene was detected in only 0.1% of 70,631 public water system samples collected in the United States between 1993 and 1997 (EPA 2001c).

Limited monitoring data are available for 1,3-dichloropropene in soil and sediment; however, the existing data indicate that this substance is not widely detected in these media (Dowty et al. 1975a, 1975b; EPA 2006; Krijgsheld and Van der Gen 1986; Otson 1987; Rogers et al. 1987). More information on the levels of 1,3-dichloropropene in soil and sediment would be helpful. 1,3-Dichloropropene has not been detected in table-ready foods (EPA 1998; FDA 2005). 1,3-Dichloropropene is not expected to be present in crops grown in soil treated with this pesticide; however, additional monitoring for 1,3-dichloropropene in these types of foods would be helpful in confirming this.

***Priority Recommendation*:** The identified need is not considered priority. Although monitoring data are available for 1,3-dichloropropene in air and water, these data do not appear to be very current. Reliable and current monitoring data for the levels of 1,3-dichloropropene in contaminated media at hazardous waste sites are needed so that the information obtained on levels of 1,3-dichloropropene in the environment and the resulting body burden of 1,3-dichloropropene can be used to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. However, ATSDR has developed a hazardous substance release/health effects database (HazDat) that includes the extant data for the 108 NPL sites at which 1,3-dichloropropene has been found. This database includes maximum concentrations of 1,3-dichloropropene in on- and off-site media, and an indication of relevant routes of exposure. Further evaluation of this database is needed first to assess if collection of additional media-specific data is assigned priority.

(2) Humans

***Purpose*:** To determine whether adequate data are available on the levels of 1,3-dichloropropene in human tissues for the general population and exposed populations for purposes of conducting meaningful follow-up exposure and health studies.

***Finding*:** A need has been identified. No data are available on the levels of 1,3-dichloropropene in body tissues or fluids for people living near hazardous waste sites.

Concentration data for 1,3-dichloropropene measured in human tissues such as blood, fat, and breast milk are not available. Dichloropropene (unspecified isomers) was qualitatively identified in 1 out of 12 samples of breast milk collected from Bayonne, New Jersey; Jersey City, New Jersey; Bridgeville, Pennsylvania; and Baton Rouge, Louisiana during the late 1970s. Biological monitoring studies involving 1,3-dichloropropene have not been located.

Available information shows that N-acetyl cysteine, the primary urinary metabolite of 1,3-dichloropropene, is present in the urine of people who were occupationally exposed to 1,3-dichloropropene (Brouwer et al. 2000; He 1993; Kezic et al. 1996; Osterloh et al. 1984, 1989a, 1989b; van Welie et al. 1991). Additional information regarding the utility of this biomarker as an indicator of general population exposure to the compound may be useful in monitoring the frequency of human exposure to 1,3-dichloropropene. Information concerning the numbers of persons potentially exposed to 1,3-dichloropropene near waste sites and manufacturing, production, and use facilities is also not available. Human exposure data for 1,1-, 1,2-, 2,3-, or 3,3-dichloropropene were not located in the literature. Although human exposure to these isomers is not expected to be important, information would be helpful in verifying this.

Priority Recommendation: The identified data need to collect additional information is not considered priority. Analytical methods are not currently available that can readily determine 1,3-dichloropropene levels in biological fluids. In addition, no standard level of the 1,3-dichloropropene mercapturic acid metabolites, cis- and trans-DCP-MA, corresponding to a level of exposure has been established.

ATSDR has developed a hazardous substance release/health effects database (HazDat) that includes the extant data for the 108 NPL sites at which 1,3-dichloropropene, have been found. This database includes maximum concentrations of 1,3-dichloropropene in on and off site media, and an indication of relevant routes of exposure. This database will not, however, supply information on the levels of 1,3-dichloropropene (or its metabolites) in the tissues of individuals living near hazardous waste sites or other exposed populations such as workers.

d. Exposures of Children

Purpose: To determine if adequate data on exposures of children to 1,3-dichloropropene are available for the purpose of conducting meaningful follow-up exposure and health studies.

***Finding*:** A data need to conduct additional studies to assess exposures of children to 1,3-dichloropropene has been identified. Data regarding the exposure of children to 1,3-dichloropropene (including body burden data, levels in breast milk, dietary exposure data, pathways of exposure, differences in intake compared to adults, and secondary exposure data) are not available. Exposure data for children who live or play near fields where 1,3-dichloropropene is applied would be particularly helpful to determine the bioavailability from soil and dust and oral, dermal, and inhalation exposure.

***Priority Recommendation*:** The identified data need to conduct additional studies to assess exposures of children to 1,3-dichloropropene is not considered a priority. Collecting information on the levels of 1,3-dichloropropene in children is important in order to determine the extent of a child's exposure to this substance as well as to identify ways to reduce the potential sources for exposure risks. However, due to the rapid biological half-life of 1,3-dichloropropene, analytical methods are not currently available that can readily determine 1,3-dichloropropene levels in biological fluids. In addition, no standard level of the 1,3-dichloropropene mercapturic acid metabolites cis- and trans-DCP-MA, corresponding to a level of exposure has been established.

e. Environmental Fate

***Purpose*:** To determine whether the available data are adequate to estimate exposure to 1,3-dichloropropene under various conditions of environmental release for purposes of planning and conducting meaningful follow-up exposure and health studies.

***Finding*:** A data need has not been identified. Information concerning the partitioning of 1,3-dichloropropene in the environment is available (Cohen 1986; Dilling 1977; EPA 1986; Kenaga 1980; Leistra 1970; Munnecke and Vangundy 1979; Roberts and Stoydin 1976; Thomas and McKenry 1974; van der Pas and Leistra 1987). Information on the transport and degradation of 1,3-dichloropropene in environmental media is also available (Cohen 1986; Dilling 1977; EPA 1986; Leistra 1970; Munnecke and Vangundy 1979; Roberts and Stoydin 1976; Swann et al. 1983; Thomas 1982; van der Pas and Leistra 1987).

1,3-Dichloropropene is expected to volatilize rapidly from soil and water surfaces based on a vapor pressure of 30 mm Hg at 20 °C and a water solubility of $2.0x10^3$ mg/L (Dilling 1977; EPA 1981b; Tomlin 2003). The estimated half-life for the volatilization of 1,3-dichloropropene from a model river (1 m deep, flowing 1 m/second, wind velocity 3 m/second) is approximately 4 hours based on a Henry's law constant of $3.55x10^{-3}$ atm-m^3/mol at 20 °C (EPA 1987; Leistra 1970; Thomas 1982). During a study of 1,3-dichloropropene volatilization from treated fields, this substance was not detected in the air above fields 14–21 days posttreatment (EPA 1998). K_{oc} values ranging from 3.19 to 60 indicate a high mobility in soil and a potential for leaching (Hamaker and Thomspon 1972; Kim et al. 2003; Swann et al. 1983). Although movement in saturated soils is possible, concurrent hydrolysis and biodegradation should attenuate the amounts of 1,3-dichloropropene that may actually leach to groundwater.

1,3-Dichloropropene in air is expected to be degraded through photooxidation with hydroxyl radicals and reactions with ozone (Atkinson et al. 1979; Thomas 1982; Tuazon et al. 1984. The half-life of 1,3-dichloropropene in ambient air is expected to range between 7 and 50 hours, depending on the concentrations of cis- and trans- isomers and reactive hydroxyl radicals (Atkinson et al. 1979). Both hydrolysis and biodegradation are expected to be important degradation pathways for 1,3-dichloropropene in soil and water (Castro and Belser 1966, 1968; EPA 1998; Guo et al. 2004; McCall 1987; Roberts and Stoydin 1976; Tabak et al. 1981a, 1981b; Tu 1988; van der Pas and Liestra 1987. A hydrolysis half-life of 11.3 days has been measured for 1,3-dichloropropene in sterile, buffered water at 20 °C (McCall 1987). During river die-away tests, 50–85% of 1,3-dichloropropene at an initial concentration of 10 ppm was degraded within 7 days (Tabak et al. 1981a, 1981b). Approximately 68–100% of 1,3-dichloropropene (16 µg/g) was degraded after 28 days in treated soils (Chung et al. 1999; Ou 1998). Degradation rates were influenced by the nature and conditions of the soil including whether there had been any previous

treatments with 1,3-dichloropropene. Half-lives as high as 64 days have been measured in soils where volatilization was hindered (Batzer et al. 1996; Boesten et al. 1991; EPA 1998).

***Priority Recommendation*:** A data need has not been identified.

f. Bioavailability and Bioaccumulation Potential

***Purpose*:** To determine whether adequate data are available to predict the potential of 1,3-dichloropropene to be taken up by people exposed via contaminated air, soil, water, and the food chain, in order to plan and conduct meaningful follow-up exposure and health studies.

***Finding*:** A data need has been identified.

Based on its high volatility and high mobility in soil, the primary routes of exposure to 1,3-dichloropropene at hazardous waste sites appear to be through inhalation of contaminated air, ingestion of contaminated drinking water, and dermal contact with contaminated soil. Case reports of people who have experienced 1,3-dichloropropene poisoning following inhalation, oral, and dermal exposure indicate that 1,3-dichloropropene can be absorbed by these routes (Albrecht 1987a; Markovitz and Crosby 1984; Osterloh et al. 1984, 1989a, 1989b). However, information regarding oral or dermal absorption of 1,3-dichloropropene in water, soil, or plant material have not been found. Studies of absorption of 1,3-dichloropropene from air, water, soil, and plant material would allow determination of the rate and extent of absorption from each of these media, and allow comparison of the potential hazard posed by 1,3-dichloropropene contained in each. A data need exists regarding the bioavailability of 1,3-dichloropropene from these media. Although measured bioconcentration data are lacking, this substance is not expected to bioconcentrate based on an estimated bioconcentration factor (BCF) of 19.5 (calculated using the measured log K_{ow} of 2.0 and a regression derived equation) and a biological half-life of <2 days (Meylan et al. 1999; Tomlin 2003).

Information concerning the potential for food chain biomagnification has not been described; however, the short biological half-life of 1,3-dichloropropene make bioaccumulation unlikely.

Priority Recommendation: The identified data need is not considered priority. Although specific data regarding rate and extent of absorption are not available, sufficient data are available

to predict the potential for 1,3-dichloropropene to be taken up by people exposed via the most relevant routes (i.e., contaminated air, soil, and water).

2. Level III Data Needs

a. Registries of Exposed Persons

***Purpose*:** To help assess long-term health consequences of exposure to 1,3-dichloropropene in the environment. The ATSDR Division of Health Studies will be asked to consider this substance for selection as a primary contaminant to establish a dichloropropene subregistry of the National Exposure Registry.

***Finding*:** A data need has been identified. 1,3-Dichloropropene have been found in at least 108 NPL hazardous waste sites, respectively. At this time, no formal registries exist that identify people known to have been exposed to 1,3-dichloropropene. The development of an exposure registry should provide an important reference tool to help assess long-term health consequences of exposure to 1,3-dichloropropene. It should also facilitate the conduct of epidemiologic or health studies to assess any increased incidence of chronic disease or late-developing effects such as cancer. An effort is currently under way at ATSDR to identify those sites where humans have been exposed to site contaminants. From those identified sites, ATSDR can determine which sites list 1,3-dichloropropene as a contaminant and the size of the potentially exposed population.

***Priority Recommendation*:** The identified data need is not considered priority. The development of a 1,3-dichloropropene subregistry at this time would not contribute significantly to the current database. The development of an exposure subregistry should await the results of needed studies on dose-response data for acute-duration via inhalation exposure and immunotoxicity battery via inhalation exposure as well as information on levels in populations living near hazardous waste sites.

B. Toxicity Data Needs (Table 2)

The five remaining "prioritizing" tenets presented in the Decision Guide address toxicity data needs.

- Studies available for all toxicological profile substances to characterize target organs and dose response.
- Disposition studies and comparative physiologically-based pharmacokinetics when a toxic end point has been determined and differences in species response have been noted.
- Mechanistic studies on substances with significant toxicity and substantial human exposure.
- Investigation of methods for mitigation of toxicity for substances where enough is known about mode of action to guide research.
- Epidemiologic studies that will provide a direct answer on human disease for a substance of known significant toxicity.

The following is a brief summary of the toxicity data needs for 1,3-dichloropropene. Please refer to the ATSDR Toxicological Profile for Dichloropropenes, chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2006). Generally, ATSDR believes that the most relevant route(s) of human exposure to 1,3-dichloropropene at waste sites is inhalation, thus ATSDR scientists believe that the proposed toxicity studies should be conducted via the inhalation route. Additionally, animal testing should be conducted on the species with metabolism most similar to humans or the most sensitive species.

1. Levels I & II Data Needs

ATSDR determines Minimal Risk Levels (MRLs) which are defined as estimates of daily human exposure to a chemical that are likely to be without appreciable risk of deleterious effects over a specified duration. In order to derive MRLs for acute, intermediate, and chronic exposure durations, ATSDR evaluates the substance-specific database to identify studies of the appropriate route and duration of exposure. Thus, in order to derive acute MRLs, ATSDR evaluates studies of 14 days or less duration that identify the target organs and levels of exposure associated with these effects. Similar studies are identified for intermediate and chronic duration exposures.

Currently, ATSDR is using tools such as physiologically-based pharmacokinetic modeling and pharmacodynamic modeling to extrapolate data across routes or durations of exposure. ATSDR acknowledges that such extrapolations may be done on a substance-by-substance basis after adequate toxicokinetics information has been collected.

As reflected in the Decision Guide, ATSDR assigns priorities to identified data needs for acute/intermediate (Level I) studies by the most relevant route of exposure at Superfund sites. Regarding the need to conduct studies by other routes of exposure, ATSDR usually first requires toxicokinetic studies for the three routes of exposure to determine the need for the additional route-specific information.

Regarding chronic studies, ATSDR acknowledges that appropriately conducted 90-day studies can generally predict the target organs for chronic exposure. However, they might fall short in accurately predicting the levels of exposure associated with these effects. Although ATSDR acknowledges this fact, it will generally await the results of prechronic and toxicokinetic studies before assigning priority to chronic toxicity studies. Note: Chronic toxicity studies may be separated from cancer bioassays; they require a one-year exposure.

a. Acute-Duration Exposure

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause acute human health effects.

***Finding*:** A data need to conduct additional studies via inhalation, oral, and dermal exposure has been identified. Information on the acute inhalation toxicity of 1,3-dichloropropene in humans comes from accidental exposures in which air concentrations were not measured. Acute inhalation effects in humans involved the respiratory system and included mucous membrane irritation, chest pain, cough, and breathing difficulties (Flessel et al. 1978; Markovitz and Crosby 1984). Most of the acute-duration inhalation toxicity data in animals comes from 1–4-hour acute lethality studies in rats. Effects in these studies occurred at near-lethal to lethal exposure levels of ≥206 ppm for Telone C-17® (21.1% chloropicrin) and ≥676 ppm for Telone II®a, and included eye irritation and atelectasis, edema, congestion, and hemorrhage of the lungs (Cracknell et al. 1987; Streeter and Lomax 1988; Streeter et al. 1987; Yakel and Kociba 1977). An acute-duration repeated-exposure developmental toxicity study found no maternal effects in rats gestationally

exposed to 300 ppm Telone II®a, although litter sizes were decreased (Kloes et al. 1983). Gestational exposure to 300 ppm Telone II®a had no effect on rabbit development, but resulted in maternal ataxia and death in six of seven does (Kloes et al. 1983). The no-observed-adverse-effect level (NOAEL) for maternal toxicity in rats and developmental toxicity in rabbits exposed to Telone II®a was 150 ppm (Kloes et al. 1983), but this value was not used as the basis for an acute-duration inhalation MRL because histological examinations of the nasal turbinates were not performed. The nasal turbinates are a likely sensitive target organ based on intermediate-duration studies, and the lack of nasal histology data in the maternal animals casts doubt on the reliability of 150 ppm as a NOAEL for systemic effects (although it appears to be a reliable NOAEL for developmental toxicity). Additional studies are needed to better characterize exposure-response relationships for sublethal concentrations, particularly for identification of a NOAEL for nasal and lung effects and effect levels for repeated acute-duration exposures (e.g., 14 days), for the purpose of providing a basis for MRL derivation. These studies could also be used to provide information on relative toxicity in young and adult animals (to address children's susceptibility as discussed in that section).

The only information on the oral toxicity of 1,3-dichloropropene in humans comes from a case report of effects following accidental ingestion of an undetermined fatal dose (Hernandez et al. 1994). Gastrointestinal effects were observed that included acute gastroenteritis, bloody diarrhea, and hemorrhagic exudate and mucosal erosions of the stomach; these findings support the significance of portal-of-entry effects of ingested 1,3-dichloropropene in animals. Other findings in the human case report included tachycardia, tachypnea, hypovolemia, adult respiratory distress syndrome, and multiorgan failure prior to death. The database for acute oral toxicity of 1,3-dichloropropene in animals consists entirely of single dose lethality studies in rats exposed by gavage under protocols that did not include a control group. Administration of near-lethal to lethal doses of 1,3-dichloropropene in these studies, as mixed isomers (92–97.54% pure), cis isomer (97.2% pure), or older formulations containing epichlorohydrin or chloropicrin, induced effects that included hyperkeratosis in the stomach, hemorrhaging in the gastrointestinal tract, lungs, and liver, and clinical signs of neurotoxicity (e.g., reduced respiratory rate, lethargy, and ataxia) (Jones 1988a; Jones and Collier 1986a; Mizell et al. 1988a). No acute-duration oral MRL was derived due to the lack of toxicity information on lower doses of 1,3-dichloropropene. Additional studies are needed to determine a suitable NOAEL or lowest-observed-adverse-effect level (LOAEL) for oral MRL derivation. Studies using gastrointestinal histological examinations

to identify sensitive irritant effects at the portal-of-entry, particularly for repeated acute-duration oral exposures (e.g., 14 days), would be particularly useful.

Contact dermatitis and delayed-type hypersensitivity developed in workers following acute dermal exposure to pesticides containing 1,3-dichloropropene (Bousema et al. 1991; Corazza et al. 2003; van Joost and de Jong 1988; Vozza et al. 1996). Acute dermal toxicity studies in animals tested Telone II®a and other older commercial formulations of 1,3-dichloropropene. Dermal application caused local erythema, edema, and at high doses, necrosis, exfoliation, and subcutaneous/skeletal muscle hemorrhage in rats, rabbits, and guinea pigs (Carreon and Wall 1983; Jeffrey 1987b; Jones and Collier 1986b; Lichy and Olson 1975; Mizell et al. 1988a, 1988b). Acute dermal exposure also induced delayed-type hypersensitivity in guinea pigs (Carreon and Wall 1983; Jeffrey 1987b; Mizell 1988), and ocular instillation resulted in severe conjunctival irritation and corneal injury in rabbits (Jeffrey 1987a; Lichy and Olson 1975). Gross necropsy of rats given a single dermal application of a high dose of cis-1,3-dichloropropene or Telone II®a showed systemic effects mainly in the lungs (congestion and hemorrhage) and gastrointestinal tract (hemorrhage and ulceration in gladular stomach, congestion and hemorrhage in intestines) (Jones 1988b; Jones and Collier 1986b). Additional studies are needed to determine single and repeated exposure (e.g., 14 days) NOAELs and LOAELs for local and systemic effects of skin exposure, as well as to identify effect levels for ocular irritation.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation exposure is considered priority. Inhalation is the primary exposure route for 1,3-dichloropropene at hazardous waste sites and additional studies are needed to identify the threshold region for nasal irritation and systemic effects and thereby provide exposure-response data suitable for benchmark dose (BMD) modeling and inhalation MRL derivation. Although additional studies are also needed to adequately define dose-response relationships for oral and dermal exposure and to derive an acute oral MRL, the needs for additional oral and dermal data are not priority because oral and dermal exposures are unlikely for populations living near hazardous waste sites.

b. Intermediate-Duration Exposure

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause subchronic human health effects.

Finding: A data need to conduct additional studies via inhalation, oral, and dermal exposure has been identified. In the only intermediate-duration inhalation study in humans, clinical chemistry tests showed no evidence of liver or kidney damage in pesticide applicators that used cis-1,3-dichloropropene over a period of 117 days (Verplanke et al. 2000). Respiratory effects and other end points were not evaluated. Information regarding the toxicity of intermediate-duration inhalation exposure in animals is available from a 4-week study in rats (Coate 1979b), 13-week studies in rats and mice (Coate 1979a; Stott et al. 1988), 6-month studies in rats and mice (Lomax et al. 1989; Torkelson and Oyen 1977), 6-month studies in guinea pigs, rabbits, and dogs (Torkelson and Oyen 1977), and a two-generation reproduction study in rats (Breslin et al. 1989). Telone II®b was tested in one of the 6-month studies (Lomax et al. 1989) and in the reproductive study (Breslin et al. 1989), whereas the remaining studies used epichlorohydrin-containing Telone II®a. All of these studies used intermittent exposures (6–7 hours/day, 5–7 days/week) and end points evaluated in some or all studies included hematology, clinical chemistry, urinalysis, and histopathology. Effects were essentially limited to histopathology in the nasal cavity of rats and mice and urinary bladder of mice. Nasal lesions, predominantly hypertrophy/hyperplasia of the nasal respiratory epithelium, were increased at concentrations as low as 60 ppm Telone II®b in mice, 90 ppm Telone II®b in rats, and 90 ppm Telone II®a in rats and mice (Breslin et al. 1989; Lomax et al. 1989; Stott et al. 1988). Bladder lesions in mice, predominantly epithelial hyperplasia, were increased at concentrations as low as 60 ppm Telone II®b and 90 ppm Telone II®a (Lomax et al. 1989; Stott et al. 1988). NOAEL and LOAEL values of 20 and 60 ppm were identified for hypertrophy/hyperplasia of the nasal respiratory epithelium in male and female mice and hyperplasia of the urinary bladder in female mice. Because the increase in bladder hyperplasia at 60 ppm only occurred in one sex (females) and had marginal statistical significance, hypertrophy/hyperplasia of the nasal respiratory epithelium was chosen as the critical effect for MRL derivation. BMD analysis of the male and female mouse nasal lesion incidence data was performed, and a point of departure based on the male data was used to derive an intermediate-duration inhalation MRL of 0.008 ppm. Additional studies are needed to verify that the bladder is less susceptible than nasal tissues and that there are no other sensitive effects for intermediate-duration inhalation (e.g., immunotoxicity).

No information was located regarding the intermediate-duration oral toxicity of 1,3-dichloropropene in humans. Information on effects of intermediate-duration oral exposure in animals is available from studies of rats, mice, and dogs exposed to Telone II®b (95.8% pure) in the diet for 13 weeks (Haut et al. 1996; Stebbins et al. 1999), rats exposed to Telone II®b by gavage on

3 days/week for 9 months (NTP 1985), and rats exposed to Telone® (78% pure) by gavage on 6 days/week for 13 weeks (Til et al. 1973). The most sensitive effects clearly attributable to 1,3-dichloropropene were nonglandular stomach lesions in rats and microcytic anemia in dogs. The lesions in the nonglandular stomach were induced by dietary exposure to Telone II®b for 13 weeks and included basal cell hyperplasia in male rats at ≥15 mg/kg/day and hyperkeratosis in female rats at 100 mg/kg/day (Haut et al. 1996). There were no gastrointestinal tract lesions in the mice similarly exposed to dietary Telone II®b (Haut et al. 1996) or in the other rat studies (NTP 1985; Til et al. 1973); histological evaluations were not conducted in the dog study. Microcytic anemia (decreased hematocrit, hemoglobin concentration, and corpuscular volume) occurred in dogs exposed to ≥15 mg/kg/day dietary Telone II®b for 13 weeks (Stebbins et al. 1999), but there were no significant hematological effects in the rats and mice similarly exposed to Telone II®b (Haut et al. 1996). A NOAEL of 5 mg/kg/day and a LOAEL of 15 mg/kg/day were identified for the nonglandular stomach basal cell hyperplasia in rats as well as for the microcytic anemia in dogs. The dog study identifying the hematological effect was not selected for MRL derivation because it used small numbers of animals (4/sex/group) and lacked histopathological examinations. Using BMD analysis of the rat nonglandular stomach hyperplasia incidence data, an intermediate-duration oral MRL of 0.04 mg/kg/day was derived. Additional studies are needed to confirm the microcytic anemia in dogs, adequately evaluate the relative sensitivity of microcytic anemia in dogs and stomach lesions in rats, and determine whether oral exposure causes gastrointestinal tract lesions in dogs; this information is needed to better assess the protectiveness of an MRL based on rat stomach lesions.

No information was located regarding effects of intermediate-duration dermal exposure to 1,3-dichloropropene in humans or animals. Studies are needed to assess the potential for dermal toxicity and species differences by identifying intermediate-duration dermal NOAELs and LOAELs for skin, eye, and systemic effects.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation, oral, and dermal exposure is not considered priority. Inhalation is the primary exposure route for 1,3-dichloropropene at hazardous waste sites. Additional studies are needed to verify that the nasal lesions are the most sensitive effect of inhalation exposure, but these are not priority because the available data are sufficient for MRL derivation. The needs for additional oral and dermal data are not priority because oral and dermal exposure are not considered primary routes

for populations living near hazardous waste sites, and additionally for oral exposure, available data were sufficient for MRL derivation.

c. Chronic-Duration Exposure

(1) Toxicity Assessment

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause chronic human health effects.

Finding: A data need to conduct additional studies via inhalation, oral, and dermal exposure has been identified. No information was located regarding the chronic toxicity of inhaled 1,3-dichloropropene in humans. Information on effects of chronic inhalation in animals is available from one study in which rats and mice were exposed to Telone II®b at vapor concentrations of 0, 5, 20, or 60 ppm for 6 hours/day, 5 days/week for 1 or 2 years (Lomax et al. 1989). This is a well-designed study that included evaluations of clinical signs, body weight, hematology, clinical chemistry, selected organ weights, and histology of an extensive array of organs and tissues. Nonneoplastic effects essentially consisted of nasal lesions in rats and mice and urinary bladder lesions in mice. Nasal lesions in mice included hypertrophy/hyperplasia of the nasal respiratory epithelium at ≥20 ppm after 1 or 2 years of exposure and degeneration of the nasal olfactory epithelium at 60 ppm after 2 years. Nasal lesions in rats included decreased olfactory epithelium thickness, erosion of the olfactory epithelium, and submucosal fibrosis, but were only detected at 60 ppm after 2 years of exposure and at lower incidences than in mice. Hyperplasia and inflammation of the urinary bladder epithelium were increased in mice exposed to ≥20 ppm for 2 years, but no histopathology of the urinary bladder was observed in rats. Hypertrophy/hyperplasia of the nasal respiratory epithelium and hyperplasia of the urinary bladder epithelium in mice exposed for 2 years were selected as co-critical effects for MRL development, and benchmark concentration analysis was used to derive a chronic inhalation MRL of 0.007 ppm. Additional studies are needed to verify that nasal and bladder lesions are the most appropriate basis for MRL derivation, i.e., that there are no other sensitive effects for chronic inhalation (e.g., immunotoxicity).

No information was located regarding the chronic oral toxicity of 1,3-dichloropropene in humans. Information on effects of chronic oral exposure in animals is available from studies of rats and

mice exposed to Telone II®b in the diet for 2 years (Stebbins et al. 2000), dogs exposed to Telone II®b in the diet for 1 year (Stebbins et al. 1999), and rats and mice exposed to Telone II®a by gavage on 3 days/week for 2 years (NTP 1985). The most sensitive nonneoplastic effects clearly attributable to 1,3-dichloropropene were nonglandular stomach lesions in rats and microcytic anemia in dogs. Basal cell hyperplasia of the nonglandular stomach mucosa was induced in rats exposed to Telone II®b in the diet at doses ≥12.5 mg/kg/day (Stebbins et al. 2000) and rats and mice exposed Telone II®a by gavage at doses ≥25 mg/kg/day (NTP 1985), but not in mice or dogs exposed to dietary Telone II®b (Stebbins et al. 1999, 2000). Hematological changes indicative of microcytic anemia (decreased mean hematocrit, hemoglobin concentration, and corpuscular volume) occurred in dogs exposed to Telone II®b at ≥15 mg/kg/day (Stebbins et al. 1999), but not in rats or mice exposed to Telone II®b or Telone II®a (NTP 1985; Stebbins et al. 2000). Effects were also observed in the liver and kidneys, but occurred inconsistently and are not as clearly associated with 1,3-dichloropropene as the stomach lesions in rats and anemia in dogs. Exposure to Telone II®a caused nephropathy in female, but not male, rats exposed to ≥25 mg/kg/day (NTP 1985) and hydronephrosis in female, but not male, mice exposed to 100 mg/kg/day (NTP 1985); no renal effects occurred in rats, mice, or dogs exposed to Telone II®b (Stebbins et al. 1999, 2000). Nonneoplastic liver effects included slight increases in eosinophilic foci in rats exposed to ≥2.5 mg/kg/day dietary Telone II®b, but the total number of altered foci (eosinophilic plus basophilic) was unchanged, and altered foci are a common spontaneous occurrence in aged Fischer 344 rats (Stebbins et al. 2000). Additionally, there were no altered foci in hepatocytes of similarly exposed mice and dogs (Stebbins et al. 2000). Hepatocyte size was decreased in male mice (but not female mice) exposed to 50 mg/kg/day Telone II®b for 1 year, but not in mice exposed for 2 years, or in rats or dogs exposed for 1 or 2 years (Stebbins et al. 2000). Basal cell hyperplasia in the nonglandular stomach of rats (Stebbins et al. 2000) and decreased hemoglobin concentration and corpuscular volume in dogs (Stebbins et al. 1999) exposed to Telone II®b were selected as co-critical effects for MRL development. The NOAEL and LOAEL values for these effects in both species were 2.5 and 12.5 mg/kg/day, and the test material was the most purified formulation tested and did not contain potentially confounding toxic materials. BMD analysis was used to identify potential points of departure for MRL derivation and the lowest BMDL (lower confidence limit [95%] on the benchmark dose) (stomach hyperplasia in rats) was used to derive an oral MRL of 0.03 mg/kg/day. Although the BMDL for decreased hemoglobin concentration in dogs (modeled as an index for microcytic anemia) was higher than the BMDL for stomach lesions in rats, confidence in the dog value is lower because group sizes were much smaller (4 dogs/sex/dose

compared to 50 rats/sex/dose). Additional studies are needed to fully evaluate the relative sensitivity of microcytic anemia in dogs and stomach lesions in rats and to better assess the protectiveness of an MRL based on the rat stomach lesions.

No information is available regarding the chronic dermal toxicity of 1,3-dichloropropene in humans or animals.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation, oral, and dermal exposure is not considered priority. Additional studies are needed to verify that the most sensitive effects were identified for inhalation and oral exposure, but are not priority because available data were sufficient for derivation of MRLs for both routes. Additionally, oral exposure is not considered a primary route for populations living near hazardous waste sites. Although dermal studies would help to evaluate consequences of repeated dermal exposure, these are not priority because this is also an unlikely route of exposure for populations living near hazardous waste sites.

(2) Cancer Assessment

***Purpose*:** To determine whether populations potentially exposed to 1,3-dichloropropene are at an increased risk for developing cancer for purposes of conducting meaningful follow-up exposure and health studies. Similar to toxicity end point assessment, when bioassays are indicated because of the potential for substantial exposure and the lack of information on carcinogenicity, ATSDR will generally only assign priority to a bioassay conducted via the most relevant route of human exposure at Superfund sites.

Comparative toxicokinetic information across routes as previously discussed will be assigned priority and conducted before assigning priority to any additional routes of exposure. In cases where the assessment of chronic toxicity and carcinogenicity can be combined, they will.

Finding: A data need has not been identified. Limited information is available on the carcinogenicity of 1,3-dichloropropene in humans. Clinical case reports describing three men who developed lymphoma or leukemia following acute inhalation (and possibly dermal) exposure (Markovitz and Crosby 1984) suggest a possible association between exposure and cancer in humans, but are inadequate to establish the association. A case-control study reported an

apparent increase in risk of death from pancreatic cancer associated with long-term (20-year) residence in three communities that used large quantities of 1,3-dichloropropene for soil fumigation (Clary and Ritz 2003). However, there were no direct exposure data for the subjects, and it is possible that carcinogenic effects could have been caused by additives (e.g., epichlorohydrin) contained in commercial products used at that time. Studies of populations exposed to higher purity formulations without potentially carcinogenic additives are needed to better assess the carcinogenicity of 1,3-dichloropropene in humans (see data needs for Epidemiologic Studies).

There is sufficient evidence for the carcinogenicity of 1,3-dichloropropene in animals. Inhalation carcinogenicity in animals was evaluated in one well-designed study that exposed rats and mice to 0, 5, 20, or 60 ppm of Telone II®b vapor for 6 hours/day, 5 days/week for 2 years (Lomax et al. 1989). Incidences of bronchioalveolar adenoma, a benign lung tumor, were significantly increased in male mice exposed to the highest concentration, but not in female mice or rats of either sex.

Information on oral carcinogenicity in animals is available from studies of rats and mice exposed to Telone II®a (89% pure containing 1% epichlorohydrin) by gavage on 3 days/week for 2 years (NTP 1985), rats and mice exposed to Telone II®b in the diet for 2 years (Stebbins et al. 2000), and dogs exposed to Telone II®b in the diet for 1 year (Stebbins et al. 1999). Rats exposed to Telone II®a developed squamous cell papillomas and carcinomas in the forestomach and neoplastic nodules in the liver (NTP 1985). Female mice exposed to Telone II®a developed squamous cell papillomas and carcinomas of the forestomach, transitional cell carcinomas of the urinary bladder, and alveolar/bronchiolar adenomas (NTP 1985). Male mice exposed to Telone II®a could not be adequately assessed for carcinogenicity due to a large number of early deaths due to myocarditis (NTP 1985). Dietary exposure to Telone II®b caused a significantly increased incidence of benign hepatocellular adenomas in male rats and a positive dose-related trend for these liver tumors in female rats (Stebbins et al. 2000). The mice and dogs exposed to dietary Telone II®b did not show any significant carcinogenic responses, although small group sizes were used in the dog study (Stebbins et al. 1999, 2000). The available data indicate that 1,3-dichloropropene induced liver tumors in rats because responses were similar following gavage exposure to Telone II®a and dietary exposure to Telone II®b. The tumors at other sites in rats (e.g., gastrointestinal tract) were only induced by Telone II®a, suggesting that epichlorohydrin and/or gavage treatment could have contributed to their development.

Limited information is available regarding the dermal carcinogenicity of 1,3-dichloropropene in animals. 1,3-Dichloropropene did not induce skin papillomas or lung or forestomach tumors in mice following thrice weekly dermal application for 74 weeks (Van Duuren et al. 1979). There was no indication of skin tumor initiation in mice given a single dermal application of 1,3-dichloropropene followed by repeated applications of the tumor promoter phorbol myristic acid for 58 weeks (Van Duuren et al. 1979). No information is available regarding the potential of 1,3-dichloropropene for tumor promotion.

Based on the inhalation and oral bioassay findings in animals, the DHHS has determined that 1,3-dichloropropene may reasonably be anticipated to be a human carcinogen (NTP 2005). Similarly, EPA has classified 1,3-dichloropropene as a probable human carcinogen (IRIS 2006), and IARC (1999) has concluded that 1,3-dichloropropene is possibly carcinogenic to humans.

The results of structure activity relationship (SAR) analyses, conducted by the ATSDR Computational Toxicology Methods Development Unit, provide supporting evidence for the carcinogenicity of 1,3-dichloropropene in animals (male rats) (ATSDR 2005b). Additional bioassays could confirm the apparent sex- and species-specificity of the response in the inhalation study, and clarify the role of bolus exposure in oral carcinogenicity, but are not necessary due to the overall adequacy of the cancer evidence. These issues could be addressed as part of inhalation and oral chronic toxicity studies, which are non-priority data needs as discussed in the previous section.

***Priority Recommendation*:** A data need has not been identified. Carcinogenicity has been demonstrated in animals exposed by inhalation (i.e., the primary exposure route for 1,3-dichloropropene at hazardous waste sites) as well as by oral exposure. The available inhalation study is well designed and used two species, large numbers of animals, three exposure levels, and a high-purity 1,3-dichloropropene formulation that did not contain potentially carcinogenic additives. The oral database includes well-designed studies of a high-purity 1,3-dichloropropene formulation in two species. SAR analyses support the carcinogenicity of 1,3-dichloropropene in animals. The animal database is sufficient for DHHS and EPA to conclude that 1,3-dichloropropene is likely to be carcinogenic in humans.

d. Genotoxicity

***Purpose*:** To evaluate the mechanism of dichloropropene-induced toxicity for purposes of future mitigation activities. Generally, priority is assigned genotoxicity studies if information is lacking to assess the genotoxic potential of this substance both *in vivo* (mouse micronucleus) and *in vitro* (Ames *Salmonella*). This is particularly true if there are human data to suggest that the substance may act by a genotoxic mechanism to cause cancer, reproductive toxicity, etc., or there exists "structural alerts" that suggest that the substance may be genotoxic. Additional studies will not be assigned priority simply to confirm or refute an equivocal database without justification.

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause chronic human health effects.

Finding: A data need to conduct additional genotoxicity studies has been identified. 1,3-Dichloropropene was determined to be mutagenic in *Salmonella typhimurium* in a number of *in vitro* assays (Creedy et al. 1984; De Lorenzo et al. 1977; Eder et al. 1982a, 1982b; Haworth et al. 1983; Neudecker and Henschler 1986; Neudecker et al. 1977, 1980; Stolzenberg and Hine 1980; Vithayathil et al. 1983), but many of the positive results appear attributable to impurities in older technical-grade test formulations (Talcott and King 1984; Watson et al. 1987). Results of *in vitro* assays with relatively pure (>95%) 1,3-dichloropropene included induction of mutations in mouse lymphoma L5178Y cells (Myhr and Caspary 1991), mitotic aberrations in Chinese hamster lung cells (Sasaki et al. 1988), sister chromatid exchanges in Chinese hamster V79 cells, Chinese hamster ovary cells, and human lymphocytes (Kevekordes et al. 1996; Loveday et al. 1989; von der Hude et al. 1987), and unscheduled DNA synthesis in HeLa cells, human lymphocytes, and rat hepatocytes (Eder et al. 1987; Martelli 1997; Matsuoka et al. 1998; Schiffmann et al. 1983), but it unclear whether these effects were caused by the parent compound, metabolism to a mutagenic metabolite, a mutagenic autoxidation product formed during storage, or an impurity remaining after manufacture. Oral exposure to 1,3-dichloropropene induced sex-linked recessive lethal mutations in *Drosophila melanogaster* (Valencia et al. 1985), but no dominant lethal mutations in rats (Gollapudi et al. 1998). Oral exposure also caused DNA fragmentation in the stomach, liver, kidneys, bladder, lung, brain, and/or bone marrow of rats and mice (Ghia et al. 1993; Kitchin and Brown 1994; Sasaki et al. 1998), but no unscheduled DNA synthesis in rats (Ghia et al. 1993). Oral exposure did not induce micronuclei in bone marrow cells or reticulocytes of rats or mice in four of five assays (Ghia et al. 1993; Kevekordes et al. 1996;

Morita et al. 1997; Sasaki et al. 1994). In an acellular test system, three minor metabolites of 1,3-dichloropropene (the cis and trans epoxides of 1,3-dichloropropene and 3-chloro-3-hydroxypropanal) formed adducts with 2'-deoxyguanosine, but not with 2'-deoxyadenosine or 2'-deoxycytidine (Schneider et al. 1998b). The results of SAR analyses, conducted by the ATSDR Computational Toxicology Methods Development Unit, provide supporting evidence that 1,3-dichloropropene is genotoxic (ATSDR 2005b). Additional studies with purified compound, particularly *in vivo* tests examining the potential for adduct formation in known target tissue (e.g., stomach, lungs, nasal epithelium, and urinary bladder), are needed to better characterize the genotoxicity of 1,3-dichloropropene. This information would help to clarify the role of epichlorohydrin and bolus exposure in the carcinogenicity induced by 1,3-dichloropropene formulations, as well as the mechanism of carcinogenic action of the pure compound.

***Priority Recommendation*:** The identified data need to conduct additional genotoxicity studies is not considered priority. Both *in vitro* and *in vivo* genotoxicity studies of 1,3-dichloropropene are available. *In vitro* findings included mutagenicity in bacteria and mammalian cells and chromosomal and DNA damage in mammalian cells. *In vivo* findings included DNA fragmentation, but no micronuclei or dominant lethal mutations, in rats and/or mice. SAR analyses indicate that 1,3-dichloropropene is genotoxic. Although additional studies would help to better characterize the genotoxicity of 1,3-dichloropropene, this is not a priority data need because it seems likely that impurities or other confounding factors contributed to many of the observed effects, there are no human data to suggest that 1,3-dichloropropene may act via a genotoxic mechanism, and there is sufficient evidence that 1,3-dichloropropene is likely to be carcinogenic in humans.

e. Endocrine Disruption

***Purpose*:** To determine whether populations potentially exposed to 1,3-dichloropropene are at an increased risk to develop toxicity of the endocrine system for purposes of conducting meaningful follow-up exposure and health studies. Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect

the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior.

Generally, when considering the need to assign priority, in the absence of all information on this end point, ATSDR will assign priority to screening studies that examine effects on a) male and female reproductive organs, and b) other endocrine organs including hypothalamus, pituitary, thyroid, parathyroid, adrenal, pancreas, paraganglia, and pineal body. Such screening level studies include, but are not limited to, *in vitro* studies [e.g., 1) Estrogen Receptor Binding/Transcriptional Activation Assay, 2) Androgen Receptor Binding/Transcriptional Activation Assay, and 3) Steroidogenesis Assay with Minced Testis], and *in vivo* studies [e.g., 1) Rodent 3-day Uterotropic Assay, 2) Rodent 20-day Pubertal Female Assay with Thyroid, 3) Rodent 5–7-day Herschberger Assay].

If any of the following is true, then ATSDR will consider assigning Level II priority to 2-generation reproductive studies: if (1) there are suggestions that 1,3-dichloropropene may have endocrine disrupting potential from Level I studies; or (2) if there have been human anecdotal reports of endocrine disrupting effects following dichloropropene exposure; or (3) if there are structurally similar compounds that affect the endocrine system.

As before, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to studies conducted via additional routes of exposure.

Finding: A data need to conduct additional studies on the endocrine system has not been identified. There are no human data on the potential of 1,3-dichloropropene to disrupt the endocrine system. The only *in vitro* endocrine disruptor screening study of 1,3-dichloropropene is a yeast two-hybrid assay system that employed expression plasmids for the estrogen receptor (Nishihara et al. 2000). 1,3-Dichloropropene was negative for estrogen receptor binding in this assay (had low agonist activity compared to 17-beta-estradiol), suggesting that it does not disrupt estradiol signalling. No *in vivo* studies of endocrine function in animals (e.g., measurements of serum hormone levels) are available. Several animal studies, however, provide data regarding a lack of effect of 1,3-dichloropropene on the histology of endocrine tissues and on reproduction. Histological examinations of endocrine tissues were performed in rats, mice, and dogs exposed to

Telone II®a or Telone II®b by inhalation or oral administration with negative results (Lomax et al. 1989; NTP 1985; Stebbins et al. 1999, 2000; Stott et al. 1988). The examinations in these intermediate- and chronic-duration studies generally included the adrenals, pancreas, parathyroids, pituitary, and thyroid. Histological examinations of pertinent reproductive tissues (e.g., testes and ovaries) in these studies also showed no effects, and a two-generation reproduction study of Telone II®b in rats exposed by inhalation (Breslin et al. 1989) indicates that 1,3-dichloropropene is unlikely to impair reproductive function. The available inhalation, oral, and *in vitro* data do not suggest that 1,3-dichloropropene has endocrine disrupting activity. No data are available for dermal exposure, but there is no clear need for screening studies by this route because the lack of effects following inhalation and oral exposure indicates that it is reasonable to conclude that effects also would not occur following dermal exposure.

***Priority Recommendation*:** A data need to conduct additional studies on the endocrine system has not been identified. The available data on estrogen receptor binding *in vitro*, and reproductive function and histology of reproductive and endocrine tissues in animals exposed by the inhalation or oral routes, do not indicate that 1,3-dichloropropene has an endocrine disrupting potential. Dermal data are not available, but effects following dermal exposure are not expected based on the inhalation and oral data; additionally, dermal exposure is not a primary route for populations near hazardous waste sites.

f. Reproductive Toxicity

***Purpose*:** To determine whether populations potentially exposed to 1,3-dichloropropene are at an increased risk to develop reproductive effects for purposes of conducting meaningful follow-up exposure and health studies. ATSDR scientists believe it is important to acquire reproductive toxicity data in order to consider the needs of susceptible populations. It is desirable to have information on reproductive toxicity before developing MRLs to ensure that target organs have been adequately evaluated.

Generally, when considering the need to assign priority, in the absence of all information on this end point, ATSDR will assign priority to the conduct of 90-day studies with special emphasis on reproductive organ pathology. If any of the following is true, then ATSDR will consider assigning priority to multigeneration animal studies: (1) If any indication is found in these studies that the reproductive system of either male or female animals is a target organ of

substance exposure; or (2) if there have been human anecdotal reports of reproductive effects following substance exposure; or (3) if there are structurally similar compounds that affect reproduction.

As before, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to studies conducted via additional routes of exposure.

***Finding*:** A data need has not been identified. No information was located regarding reproductive effects of 1,3-dichloropropene in humans. A two-generation reproductive toxicity study in which male and female rats were exposed to Telone II®b by inhalation found no effects on reproductive function in parental animals or progeny (Breslin et al. 1989). Effects of oral or dermal exposure to 1,3-dichloropropene on reproductive function have not been studied in animals. Histological evaluation of reproductive tissues showed no effects in rats in the two-generation inhalation study of Telone II®b (Breslin et al. 1989), in rats and mice exposed to Telone II®b by inhalation for 2 years (Lomax et al. 1989), rats exposed to Telone II®a by inhalation for 13 weeks (Stott et al. 1988), rats and mice orally exposed to Telone II®a or Telone II®b for 2 years (NTP 1985; Stebbins et al. 2000), or dogs orally exposed to Telone II®b for 1 year (Stebbins et al. 1999). Reproductive tissues that were examined in these studies included testes, epididymides, seminal vesicles, prostate, ovaries, oviduct, and uterus. No information is available on histopathology of reproductive tissues in dermally exposed animals. Additional reproductive testing could be used to address the limitations of the available data, particularly the lack of information on reproductive function in mice exposed by inhalation (i.e., the species used for intermediate- and chronic-duration inhalation MRL derivation), reproductive function following oral exposure, and reproductive organ histopathology and function following dermal exposure, but the available evidence adequately indicates that the reproductive system is not a target of 1,3-dichloropropene. The evidence is considered adequate because the negative results of the two-generation inhalation reproductive toxicity study in rats are supported by negative reproductive organ histopathology findings in intermediate- and chronic-duration inhalation and oral studies in rats, mice, and dogs.

***Priority Recommendation*:** A data need has not been identified. Based on a lack of effects in the two-generation inhalation reproductive toxicity study in rats, and the supporting negative reproductive organ pathology findings in intermediate- and chronic-duration inhalation and oral

studies in rats, mice, and dogs, the available evidence adequately indicates that 1,3-dichloropropene is not a reproductive toxicant.

g. Developmental Toxicity

***Purpose*:** To determine whether populations potentially exposed to 1,3-dichloropropene are at an increased risk for developmental effects for purposes of conducting meaningful follow-up exposure and health studies. Similar to reproductive toxicity assessment, Agency scientists believe it is important to assess the developmental toxicity data.

In the absence of any reproductive or teratologic information, ATSDR will consider proposals to simultaneously acquire reproductive and teratological information. ATSDR acknowledges that, in some circumstances, developmental studies may be assigned priority if the following statements are true: (1) if a two-generation reproductive study provides preliminary information on possible developmental toxicity of 1,3-dichloropropene, (2) if there are human anecdotal reports of developmental effects following 1,3-dichloropropene exposure, *or* (3) if structurally similar compounds have caused developmental effects.

As for reproductive toxicity, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to the conduct of studies via additional routes of exposure.

***Finding*:** A data need to conduct additional developmental studies via oral and dermal exposure has been identified. No studies were located regarding developmental effects of 1,3-dichloropropene in humans by any route of exposure or in animals exposed orally or dermally. Developmental toxicity studies of Telone II®a and Telone II®b were conducted in rats and rabbits exposed by inhalation for 6 hours/day during gestation days 6–15 and 6–18, respectively (Hanley et al. 1987; Kloes et al. 1983). The Telone II®a study (Kloes et al. 1983) was limited in scope as it was designed only to establish the maximum tolerated dose in pregnant rats and rabbits; developmental toxicity end points essentially consisted of numbers of corpora lutea, implantations, resorptions, fetuses, and litters (fetal examinations were not performed). Telone II®a caused increased resorptions and decreased litter size in rats exposed to 300 ppm, a maternally toxic concentration as shown by urine and fecal staining, nasal exudate, and decreases in food and water consumption and body weight (Kloes et al. 1983). Maternal toxicity also

occurred in rabbits exposed to 300 ppm Telone II®a, but the severity of the effects (moribundity or death in most animals) precluded evaluation of embryo/fetotoxicity. No embryo/fetotoxicity occurred in either species at ≤150 ppm Telone II®a. The developmental toxicity study of Telone II®b (Hanley et al. 1987) was well-designed, included comprehensive fetal evaluations, and tested concentrations as high as 120 ppm in rats and rabbits. Effects in the rats included reduced maternal body weight gain and food consumption at ≥20 ppm and delayed ossification of the vertebral centra in fetuses at 120 ppm. Maternal weight gain was also reduced in rabbits at ≥60 ppm, but there was no indication of developmental toxicity in this species. A two-generation reproduction study in rats provides limited information on the developmental toxicity of inhaled Telone II®b; concentrations as high as 90 ppm had no effects on litter size, body weight or survival of pups through postnatal day 28, or gross pathology of pups on postnatal day 28 (Breslin et al. 1989). The available experimental data indicate that inhalation of 1,3-dichloropropene as Telone II®a or Telone II®b was not teratogenic in rats or rabbits, although fetotoxicity occurred in rats at concentrations that were maternally toxic and higher than the intermediate-duration LOAELs for nasal and bladder lesions in rats and mice. The results of SAR analyses, conducted by the ATSDR Computational Toxicology Methods Development Unit, do suggest that developmental toxicity is an effect of concern for 1,3-dichloropropene (ATSDR 2005b). Additional inhalation testing could address the failure of the available developmental toxicity studies to examine maternal nasal turbinates and test the species used for intermediate-duration inhalation MRL derivation (mice). However, because developmental toxicity does not appear to be the most sensitive effect for inhaled 1,3-dichloropropene based on data in two species and results of SAR analyses, there is no clear need for additional inhalation testing. Studies by the oral and dermal routes would provide data for corroborating the inhalation findings and establishing dose-response relationships by these routes.

***Priority Recommendation*:** The identified data need to conduct additional developmental toxicity studies via oral and dermal exposure is not considered priority. There are no human anecdotal reports of developmental effects following exposure to 1,3-dichloropropene. Data from animal inhalation studies indicate that 1,3-dichloropropene may cause fetotoxicity, but effects were observed only at maternally toxic concentrations and were mild (delayed ossification in fetuses) at concentrations that caused critical systemic effects (nasal and bladder lesions) in intermediate- and chronic-duration studies. Additionally, results of SAR analyses do suggest that developmental toxicity is an effect of concern for 1,3-dichloropropene. Because there are sufficient data indicating that it is unlikely that developmental toxicity will be the most sensitive

effect following inhalation exposure, there is no clear need to conduct additional studies by the inhalation route (the primary route of 1,3-dichloropropene exposure for populations surrounding hazardous waste sites). Although developmental data for the oral and dermal routes are not available, this need is not considered priority because these are unlikely exposure routes for populations near hazardous waste sites.

h. Immunotoxicity

***Purpose*:** To evaluate the mechanism of dichloropropene-induced toxicity for purposes of defining target organs and future mitigation activities. There is increasing evidence to suggest that the immune system might be a susceptible target organ for many environmental contaminants. In the absence of any information on the immune system as a target organ, priority will be assigned to the evaluation of the immune system (lymphoid tissue, blood components) as an end point in 90-day studies (Level I) before assigning priority to an immunotoxicology battery as recently defined by the NTP.

For those substances that either (1) show evidence of immune system effects in 90-day studies, (2) have human anecdotal data to suggest that the immune system may be affected, or (3) are structurally similar to known immunotoxicants, an immunotoxicology battery of tests will be assigned priority.

***Finding*:** A data need to conduct additional immunotoxicity studies via inhalation, oral, and dermal exposure has been identified. Information on immunological effects in humans consists of four case reports of skin sensitization reactions (delayed-type hypersensitivity) after dermal contact in workers involved in the production or use of pesticides containing 1,3-dichloropropene (Bousema et al. 1991; Corazza et al. 2003; van Joost and de Jong 1988; Vozza et al. 1996). Positive patch tests for 1,3-dichloropropene confirmed the sensitization in all four cases. Delayed-type hypersensitivity reactions were also observed in guinea pigs that were dermally exposed to Telone II®a or Telone C-17® (Carreon and Wall 1983; Jeffrey 1987b; Mizell 1988) and guinea pigs developed contact sensitization to cis-1,3-dichloropropene (Jones 1988b). The results of SAR analyses, conducted by the ATSDR Computational Toxicology Methods Development Unit, provide supporting evidence suggesting that 1,3-dichloropropene is a weak skin sensitizer (ATSDR 2005b). The only other information pertaining to the immunotoxicity of 1,3-dichloropropene is the lack of lymphocyte changes in blood and the lack of histopathology in

immune system tissues (bone marrow, lymph nodes, spleen, and thymus) in animals exposed by inhalation or ingestion in intermediate- and chronic-duration studies; these evaluations were mainly in rats, mice, and dogs exposed to Telone II®a or Telone II®b (Haut et al. 1996; Lomax et al. 1989; NTP 1985; Stebbins et al. 1999, 2000; Stott et al. 1988; Til et al. 1973; Torkelson and Oyen 1977). None of these studies utilized comprehensive immunological testing that might have detected functional effects. Considering this, as well as the evidence for delayed-type hypersensitivity in dermally exposed humans and animals, there is a need for additional studies to assess whether exposure to 1,3-dichloropropene by the inhalation, oral, and dermal routes represent an immunotoxic concern.

***Priority Recommendation*:** The identified data need to conduct additional immunotoxicity studies via inhalation exposure is considered priority. Human and animal data indicate that dermal exposure to 1,3-dichloropropene can induce delayed-type hypersensitivity, and the results of SAR analyses suggest that 1,3-dichloropropene is a weak skin sensitizer. Although intermediate- and chronic-duration inhalation and oral exposure to 1,3-dichloropropene did not induce adverse changes in circulating lymphocytes or histopathology in immune system tissues in animals, the human and animal skin sensitization findings and supporting results of SAR analyses indicate that immunotoxicity is a possible effect of concern. Therefore, the need to conduct an immunotoxicity battery (EPA 2004; Luster et al. 1988) by the inhalation route is assigned priority because this is the primary route of 1,3-dichloropropene exposure for populations surrounding hazardous waste sites. Although oral immunotoxicity data are lacking and dermal immunotoxicity data are limited in scope, the needs for additional studies by these routes are not considered priority because oral and dermal exposures are not primary routes for populations near hazardous waste sites.

i. Neurotoxicity

***Purpose*:** To evaluate the mechanism of dichloropropene-induced toxicity to define target organs and future mitigation activities. Similar to immunotoxicity, there is a growing body of data to suggest that the nervous system is a very sensitive target organ for many environmental chemicals. In the absence of any information on the nervous system as a target organ, priority will be assigned evaluation of the nervous system as an end point in 90-day studies (Level I) before assigning priority to a neurotoxicology battery.

It may be possible to assign priority to evaluation of demeanor in 90-day studies along with neuropathology. For those substances that either (1) show evidence of nervous system effects in 90-day studies, (2) have human anecdotal data to suggest that the nervous system may be affected, or (3) are structurally similar to known neurotoxicants, a neurotoxicology battery of tests will be assigned priority.

***Finding*:** A data need to conduct additional neurotoxicity studies via inhalation, oral, and dermal exposure has been identified. No symptoms or signs of neurotoxicity were observed in 10 humans following inhalation exposure to 1,3-dichloropropene at levels high enough to cause breathing difficulties, nasal irritation, and other effects; nine cases were exposed during the cleanup of a 1,3-dichloropropene spill, and one case was exposed during soil fumigation and also had dermal exposure (Markovitz and Crosby 1984). No information is available regarding neurotoxicity in orally exposed humans. Clinical signs of neurotoxicity have been documented in rats and rabbits following high-level acute inhalation, oral, and dermal exposure to 1,3-dichloropropene, mainly as pure compound or Telone II®a; these effects typically included ataxia, loss of righting reflex, salivation, lethargy, and labored respiration (Dietz et al. 1985; Jeffrey et al. 1987a; Jones 1988a, 1988b; Jones and Collier 1986b; Kloes et al. 1983; Mizell et al. 1988b). No overt signs of neurotoxicity or histopathological changes in nervous system tissues (brain, spinal cord, or nerves) were observed in animals exposed to lower levels of 1,3-dichloropropene by inhalation or ingestion in intermediate- and chronic-duration studies; these findings were mainly in rats, mice, and dogs exposed to Telone II®a or Telone II®b (Coate 1979a; Haut et al. 1996; Lomax et al. 1989; NTP 1985; Stebbins et al. 1999, 2000; Stott et al. 1988; Til et al. 1973; Torkelson and Oyen 1977). None of the available studies utilized neurobehavioral testing that may have detected subtle functional effects, indicating that there is a need for a comprehensive battery to assess whether low levels of 1,3-dichloropropene by the inhalation, oral, and dermal routes represent a neurotoxic concern.

***Priority Recommendation*:** The identified data need to conduct additional neurotoxicity studies via inhalation, oral, and dermal exposure is not considered priority. Acute-duration inhalation, oral, and dermal exposure to high levels of 1,3-dichloropropene caused clinical signs of neurotoxicity in animals, but not in humans following acute inhalation exposure to unknown concentrations high enough to cause breathing difficulties, or in animals exposed to lower levels by inhalation or oral administration in intermediate- and chronic-duration studies. These inhalation and oral intermediate- and chronic-duration studies in animals also found no

histopathological changes in nervous system tissues. Therefore, the identified need to conduct a neurotoxicology battery of tests by the inhalation route (the primary route of 1,3-dichloropropene exposure for populations surrounding hazardous waste sites) is not assigned priority. This is because neurotoxicity does not appear to be an effect of major concern for low-to-moderate levels of 1,3-dichloropropene exposure based on the available data. Additional studies by the oral and dermal routes are not considered priority because oral and dermal exposures are not primary routes for populations near hazardous waste sites.

j. Toxicokinetics

***Purpose*:** To evaluate the disposition of 1,3-dichloropropene across species and routes of exposure to elucidate target organs and mechanisms of toxicity, and to assess the need to conduct studies by routes other than the primary route of exposure.

***Finding*:** A data need to assess the toxicokinetics of 1,3-dichloropropene following inhalation, oral, and dermal exposure has been identified. Information on the toxicokinetics of 1,3-dichloropropene in humans consists of several studies providing limited data on absorption, metabolism, and elimination following acute inhalation or dermal exposure to Telone II®, Telone II®a, or cis-1,3-dichloropropene (Kezic et al. 1996; Osterloh and Feldman 1993; Osterloh et al. 1984; Van Welie et al. 1989; Waechter et al. 1992). This information is generally consistent with available animal data, which mainly consist of findings from single exposure studies in rats exposed to cis and trans isomers of 1,3-dichloropropene and, to a lesser extent, Telone II®a. Inhalation absorption in humans and rats (Stott and Kastl 1986; Waechter et al. 1992) and gastrointestinal absorption in rats (Climie et al. 1979; Hutson et al. 1971; Stott et al. 1998; Waechter and Kastl 1988) is rapid and extensive, generally in the 60–80% range for both routes. Dermal absorption of 1,3-dichlorpropene vapor has been demonstrated in humans (Kezic et al. 1996), but no data are available on dermal absorption of liquid 1,3-dichlorpropene in humans or animals. Information on tissue distribution is essentially limited to one oral study in rats showing that 1,3-dichloropropene widely distributed throughout the body and occurred at the highest levels in the nonglandular stomach and urinary bladder (Waechter and Kastl 1988). Studies in occupationally exposed humans and rats exposed by inhalation or oral administration indicate that 1,3-dichloropropene is rapidly and extensively metabolized and eliminated, mainly via glutathione conjugation and excretion of the mercapturic acid conjugate in the urine (Climie et al. 1979; Fisher and Kilgore 1989; Hutson et al. 1971; Osterloh and Feldman 1993; Osterloh et al. 1984;

Stott and Kastl 1986; Stott et al. 1998; Van Welie et al. 1989; Waechter and Kastl 1988). 1,3-Dichoropropene may also undergo hydrolysis and dechlorination to form 1-chloroallyl alcohol, an intermediate that reacts with alcohol dehydrogenase to form 1-chloroacrolein. Another minor pathway involves reaction with cytochrome P-450 to form mutagenic cis and trans epoxides that convert to the mutagen 3-chloro-2-hydroxy-propanal (Schneider et al. 1998a).

Additional data are needed to better characterize the toxicokinetics of 1,3-dichloropropene for all routes of exposure. Inhalation and dermal studies investigating the distribution of 1,3-dichloropropene would help to identify target organs beyond the initial point of respiratory and skin contact and across routes of exposure. Additional information is needed on the rates of absorption, distribution, metabolism, and elimination, particularly for acute dermal exposure and for repeated exposures by all routes. Although the available data are generally similar in rats and humans, the animal species that serves as the best model for extrapolating results to humans remains unknown; additional studies comparing the toxicokinetic properties of 1,3-dichloropropene in several animal species would be useful for identifying potential interspecies differences. Dose-response information on the relative depletion of glutathione stores in target organs would help to define conditions under which toxicity would be increased. Limited evidence suggests that the mu class of glutathione S-transferase may not play a significant role in the metabolism of 1,3-dichloropropene in humans (Vos et al. 1991); this indicates that evaluation of the isoforms of enzymes involved in the metabolism of 1,3-dichloropropene (glutathione S-transferase and cytochrome P-450) would be useful, because enzyme polymorphisms could contribute to individual variations in human studies, and possibly identify vulnerable populations or strain differences in responses in animal studies.

***Priority Recommendation*:** The identified data need to assess the toxicokinetics of 1,3-dichloropropene following inhalation, oral, and dermal exposure are not considered priority. Additional inhalation toxicokinetic studies would be useful because inhalation is the main route of 1,3-dichloropropene exposure for populations surrounding hazardous waste sites, but are not considered priority because sufficient data are available indicating that the main effects of inhalation are due to direct effects of unabsorbed 1,3-dichloropropene at the point of contact (i.e., the nasal turbinates). Studies by the oral and dermal routes are not priority for reasons similar to inhalation exposure; i.e., because the main targets of toxicity are the tissues in direct contact with unabsorbed 1,3-dichloropropene at the site of exposure (the gastrointestinal tract and skin).

Additionally, oral and dermal exposures are not primary routes for populations near hazardous waste sites.

2. Level III Data Needs

a. Epidemiologic Studies

***Purpose*:** To evaluate the extant epidemiologic database and to propose the conduct of additional studies that may lead to cause- and effect- findings. The ATSDR Division of Health Studies will be informed of all candidate substances.

***Finding*:** A data need has been identified. Most of the available information on the toxicity of 1,3-dichloropropene in humans pertains to local effects of acute exposure observed in small numbers of people. Respiratory effects (e.g., mucous membrane irritation, chest pain, and cough) were found in cases of accidental exposure to presumed high inhalation concentrations of 1,3-dichloropropene (Flessel et al. 1978; Markovitz and Crosby 1984). Gastrointestinal effects occurred in a case of fatal ingestion; these included acute gastroenteritis, bloody diarrhea, and hemorrhagic exudate and mucosal erosions in the stomach (Hernandez et al. 1994). Dermal exposure to liquid 1,3-dichloropropene caused contact dermatitis and sensitization in humans (Bousema et al. 1991; Corazza et al. 2003; van Joost and de Jong 1988; Vozza et al. 1996). These limited human findings are consistent with animal data in indicating that 1,3-dichloropropene causes effects at the point of contact with tissues, particularly the nasal epithelium following inhalation exposure, stomach following oral exposure, and skin following dermal exposure, but provide no information on the sensitivity of these or other effects for long-term, low-level exposures. Epidemiological studies would be useful for assessing the lack of human toxicity data for intermediate- and chronic-duration exposures, and should focus on inhalation (i.e., the primary route through which the general population is exposed), and the most sensitive targets identified in the inhalation and oral MRL studies in animals (i.e., the nasal epithelia, bladder, stomach, and erythrocytes).

Limited information is also available on the carcinogenicity of 1,3-dichloropropene in humans. Clinical case reports described three men who developed lymphoma or leukemia following acute inhalation (and possibly dermal) exposure to relatively high levels of 1,3-dichloropropene (Markovitz and Crosby 1984); these findings suggest, but do not establish, a possible association

between exposure and cancer in humans. The only epidemiologic study of 1,3-dichloropropene is a case-control study that found an apparent increase in risk of death from pancreatic cancer associated with long-term (20-year) residence in three communities that used large amounts of 1,3-dichloropropene for soil fumigation (Clary and Ritz 2003). However, there were no direct exposure data for the subjects, and it is possible that carcinogenic effects could have been caused by additives (e.g., epichlorohydrin) contained in commerical 1,3-dichloropropene products used at that time. Carcinogenicity was demonstrated in animals exposed to commercial 1,3-dichloropropene products by inhalation (lung tumors) or oral exposure (stomach, liver, and bladder tumors), although epichlorohydrin might have contributed to some of the effects; the animal data were sufficient for DHHS and EPA to conclude that 1,3-dichloropropene is likely to be carcinogenic in humans. Studies of agricultural workers or other worker populations exposed to higher purity formulations without potentially carcinogenic additives are needed to adequately determine the carcinogenicity of 1,3-dichloropropene in humans.

Priority Recommendation: The identified data need to conduct epidemiologic studies on 1,3-dichloropropene is not considered priority. Epidemiologic data would be useful because animal studies have documented sensitive target organs for toxicity and carcinogenicity that may be of concern for exposed humans. Although identification of populations with appropriate exposures might be feasible (e.g., agricultural workers exposed to high purity formulations without potentially carcinogenic additives), epidemiologic studies are not a priority due to the unavailability of a biomarker of exposure for nonrecent exposures. The N-acetyl cysteine (mercapturic acid) urinary metabolite of 1,3-dichloropropene is a reliable biomarker of exposure, but the rapid excretion of this glutathione conjugate limits its usefulness as a biomarker to several days after exposure. Similarly, because 1,3-dichloropropene does not concentrate in the body due to its rapid and extensive clearance, the use of blood or tissue levels of the parent compound as a biomarker would only be feasible for recent exposures.

b. Mechanism of Toxic Action

***Purpose*:** To evaluate the mechanism of 1,3-dichloropropene-induced toxicity to define target organs and future mitigation activities.

***Finding*:** A data need has been identified. 1,3-Dichloropropene is a reactive chemical that mainly causes effects in humans and animals at the point of contact with tissues, particularly the

nasal epithelium following inhalation exposure, stomach following oral exposure, and skin and eyes following dermal exposure. It is not clear whether effects in other tissues (e.g., urinary bladder in mice following inhalation exposure, erythrocytes in dogs following oral exposure) reflect the presence of parent compound or reactive metabolites. Metabolic processes may contribute to toxicity. The mutagenicity of cis- or trans- 1,3-dichloropropene was attributed to its biotransformation by cytochrome P-450 to stereospecific epoxides and the hydrolysis product, 3-chloro-2-hydroxypropanal (Schneider et al. 1998a). It is likely that depletion of glutathione would block the major detoxification pathway for 1,3-dichloropropene, possibly resulting in increased toxicity in tissues such as liver and kidneys due to binding of reactive intermediates to cellular macromolecules. There is some evidence that the cytotoxicity of hepatic cells exposed to 1,3-dichloropropene *in vitro* is preceded by increased levels of phospholipid hydroperoxides (phosphatidylcholine hydroperoxide and phosphatidylethanolamine hydroperoxide) (Suzuki et al. 1994); this appears to confirm the role of reactive intermediates inducing lipid peroxidation as a significant mechanism of toxicity for 1,3-dichloropropene. Although information is available on the general mechanisms of toxicity for the main irritant effects of 1,3-dichloropropene, detailed mechanisms for effects of systemically absorbed compound need to be elucidated.

***Priority Recommendation*:** The identified data need is not considered priority. It is reasonably well established that the local irritant effects of 1,3-dichloropropene are due to its chemical reactivity. Although research is needed to elucidate mechanisms for effects of systemically absorbed 1,3-dichloropropene, this research is not given priority because the preponderance of available evidence indicates that the main effects of inhalation, oral, and dermal exposure are due to irritation at the site of contact.

c. Biomarkers

***Purpose*:** To evaluate the need to develop additional biomarkers of exposure and effect for purposes of future medical surveillance that can lead to early detection and treatment.

***Finding*:** A data need has been identified. The primary biomarker of exposure for 1,3-dichloropropene is its N-acetyl cysteine (mercapturic acid) metabolite, which has been detected in the urine of occupationally exposed humans (Osterloh and Feldman 1993; Osterloh et al. 1984; Van Welie et al. 1989) and animals exposed by inhalation (Fisher and Kilgore 1988b) and orally (Climie et al. 1979; Hutson et al. 1971). A strong correlation was found between inhalation

levels of 1,3-dichloropropene in workers exposed to Telone II®a and urinary excretion of the N-acetyl cysteine metabolite (Osterloh et al. 1984); human dermal exposure to cis-1,3-dichloropropene vapor was successfully monitored by the urinary level of the mercapturic acid metabolite (Kezic et al. 1996). A study in rats suggests that blood levels of the glutathione conjugate could also serve as a biomarker of exposure (Fisher and Kilgore 1989). Depletion of glutathione stores is another possible biomarker of exposure, but would not be practical in the absence of data on preexposure glutathione levels and is not necessarily specific for 1,3-dichloropropene. The rapid excretion of the glutathione conjugate limits its usefulness as a biomarker to several days after exposure. Similarly, because 1,3-dichloropropene does not concentrate in the body due to its rapid and extensive clearance, the use of blood or tissue levels of the parent compound as a biomarker would only be feasible for recent exposures. Additional research is needed to identify a biomarker suitable for assessing exposures that are not in the recent past. Three minor metabolites of 1,3-dichloropropene (the cis and trans epoxides of 1,3-dichloropropene and 3-chloro-3-hydroxypropanal) formed adducts with 2'-deoxyguanosine in an acellular test system (Schneider et al. 1998b). This finding suggests that DNA adduct formation (e.g., in blood cells) could possibly be developed as a useful biomarker for past exposures.

Local irritant effects were observed in cases of humans acutely exposed to high levels of 1,3-dichloropropene by inhalation or orally, and dermal exposure resulted in contact dermatitis and delayed sensitivity reactions in humans. The main effects identified in animal studies include portal-of-entry effects such as hyperplasia/hypertrophy of the nasal respiratory epithelium in rats and mice, and hyperplasia of the nonglandular stomach in rats and mice, as well as hyperplasia of the urinary bladder in mice exposed by inhalation and microcytic anemia in orally exposed dogs. None of these effects are specific to 1,3-dichloropropene, and it is not known if the anemia observed in dogs is relevant to humans. Analysis of serum and urinary biomarkers for liver and renal effects showed no significant changes in workers exposed to 1,3-dichloropropene, although slight increases in urinary N-acetylglucosamidase and retinol binding protein (possible markers for subclinical renal tubular damage) were detectable several days following exposure (Boogard et al. 1993; Osterloh and Feldman 1993; Osterloh et al. 1989; Verplanke et al. 2000). Development of specific biomarkers of effect will require a more thorough knowledge of the toxicity and subtle physiological or biochemical changes caused by 1,3-dichloropropene.

***Priority Recommendation*:** The identified data need is not considered priority. Although there are no reliable biomarkers of exposure for nonrecent exposures and no specific biomarkers of

effects for 1,3-dichloropropene, the development of biomarkers is not a priority because urinary excretion of the N-acetyl cysteine metabolite appears to be a useful biomarker for the main type of exposure expected to occur in the vicinity of hazardous waste sites (i.e., ongoing inhalation exposures).

d. Clinical Methods for Mitigating Toxicity

***Purpose*:** To determine whether any efforts are currently under way to mitigate the effects of exposure to 1,3-dichloropropene.

***Finding*:** A data need has not been identified. Information on the metabolism of 1,3-dichloropropene in humans (Osterloh and Feldman 1993; Osterloh et al. 1984; Van Welie et al. 1989) and animals (Bond et al. 1985; Dietz et al. 1982; Eder and Dornbusch 1988; Fisher and Kilgore 1988a; Waechter and Kastl 1988) indicates that the major detoxifying pathway occurs via conjugation with glutathione, which can occur in target organs such as portal-of-entry tissues (nasal epithelia and the stomach) as well as the liver and kidney. Since depletion of glutathione results in saturation of the detoxification pathway resulting in the use of secondary metabolic pathways that result in epoxidation and the formation of toxic metabolites (Schneider et al. 1998a), research on therapies that increase tissue levels of glutathione (e.g., N-acetylcysteine) could be useful. Additional information on the mechanisms responsible for the toxic effects of 1,3-dichloropropene could aid in the development of effective treatments. Studies directed at finding an efficient way to remove 1,3-dichloropropene from the body, as well as treatment strategies for long-term, low-level exposures, would be beneficial. However, because 1,3-dichloropropene is a point-of-contact irritant, measures to dilute the concentration at the respiratory, gastrointestinal, or dermal tissue surfaces are likely to mitigate the main effects of exposure.

***Priority Recommendation*:** A data need has not been identified. Human case reports and animal studies suggest that point-of-contact toxicity dominates the onset of adverse health effects. For this reason, simple dilution of 1,3-dichloropropene at the point of tissue contact is likely to provide protection against 1,3-dichloropropene-induced injury, and obviate the need for additional data concerning the mitigation of toxic effects post-absorption.

e. Children's Susceptibility

***Purpose*:** To determine whether adequate data exist to identify potential health effects from exposures to 1,3-dichloropropene during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation.

***Finding*:** A data need to conduct additional studies relevant to children's susceptibility via inhalation, oral, and dermal exposure has been identified. No information was located on health effects of 1,3-dichloropropene in children. Although the available animal data in rats and rabbits suggest that the developing organism may be susceptible to 1,3-dichloropropene, developmental toxicity was only observed at doses that were maternally toxic (Hanley et al. 1987; Kloes et al. 1983). Because physiological parameters differ in fetuses, newborns, young children, and adults (EPA 2001d), studies in animals should be conducted to determine effects of those differences on the toxicity of 1,3-dichloropropene. Particularly since children and adults differ with respect to respiratory parameters, animal testing should be conducted by the inhalation route to determine whether juveniles are at greater or lesser risk compared to adults. Studies in children would be especially useful for determining if they have an increased sensitivity to 1,3-dichloropropene, particularly for respiratory effects of inhalation in children with pre-existing conditions such as asthma and reactive airway dysfunction. Toxicokinetic studies examining how aging can influence absorption, distribution, metabolism, and excretion of 1,3-dichloropropene would also help in assessing the susceptibility of children. More information is needed on transfer of 1,3-dichloropropene across the placenta, the kinetics of transfer, and placental metabolism of 1,3-dichloropropene. Since depletion of glutathione stores is possibly related to increased use of bioactivating metabolic pathways by 1,3-dichloropropene, studies monitoring the conditions under which placental glutathione stores are depleted would be useful. Dichloropropene (unspecified isomers) was detected in one of eight samples of human breast milk (Pellizzari et al. 1982), indicating that additional toxicokinetic research is needed to define the risk associated with breast feeding.

Priority Recommendation: The identified data need to conduct additional studies on children's susceptibility via inhalation exposure is not considered priority. There are no human anecdotal reports of toxic effects in children following 1,3-dichloropropene exposure and there are no

current data to suggest that children may be more susceptible than adults to 1,3-dichloropropene-induced adverse health effects. Also, the available animal data indicate that developmental toxicity is a concern only at maternally toxic doses. Additional studies on mechanisms of action and toxicokinetics of 1,3-dichloropropene in immature and adult animals need to be conducted and evaluated before assigning priority to the identified data need. Studies by the oral and dermal routes are not considered priority because these are not primary routes of exposure for populations near hazardous waste sites.

IV. Summary: Prioritization of Data Needs for 1,3-Dichloropropene

A. Exposure

Application of the hierarchy of research priorities presented in the Decision Guide begins with the evaluation of available analytical methods for 1,3-dichloropropene and proceeds through assessing the need for epidemiologic studies. As stated previously, much information is available on 1,3-dichloropropene, though some of the studies are very old. This does not mean that data derived from older studies are not adequate. ATSDR agrees with the National Research Council in that it is not appropriate to judge the quality of past and future studies solely by the standards of today.

Building a sound basic data foundation for higher level environmental research via the Decision Guide requires the determination of human exposure levels and media-specific data on dichloropropenes. Although a lot of information is available, a need to evaluate existing data on concentrations of 1,3-dichloropropene in contaminated environmental media at hazardous waste sites has been identified.

Furthermore, a need to collect data on levels of 1,3-dichloropropene in body tissues and fluids for populations living near hazardous waste sites has been identified. This information is necessary to establish a database that can be used to assess the need to conduct follow-up human health studies of adult and children populations exposed to 1,3-dichloropropene.

One effort is now under way at ATSDR that will examine the extant data at the 112 NPL sites at which 1,3-dichloropropene has been found. When complete, this database will include maximum concentrations of 1,3-dichloropropene in on-site and off-site media, and an indication of relevant

routes of exposure. This database will be developed and evaluated before the need to collect additional media-specific data is assigned priority. This database will not, however, supply information on the levels of 1,3-dichloropropene (or its metabolites) in the tissues of adults and children living near hazardous waste sites or other exposed populations such as workers.

Although there is a need to collect data on levels of 1,3-dichloropropene in body tissues and fluids for populations living near hazardous waste sites, it is not considered a priority at this time. Due to the rapid biological half-life of 1,3-dichloropropene, analytical methods are not currently available that can readily determine 1,3-dichloropropene levels in biological fluids. In addition, no standard level of the 1,3-dichloropropene mercapturic acid metabolites, cis- and trans-DCP-MA, corresponding to a level of exposure has been established.

Thus, on the basis of the findings given in Section II and above, ATSDR is recommending the initiation of research or studies to fill the following exposure priority data needs (Table 3):

- None of the identified exposure data needs are considered to be priority at this time.

B. Toxicity

The toxicity of 1,3-dichloropropene has been studied by all routes of exposure. The primary target of toxicity in humans and animals is the site of tissue contact, as shown by irritant effects in the respiratory tract (particularly nasal epithelium) following inhalation exposure, gastrointestinal tract (particularly stomach) following oral exposure, and skin and eyes following dermal or ocular exposure. Systemic effects occurred in some of the inhalation and oral studies, but were essentially minor, not clearly toxicologically significant, and/or occurred at exposure levels similar to or higher than those causing respiratory or gastrointestinal effects; main systemic effects were urinary bladder hyperplasia and microcytic anemia. Additional acute inhalation studies are needed for identifying sensitive targets, establishing dose-response relationships, and deriving an acute-duration inhalation MRL. Human and skin sensitization studies and SAR analysis indicate that immunotoxicity is a possible systemic effect of concern, indicating an additional need for immune function studies by the inhalation route.

These nonhuman research needs are justified because of the widespread domestic and environmental contamination of 1,3-dichloropropene, and the possibility that significant past exposures have affected many people.

Thus, on the basis of the findings given in Section II and above, ATSDR recommends the initiation of research or studies to fill the following toxicity priority data needs (Table 3):

- Dose-response data for acute-duration via inhalation exposure
- Immunotoxicity battery via inhalation exposure

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Table 1. Exposure Data Needs

Exposure	Level I	Level II	Level III
Analytical	Methods for parent compound in REM*	Methods for degradation products in REM*	
	Methods for parent compound in blood or urine	Methods for parent compound/metabolites/ biomarkers	
	Structure-activity relationships (SAR)		
Physical chemical properties	Water solubility		
	Volatility/vapor pressure		
	K_{ow}		
	Henry's law		Registries of exposed persons
Exposure levels	Production volume (may be used in lieu of monitoring data)	Monitoring in REM*	Human dosimetry studies
	Use (may be used in lieu of monitoring data)	Monitoring for human exposure (personal sampling, biomarkers of exposure, tissue levels)	Epidemiology
	Release/ disposal (may be used in lieu of monitoring data)		Disease registries
		Exposures of children	
Environmental fate	Aerobic/anaerobic Biodegradation in H_2O Oxidation Hydrolysis Aerosolization Photoreactivity Volatilization Soil adsorption/desorption	Small field plot studies	
		Monitoring for products in REM*	
Bioavailability		Food chain bioaccumulation	
		Availability from REM* (analytical or toxicity) emphasize *in vivo*	

*REM = Relevant Environmental Media

Table 2. Toxicity Data Needs

Toxicity	Level I	Level II	Level III
Single dose exposure	Single dose disposition Skin/eye irritation Acute toxicity		
Repeated dose exposure	14-day by relevant route 90-day subchronic	Comparative toxicokinetics*	
Chronic exposure	Structure-activity relationships (SAR)	1-Year chronic 2-Year bioassay	Epidemiology*
Genotoxicity*	Ames Micronucleus	Additional genotoxicity studies*	Mechanism of toxic action*
Endocrine disruption	*In vivo* & *in vitro* screen	2-Generation reproductive study	
Reproductive toxicity	Extended repro workup in subchronic	2-Generation or continuous breeding	Biomarkers*
			Clinical methods for mitigating toxicity*
Developmental toxicity*	Short term *in vivo* screen*	2-Species developmental*	Children's susceptibility**
Immunotoxicity	Use subchronic results	Immunotox battery	
Neurotoxicity	Neuropath in subchronic	Neurotox battery	
Sensitization	Dermal sensitization		
Carcinogenicity	Use muta & subchronic results	2-Year bioassay	

*Useful data for examining children's susceptibility issues

**Data needed for addressing children's susceptibility issues include genotoxicity (Level II), developmental toxicity (Levels I and II), epidemiology, mechanism of toxic action, biomarkers, and clinical methods for mitigating toxicity (Level III)

Table 3. ATSDR Substance-Specific Applied Research Program for 1,3-Dichloropropene

	EXPOSURE		
	Level I	Level II	Level III
Analytical	methods for parent compound in biological materials	refinement of methods for detecting urinary metabolites	
Physical chemical properties		monitoring in soil and sediment	
Exposure levels		exp levels in env media	potential candidate for exposure registry
		exp levels in humans	
		exp levels in children	
Environmental fate			
Bioavailability		soil, plant	
	TOXICITY		
	Level I	Level II	Level III
Acute	*INHAL*, oral, dermal		
Repeated	inhal, oral, dermal	Toxicokinetics	Biomarkers
Chronic		inhal, oral, dermal	Epidemiology
Genotoxicity		Additional genotoxicity studies	Mechanisms
Endocrine disruption			
Reproductive toxicity			
Developmental toxicity		oral, dermal	Children's susceptibility
Immunotoxicity	*INHAL IMMUNOTOX BATTERY*, oral, dermal		
Neurotoxicity	Neurotox battery, inhalation, oral, dermal		
Carcinogenicity			

UPPER CASE: Priority Data Needs identified for 1,3-dichloropropene