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Health Effects Support Document for 1,3-Dichloropropene

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U.S. Environmental Protection Agency
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Health and Ecological Criteria Division
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FOREWORD

The Safe Drinking Water Act (SDWA), as amended in 1996, requires the Administrator of the Environmental Protection Agency (EPA) to establish a list of contaminants to aid the Agency in regulatory priority setting for the drinking water program. In addition, the SDWA requires EPA to make regulatory determinations for no fewer than five contaminants by August 2001 and every five years thereafter. The criteria used to determine whether or not to regulate a chemical on the Contaminant Candidate List (CCL) are the following:

- The contaminant may have an adverse effect on the health of persons.
- The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern.
- In the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The Agency's findings for all three criteria are used in making a determination to regulate a contaminant. The Agency may determine that there is no need for regulation when a contaminant fails to meet one of the criteria. The decision not to regulate is considered a final Agency action and is subject to judicial review.

This document provides the health effects basis for the regulatory determination for1,3-dichloropropene. In arriving at the regulatory determination, data on toxicokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology, and mechanisms of toxicity were evaluated. In order to avoid wasteful duplication of effort, information from the following risk assessments by the EPA and other government agencies were used in development of this document.

U.S. EPA (United States Environmental Protection Agency). 1998c. Reregistration Eligibility Decision (RED): 1,3-dichloropropene. Prepared by the Office of Prevention, Pesticides, and Toxic Substances. EPA 738-R-98-016. Available from: <http://www.epa.gov/oppsrrd1/REDs/0328red.pdf>.

U.S. EPA (United States Environmental Protection Agency). 2000e. Toxicological Review of 1,3-dichloropropene. Prepared by the National Center for Environmental Assessment. NCEA S-0660.

U.S. EPA (United States Environmental Protection Agency). 2000g. IRIS substance file: 1,3-dichloropropene (Section II, Carcinogenicity Assessment for Lifetime Exposure, last update 5/25/2000). Available from: <http://www.epa.gov/iris/subst/0224.htm>.

ATSDR (Agency for Toxic Substances and Disease Registry). 1992. Toxicological profile for 1,3-dichloropropene. Available from: <http://www.atsdr.cdc.gov/toxprofiles/tp40.html or from NTIS>.

Information from the published risk assessments was supplemented with information from the primary references for key studies and recent studies of 1,3-dichloropropene identified by a literature search conducted in 2004 with a focused update in 2008.

A Reference Dose (RfD) is provided as the assessment of long-term toxic effects other than carcinogenicity. RfD determination assumes that thresholds exist for certain toxic effects, such as cellular necrosis, significant body or organ weight changes, blood disorders, etc. It is expressed in terms of milligrams per kilogram per day (mg/kg-day). In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

The carcinogenicity assessment for 1,3-dichloropropene includes a formal hazard identification and an estimate of tumorigenic potency when available. Hazard identification is a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen via the oral route and of the conditions under which the carcinogenic effects may be expressed.

Development of these hazard identification and dose-response assessments for 1,3-dichloropropene has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA guidelines that were used in the development of this assessment may include the following: *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986a), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986b), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996a), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998a), *Draft Revised Guidelines for Carcinogen Assessment* (U.S. EPA, 1999), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988), (proposed) *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b), *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 1998b, 2000a), *Science Policy Council Handbook: Risk Characterization* (U.S. EPA, 2000b), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000c), *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000d), and *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002a).

The chapter on occurrence and exposure to 1,3-dichloropropene through potable water was developed by the Office of Ground Water and Drinking Water. It is based primarily on unregulated contaminant monitoring (UCM) and first Unregulated Contaminant Monitoring Rule (UCMR 1) data collected under the SDWA. The UCM and UCMR 1 data are supplemented

with ambient water data, as well as data from the states, and published papers on occurrence in drinking water.

ACKNOWLEDGMENT

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 EXECUTIVE SUMMARY

The U.S. Environmental Protection Agency (EPA) has prepared this Health Effects Support Document for 1,3-dichloropropene to assist in determining whether to regulate 1,3-dichloropropene with a National Primary Drinking Water Regulation (NPDWR). The available data on occurrence, exposure, and other risk considerations suggest that, based on monitoring conducted from 1988 to 1997, 1,3-dichloropropene does not occur in public water systems at a frequency and at levels of public health concern at the present time. Based on the low occurrence of 1,3-dichloropropene in the potable water, 1,3-dichloropropene does not present a meaningful opportunity for health risk reduction for persons served by public water systems. EPA presents its determination and data analysis in the Federal Register Notice covering the Contaminant Candidate List (CCL) regulatory determinations.

1,3-Dichloropropene (Chemical Abstracts Services Registry Number 542-75-6) is a chlorinated hydrocarbon that is used commercially in the agricultural industry as a nematicide (EPA, 1998c). At room temperature, 1,3-dichloropropene is a colorless to straw-colored liquid with a sharp, sweet, penetrating, chloroform-like odor. It is miscible in most organic solvents and evaporates easily (HSDB, 2000). 1,3-Dichloropropene, marketed under the trade name "Telone," is used in agriculture on both food and non-food crops as a pre-planting fumigant, primarily for the control of nematodes affecting the roots of plants (U.S. EPA, 1998c). 1,3-Dichloropropene was first introduced as a pesticide in 1956 (Hayes, 1982), and is currently registered for commercial cultivation of all types of food and feed crops, including vegetable, fruit and nut crops, forage crops (grasses, legumes and other non-grass forage crops), tobacco, fiber crops, and nursery crops (ornamental, non-bearing fruit/nut trees and forestry crops). It is not registered for household use (U.S. EPA, 1998c). Commercial formulation of 1,3-dichloropropene is a mixture of *cis* (Z) and *trans* (E) isomers, of which the (Z) isomer is the more nematicidally active. Commercial formulations under different trademarks differ by the amounts of 1,3-dichloropropene they contain.

Air emissions constitute most of the on-site releases (and total releases), and generally decrease from 1988 to 2001. A sharp decline is evident between 1995 and 1996, and a modest increase in 2000 and 2001. Surface water discharges are of secondary importance, and no obvious trend is evident.

When 1,3-dichloropropene is used in farm fields, it is sprayed directly on the ground or injected into the soil. Once in the soil, it can exist as a gas or dissolved in water, with the absorption characteristic for each form (*cis*- or *trans*-) being different. 1,3-Dichloropropene adsorbs more strongly to soil when it is in the vapor phase than when it is dissolved in water (Munnecke and Vangundy, 1979). Adsorption in the vapor phase depends partly on the soil's temperature and organic content (Leistra, 1970). Soil adsorption isotherms indicate increasing adsorption with increasing organic content and decreasing temperature. Its K_{oc} values suggest medium to low soil mobility for 1,3-dichloropropene in the vapor phase in soil (Swann et al., 1983). The persistence of 1,3-dichloropropene in soil has been reported to be up to a half-life of 69 days, depending on the type of soil tested. 1,3-Dichloropropene dissipates from soil primarily through volatilization, leaching, abiotic hydrolysis, and aerobic soil metabolism. Runoff of this

chemical from soil to water was determined to be, on average, very low. 1,3-Dichloropropene is released into the air during its production and use as a soil fumigant and chemical intermediate (HSDB, 2004). In the air, 1,3-dichloropropene exists primarily in the vapor phase (Eisenreich et al., 1981). The important environmental fate process for the degradation of 1,3-dichloropropene in ambient air is the vapor phase reaction with photochemically produced hydroxyl radicals. In surface waters, volatilization of 1,3-dichloropropene is an important fate process that will compete with the transformation processes of biodegradation or slow hydrolysis. The Henry's Law constants of 1,3-dichloropropene indicate that, if discharged to surface water, this chemical is likely to volatilize quickly, with a maximum estimated half-life in water of 50 hours. The half-life estimates for 1,3-dichloropropene suggest that volatilization from natural waters is an important fate process for 1,3-dichloropropene (ATSDR, 1992).

Most exposure to 1,3-dichloropropene appears to occur through air. 1,3-Dichloropropene is not a widely occurring atmospheric pollutant, although it is a volatile compound and may enter into the atmosphere after its application to soils. Concentration data for 1,3-dichloropropene in air have primarily been reported for workplaces, although several studies have measured ambient concentrations. Ambient air samples analyzed for *cis*-1,3-dichloropropene were collected during the period of 1970-1987 from urban areas throughout the United States. The median urban atmospheric concentration of *cis*-1,3-dichloropropene in 148 samples was 0.0239 ppmV (parts per million by volume) (0.11 mg/m^3). Information on rural, suburban, source-dominated, or indoor air concentrations of *cis*- or *trans*-1,3-dichloropropene were not available from this study (Shah and Heyerdahl, 1989).

Cross-sectional monitoring data from two rounds of sampling conducted under EPA's Unregulated Contaminant Monitoring (UCM) program indicate that the frequency of detection of 1,3-dichloropropene in public water system (PWS) is low. The data appear to show a decline in the populations exposed to ½ the HRL and the HRL in Round 1 (1988-1992), as compared to Round 2 (1993-1997). The Round 1 estimate for exposure above the HRL was approximately 1.8 million people, compared to about 700,000 people in Round 2. Similarly, the estimated population exposed at greater than ½ the HRL in Round 1 was also 1.8 million people, as compared to the approximately 900,000 suggested by Round 2 data. The decline in the populations exposed to ½ the HRL and the HRL is supported by the ambient data for 1,3-dichloropropene that show no detections at reporting levels from 0.024 to 0.2 µg/L between 1991 and 2001. During the supplementary first Unregulated Contaminant Monitoring Rule (UCMR 1) data collection efforts between 2001 and 2003, neither *cis*- nor *trans*-1,3-dichloropropene was detected (reporting limit for each isomer of 0.50 µg/L).

Chronic and subchronic exposures to 1,3-dichloropropene at doses of 12.5 mg/kg/day and above in animal dietary studies indicate that 1,3-dichloropropene is toxic to organs involved in metabolism (liver), excretion of conjugated metabolites (e.g., urinary bladder and the kidney) and organs along the portals of entry (e.g., forestomach for oral administration; mucous membrane of the nasal passage and lungs for inhalation exposure). Exposure to 1,3-dichloropropene has not been shown to cause reproductive or developmental effects. Neither reproductive nor developmental toxicity was observed in a two-generation reproductive study in rats or in developmental studies in rats and rabbits at maternal inhalation concentrations up to

376 mg/m^3 (U.S. EPA, 2000e). Even concentrations that produced parental toxicity did not produce reproductive or developmental effects (U.S. EPA, 2000e).

An RfD of 0.03 mg/kg/day for 1,3-dichloropropene has been established using a benchmark dose (BMD) analysis based on a two-year chronic bioassay (Stott et al., 1995) in which chronic irritation (forestomach hyperplasia) and significant body weight reduction were the critical and co-critical effects, respectively. An RfC of 0.02 mg/m^3 was derived from a two-year bioassay (Lomax et al., 1989), which observed histopathology in the nasal epithelium.

Under the proposed cancer risk assessment guidelines, the weight of evidence for evaluation of 1,3-dichloropropene's ability to cause cancer suggests that it is likely to be carcinogenic to humans (U.S. EPA, 2000e). This characterization is supported by tumor observations in chronic animal bioassays for both inhalation and oral routes of exposure.

The oral cancer slope factors calculated from chronic dietary, gavage and inhalation data ranged from 5×10^{-2} to 1×10^{-1}(mg/kg/day)$^{-1}$. Due to uncertainties in the delivered doses in some studies, EPA (IRIS) recommended using the oral slope factor of 1×10^{-1} (mg/kg/day)$^{-1}$ from an NTP (1985) study. Using this oral slope factor, EPA calculated an HRL of 0.4 µg/L at the 10^{-6} cancer risk level.

EPA also evaluated whether health information is available regarding the potential effects on children and other sensitive populations. No human or animal studies are available that have examined the effect of 1,3-dichloropropene exposure on juvenile subjects. Therefore, its effects on children are unknown. Developmental studies in rats and rabbits show no evidence of developmental effects and therefore it is unlikely that 1,3-dichloropropene causes developmental toxicity.

2.0 IDENTITY: CHEMICAL AND PHYSICAL PROPERTIES

1,3-Dichloropropene is a chlorinated hydrocarbon that is used commercially in the agricultural industry as a nematicide (U.S. Environmental Protection Agency [U.S. EPA], 1998c). Common and trade names for 1,3-dichloropropene are presented in Table 2-1.

Table 2-1 Common and Trade Names of 1,3-Dichloropropene

Synonyms	1,3-D 1-Propene-1,3-dichloro- Propene,1,3-dichloro- Gamma-Chlorpallyl Chloride 3-Chloropropenyl Chloride DCP *cis*,*trans*-1,3-Dichloropropene Dichloro-1,3-propene 1,3-Dichloropropene-1 1,3-Dichloro-2-Propene Alpha,Gamma-Dichloropropylene 1,3-Dichloropropylene 1,3-dichloro-1-propylene Di-Trapex Di-Trapex CP Dorlone Nematox Caswell No. 324A 1,3-dichloro-propene
Registered Trade Name(s)	NCI-C03985® Nemex® Telone® Telone C17® Telone II® Telone II®a Telone II®b Vidden D® Vorlex® Vorlex 201® M-3993 DD® DD-92®

Sources: ATSDR (1992); HSDB (2004); U.S. EPA (1998c)

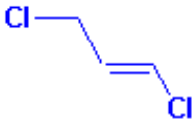
At room temperature, 1,3-dichloropropene is a colorless to straw-colored liquid with a sharp, sweet, penetrating, chloroform-like odor (HSDB, 2000). It is miscible in most organic solvents and evaporates easily (HSDB, 2000). The chemical structure of 1,3-dichloropropene is shown in Figure 2-1. Figure 2-2 presents the structural formulas for the *cis*- and *trans*- isomers of 1,3-dichloropropene. Its physical and chemical properties and other reference information are listed in Table 2-2.

Figure 2-1 Chemical Structure of 1,3-Dichloropropene

Source: ChemIDPlus (2004)

Figure 2-2 Structural Formulas for *Cis*- and *Trans*-1,3-Dichloropropene

***cis*-1,3-dichloropropene**



***trans*-1,3-dichloropropene**

Source: ChemIDPlus (2004)

Table 2-2 Chemical and Physical Properties of 1,3-Dichloropropene

Parameter	Data
Chemical Abstracts Registry (CAS) No.:	542-75-6
EPA Pesticide Chemical Code:	029001
Chemical Formula:	$C_3H_4C_{l2}$
Molecular Weight:	110.98
Physical State:	Amber; colorless to straw-colored liquid
Boiling Point:	108°C
Melting Point:	<-50°C
Density (at 25°C):	1.220
Vapor Pressure:	
At 20°C	3.7 Pa
At 25°C	34 mm Hg
Partition Coefficients:	
Log K_{ow}	1.82
Log K_{oc}	1.36-1.41 (1.36 for *cis* and 1.41 for *trans*)
Solubility in:	
Water	2800 mg/L at 20°C
Other Solvents	Soluble in toluene, acetone, octane; miscible with hydrocarbons, halogenated solvents, esters, and ketones
Conversion Factors: (at 25°C, 1 atm)	1 ppm= 4.54 mg/m^3 1 mg/m^3= 0.220 ppm

Sources: ATSDR (1992); HSDB (2004); U.S. EPA (1998c)

3.0 USES AND ENVIRONMENTAL FATE

3.1 Production and Use

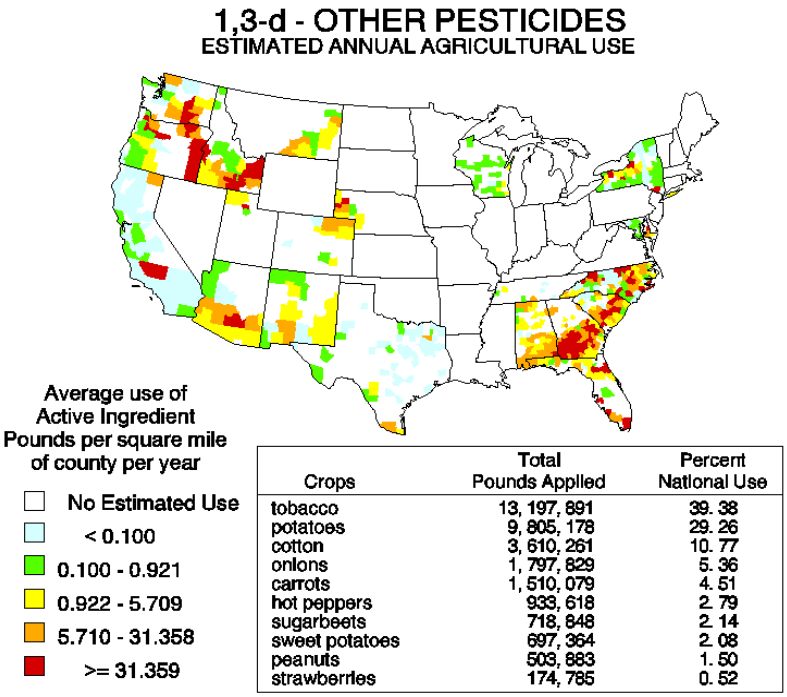
1,3-Dichloropropene, marketed under the trade name "Telone," is used in agriculture on both food and non-food crops as a pre-planting fumigant, primarily for the control of nematodes affecting the roots of plants (U.S. EPA, 1998c). 1,3-Dichloropropene was first introduced as a pesticide in 1956 (Hayes, 1982). It is currently registered for commercial cultivation of all types of food and feed crops, including vegetable, fruit and nut crops, forage crops (grasses, legumes and other non-grass forage crops), tobacco, fiber crops, and nursery crops (ornamental, non-bearing fruit/nut trees and forestry crops). It is not registered for household use (U.S. EPA, 1998c). Commercial formulation of 1,3-dichloropropene is a mixture of *cis* (Z) and *trans* (E) isomers, of which the (Z) isomer is the more nematicidally active. Commercial formulations of 1,3-dichloropropene include those under the trademarks Telone®, Telone II®, and Telone C17®, which differ by the amounts of 1,3-dichloropropene they contain. Commercial formulations that contain other dichloropropenes and/or dichloropropanes and other chemicals include Nematox, Di-Trapex, and Vorlex® (HSDB, 2004).

When 1,3-dichloropropene is used, it is applied to soil before planting, except for pineapples where it is applied at the time of planting. 1,3-Dichloropropene is normally applied to the soil as a mixture of the *cis*- and *trans*-isomers at an application rate of several hundred pounds per acre and a depth of approximately one foot below the soil surface. Application is accomplished by either soil injection (using a chisel, Noble plow, or plow-sole) or by deep drip irrigation (6 or more inches deep) (U.S. EPA, 1998c).

National use estimates are available. Using data from a variety of published sources and its own proprietary data, mostly from a 1991 data call-in (DCI), U.S. EPA (1998c) estimated that approximately 23 million pounds of active ingredient (a.i.) were used annually to treat approximately 372 thousand acres during the years 1990-1995. The United States Geological Survey (USGS) used data collected by the National Center for Food and Agricultural Policy (NCFAP) and the Census of Agriculture (CA) to estimate that 40,023,187 lbs a.i./yr of 1,3-dichloropropene were used in agriculture in the early 1990s (Thelin and Gianessi, 2000). The National Center for Food and Agricultural Policy (NCFAP) itself lists uses of 1,3-dichloropropene on 19 crops totaling approximately 40,083,610 lbs a.i./yr in 1992, and uses on 18 crops totaling approximately 34,717,237 lbs a.i./yr in 1997 (NCFAP, 2003).

Figure 3-1 shows the estimated geographic distribution and intensity of typical annual 1,3-dichloropropene use in the United States in the late 1990s. A breakdown of use by crop also is included. The map was created by the United States Geological Survey (USGS) using State-level data sets on pesticide use rates from 1995-1998 compiled by the National Center for Food and Agricultural Policy (NCFAP), and from county-level data on harvested crop acreage obtained from the 1997 Census of Agriculture (USGS, 2004). Due to the nature of the data sources, non-agricultural uses are not reflected here, and variations in use at the county level are also not well represented (Thelin and Gianessi, 2000). However, because there are no registered residential uses for 1,3-dichloropropene, non-agricultural use is expected to be insignificant (U.S. EPA, 1998c).

Figure 3-1 Estimated Annual Agricultural Use of 1,3-Dichloropropene, 1997



Crops	Total Pounds Applied	Percent National Use
tobacco	13, 197, 891	39. 38
potatoes	9, 805, 178	29. 26
cotton	3, 610, 261	10. 77
onions	1, 797, 829	5. 36
carrots	1, 510, 079	4. 51
hot peppers	933, 618	2. 79
sugarbeets	718, 848	2. 14
sweet potatoes	697, 364	2. 08
peanuts	503, 883	1. 50
strawberries	174, 785	0. 52

3.2 Environmental Release

1,3-Dichloropropene also is listed as a toxic release inventory (TRI) chemical (U.S. EPA, 1996b). The Emergency Planning and Community Right-to-Know Act (EPCRA) of 1986 established the TRI in order to make information about releases of hazardous chemicals available to the public (U.S. EPA, 2000f). The EPCRA requires disclosure of releases of TRI chemicals from facilities with more than 10 full-time employees that annually manufacture or process more than 25,000 pounds of any listed TRI chemical, or otherwise use more than 10,000 pounds of a TRI chemical (U.S. EPA, 2003a). Facilities are required to report the pounds per year of TRI chemicals released into the environment both on- and off-site. The on-site quantity is subdivided into air emissions, surface water discharges, underground injections, and releases to land. TRI data are housed on the EPA website (U.S. EPA, 2002b).

TRI data for 1,3-dichloropropene (Table 3-1) are reported for the years 1988 to 2001 (U.S. EPA, 2002b). Air emissions constitute most of the on-site releases (and total releases), and generally decrease throughout the period of record. A sharp decline is evident between 1995 and 1996, and a modest increase in 2000 and 2001. Surface water discharges are of secondary importance, and no obvious trend is evident. Reported underground injection, releases to land, and off-site releases are generally insignificant. TRI releases of 1,3-dichloropropene were reported from 17 states (AR, CA, DE, FL, GA, HI, IL, KY, LA, MI, MS, NJ, NC, OH, SC, TX, and WA), although not all states reported releases every year.

Table 3-1 Environmental Releases (in pounds) of 1,3-Dichloropropene in the U.S., 1988-2001

Year	On-Site Releases				Off-Site Releases	Total On- & Off-site Releases
	Air Emissions	Surface Water Discharges	Underground Injection	Releases to Land		
2001	13,062	460	0	0	505	14,027
2000	10,295	288	2	200	10	10,795
1999	6600	68	0	0	168	6836
1998	11,566	61	0	1	0	11,628
1997	10,131	67	0	0	0	10,198
1996	10,875	1270	0	0	0	12,145
1995	32,977	193	0	0	0	33,170
1994	24,670	86	0	0	0	24,756
1993	33,348	2	0	0	0	33,350
1992	37,711	69	0	0	0	37,780
1991	20,405	0	0	0	0	20,405
1990	59,473	310	0	0	0	59,783
1989	50,917	340	0	0	3354	54,611
1988	54,590	250	0	0	0	54,840

Source: U.S. EPA (2002b)

Although the TRI can provide a general idea of release trends, it is far from exhaustive and has significant limitations. For example, small facilities (those with fewer than 10 full-time employees, and those that manufacture or process less than 25,000 lbs/yr and use less than 10,000 lbs/yr) are not required to report releases. In addition, the reporting threshold for the manufacturing and processing of TRI chemicals changed between 1987 and 1989, dropping from 75,000 lbs/yr in 1987 to 50,000 lbs/yr in 1988 to the current 25,000 lbs/yr in 1989; this could create misleading data trends (U.S. EPA, 1996b). Finally, the TRI data are meant to reflect releases and should not be used to estimate general public exposure to a chemical (U.S. EPA, 2002a).

3.3 Environmental Fate

3.3.1 Soil

When 1,3-dichloropropene is used in farm fields, it is sprayed directly on the ground or injected into the soil. Once in the soil, it can exist as a gas or dissolved in water, with the absorption characteristic for each form (*cis*- or *trans*-) being different. For instance, Kenaga (1980) reported an experimental organic carbon partition coefficient (K_{oc}) in aqueous solutions of 23 and 26 for *cis*- and *trans*-1,3-dichloropropene, respectively. These K_{oc} values indicate a high mobility in soil and thus, a potential for leaching (Swann et al., 1983).

1,3-Dichloropropene adsorbs more strongly to soil when it is in the vapor phase than when it is dissolved in water (Munnecke and Vangundy, 1979). Adsorption in the vapor phase depends partly on the soil's temperature and organic content (Leistra, 1970). Soil adsorption isotherms indicate increasing adsorption with increasing organic content and decreasing temperature. For example, adsorption is approximately 3-times greater at 2°C than it is at 20°C, and adsorption isotherms measured for humus sand, peaty sand, and peat indicate vapor-phase K_{oc} values ranging from 450 to 750. These K_{oc} values suggest medium to low soil mobility for 1,3-dichloropropene in the vapor phase in soil (Swann et al., 1983).

The persistence of 1,3-dichloropropene in soil has been measured by a number of investigators. Van der Pas and Leistra (1987) reported a half-life of 3 to 4 days in fields used for planting flower bulbs. Only very small amounts of 1,3-dichloropropene remained after periods up to 49 days. Leistra (1970) reported a much slower degradation rate of 0.035/day for a loam soil, which corresponds to a half-life of 19.8 days, and a degradation rate of 0.01/day for sand and peat soils, which corresponds to a half-life of 69 days. Albrecht and Chenchin (1985) have reported half-lives of 3 to 25 days at 20°C for 1,3-dichloropropene in various soils.

Increases in degradation reportedly occurred as soil temperatures increased from 20°C to 50°C and as soil moisture content increased from 1.8% to 16% in a Californian soil, Carsitas loamy sand (Gan et al., 1999). Increases in soil moisture contents of 25, 50, and 75% of its maximum water holding capacity in a Californian soil (Arlington sandy loam) did not affect degradation (Gan et al., 1999). Addition of certain soil amendments including composted chicken and steer manures increased degradation 2.3 and 3.3 times, respectively (Dungan et al., 2001).

1,3-Dichloropropene dissipates primarily through volatilization, leaching, abiotic hydrolysis, and aerobic soil metabolism. Field volatility studies have shown that 45 to 53% of 1,3-dichloropropene is volatilized during the first two weeks following application (Kim et al., 2003). Hydrolysis is temperature dependent, and there is an increase in stability at lower temperatures. At 2°C, for both pH 5.5 and 7.5, the half-life of the parent compound is 90 to 100 days. Under aerobic conditions, half-lives ranging from 12 to 54 days were reported for the parent compound. When 1,3-dichloropropene dissipates, the main hydrolytic degradation product is expected to be 3-chloroallyl alcohol, and the major aerobic metabolite is 3-chloroacrylic acid (U.S. EPA, 1998c). The potential for soil-injected 1,3-dichloropropene to

contribute to water contamination via runoff was found to be low, on the order of 0.002% (Heim et al., 2002).

An alternate degradation pathway occurs in which bacteria biodegrade 1,3-dichloropropene in soil (Belser and Castro, 1971). The initial step of the reaction involves allylic dechlorination of 1,3-dichloropropene and hydroxyl substitution to form the corresponding chloroallylalcohol (Castro and Belser, 1966; Roberts and Stoydin, 1976). Both *cis*- and *trans*-chloroallylalcohols undergo oxidation, resulting in the formation of the corresponding chloroacrylic acids (Castro and Belser, 1968; Roberts and Stoydin,1976). Next, vinylic chlorines are removed and subsequent, propanoic acid 3-aldehyde is oxidized to carbon dioxide (Belser and Castro, 1971).

3.3.2 Air

1,3-Dichloropropene is released into the air during its production and use as a soil fumigant and chemical intermediate (HSDB, 2004). In the air, 1,3-dichloropropene exists primarily in the vapor phase (Eisenreich et al., 1981), with vapor pressures of 43 and 34 mmHg at 25°C for *cis*- and *trans*- 1,3-dichloropropene, respectively (Dilling, 1977). The water solubilities of *cis*- and *trans*-1,3-dichloropropene (2700 and 2800 ppm, respectively) indicate that wet deposition may remove them from the atmosphere (Dilling, 1977).

Volatilization and air emissions of 1,3-dichloropropene during and after application are affected by the rate of degradation of 1,3-dichloropropene in the soil and the application method. As stated previously, degradation of 1,3-dichloropropene is dependent on soil temperature, moisture content in certain soil types, and addition of soil amendments. Schneider et al. (1995) evaluated differences in air emissions between the single-chisel injection application method and the more commonly used double-chisel injection method in pineapple fields in Hawaii. A small-plot field experiment (using three application rates) and two large-scale field experiments (double-chisel injection with high barrier polyethylene mulch; single-chisel injection with mulch film; and single-chisel injection without mulch) were conducted. Single-chisel injection reduced peak air emissions of 1,3-dichloropropene as compared to double-chisel injection at 45-cm depth.

The important environmental fate process for the degradation of 1,3-dichloropropene in ambient air is the vapor phase reaction with photochemically produced hydroxyl radicals. 1,3-Dichloropropene also is removed from air via reaction with ozone; however, this reaction is expected to be secondary to photooxidation with hydroxyl radicals (Tuazon et al., 1984). Assuming that the average yearly troposphere hydroxyl radical and ozone molecule concentrations are 5.0×10^5 and 7.0×10^{11} molecules/cm^3, respectively, Atkinson et al. (1979) reported that the corresponding half-lives for *cis*-1,3-dichloropropene in air would be about 2.1 days and 76 days, while the corresponding half-lives for *trans*-1,3-dichloropropene in air would be about 1.2 days and 17 days. Using an average background tropospheric concentration for hydroxyl radicals and ozone of 2.0×10^6 and 1.0×10^{12} molecules/cm, respectively, Tuazon et al. (1984) calculated half-lives of 12 hours and 52 days for *cis*-1,3-dichloropropene 7 hours and 12 days for *trans*-1,3-dichloropropene.

Formyl chloride and chloroacetaldehyde have been identified as reaction products of 1,3-dichloropropene with both hydroxyl radicals and ozone. Reaction with ozone also yields chloroacetic acid, formic acid, hydrogen chloride, carbon dioxide, and carbon monoxide (Tuazon et al., 1984).

1,3-Dichloropropene also is susceptible to photolysis in air. However, direct photodegradation of 1,3-dichloropropene should not be an important fate process, compared to its reaction with hydroxyl radicals (Mabey et al., 1981). Nevertheless, some evidence that the photodecomposition of 1,3-dichloropropene may be enhanced by the presence of atmospheric particulates exists (Tuazon et al., 1984).

3.3.3 Water

1,3-Dichloropropene is released into waste water during its production and use as a soil fumigant and chemical intermediate (HSDB, 2004). A survey of sewage treatment facilities demonstrated that 1,3-dichloropropene may be released to surface waters via primary and secondary effluents (Rawlings and Samfield, 1979; Lao et al., 1982). In addition, trace quantities of 1,3-dichloropropene are formed during the chlorination of cooling water, which prevents the growth of microorganisms at electricity-generating power facilities (Bean et al., 1985). Consequently, discharged cooling waters from electricity-generating stations and industrial facilities may release 1,3-dichloropropene to surface waters. Treated waste water from paint and ink formulation processes also can release 1,3-dichloropropene to surface waters (U.S. EPA, 1981).

Chlorination of organic substances in treated water supplies also can form 1,3-dichloropropene, releasing it to drinking water (Dowty et al., 1975a,b; Krijgsheld and Van der Gen, 1986; Otson, 1987; Rogers et al., 1987).

Groundwater contamination can occur at and near agricultural fields where 1,3-dichloropropene has been used as a soil fumigant (Maddy et al., 1982; Cohen, 1986; Krijgsheld and Van der Gen, 1986; U.S. EPA, 1998c). 1,3-Dichloropropene also may be released to groundwater via landfills and hazardous waste sites (Hauser and Bromberg, 1982; Sable and Clark, 1984).

In surface waters, volatilization of 1,3-dichloropropene is an important fate process that will compete with the transformation processes of biodegradation or slow hydrolysis. Experimentally measured Henry's law constants for *cis*- and *trans*-1,3-dichloropropene are 1.2 x 10^{-3} and 8.0 x 10^{-4} atm-m^3/mol at 20°C, respectively (Leistra, 1970). These values suggest that volatilization from environmental waters is probably significant (Thomas, 1982). Using the method of Thomas (1982), the estimated volatilization half lives of *cis*- and *trans*-1,3-dichloropropene from a model river 1 meter deep, flowing at a velocity of 1m/sec with a wind velocity of 3 m/sec are 3.8 and 4.2 hours, respectively. Using EPA's EXAMS II computer simulation model (U.S. EPA, 1986c), which considers the effects of adsorption, the corresponding estimated volatilization half-lives from a model pond with a depth of 2 meters are

46 and 50 hours. These half-life estimates suggest that volatilization from most natural waters is an important fate process for 1,3-dichloropropene (ATSDR, 1992).

The relatively high water solubilities of 2700 and 2800 mg/L for *cis*- and *trans*-1,3-dichloropropene, respectively, suggest that 1,3-dichloropropene is more likely to remain in solution than become adsorbed to suspended aquatic materials and sediment (Dilling, 1977).

Several aerobic biological screening studies, which used settled domestic waste water for inocula, demonstrated that 1,3-dichloropropene is biodegradable (Tabak et al., 1981a,b). Within 7 days, the original cultures, added to synthetic media that contained 5 mg yeast extract/L, were able to degrade about 50% of the 1,3-dichloropropene at an initial concentration of 10 ppm (Tabak et al., 1981a,b). Acclimation to a series of subcultures also was demonstrated. The third subculture, with identical concentrations and under identical conditions, showed an approximate 85% removal of 1,3-dichloropropene within the same period of time (Tabak et al., 1981a,b). Nevertheless, the rate of biodegradation for 1,3-dichloropropene in natural waters cannot be inferred from screening study data.

In addition to losses via biodegradation, 1,3-dichloropropene may undergo slow hydrolysis in natural waters. Castro and Belser (1966) found that 1,3-dichloropropene hydrolyzed about 1.4 times slower in buffered solution in soil-water suspensions with a soil:water ratio of 2:1.

3.4 Summary

In soil, the K_{oc} values of 1,3-dichloropropene suggest medium to low soil mobility in the vapor phase. The persistence of 1,3-dichloropropene in soil has been reported to be up to a half-life of 69 days, depending on the type of soil tested. 1,3-Dichloropropene dissipates from soil primarily through volatilization, leaching, abiotic hydrolysis, and aerobic soil metabolism. Runoff of this chemical from soil to water was determined to be, on average, very low.

Volatilization and air emissions of 1,3-dichloropropene during and after application are affected by the rate of degradation of 1,3-dichloropropene in the soil and the application method. Degradation of 1,3-dichloropropene is dependent on soil temperature, moisture content in certain soil types, and addition of soil amendments. Depending on the reaction of 1,3-dichloropropene in air with hydroxyl radicals and ozone molecules, the maximum estimated half-life in air was about 76 days.

The Henry's Law constants of 1,3-dichloropropene indicate that, if discharged to surface water, this chemical is likely to volatilize quickly, with a maximum estimated half-life in water of 50 hours.

4.0 EXPOSURE FROM DRINKING WATER

4.1 Introduction

EPA used data from several sources to evaluate the potential for occurrence of 1,3-dichloropropene in Public Water Systems (PWSs). The primary source of drinking water occurrence data for 1,3-dichloropropene was the Unregulated Contaminant Monitoring (UCM) program. The Agency also looked at the results of supplementary first Unregulated Contaminant Monitoring Rule (UCMR 1) data collection efforts. In addition, the Agency evaluated ambient water quality data from the United States Geological Survey (USGS).

4.2 Ambient Occurrence

4.2.1 Data Sources and Methods

USGS instituted the National Water Quality Assessment (NAWQA) program in 1991 to examine ambient water quality status and trends in the United States. NAWQA is designed to apply nationally consistent methods to provide a consistent basis for comparisons between study basins across the country and over time. These occurrence assessments serve to facilitate interpretation of natural and anthropogenic factors affecting national water quality. For more detailed information on the NAWQA program design and implementation, please refer to Leahy and Thompson (1994) and Hamilton and colleagues (2004).

Study Unit Monitoring

The NAWQA program conducts monitoring and water quality assessments in significant watersheds and aquifers referred to as "study units." NAWQA's sampling approach is not "statistically" designed (i.e., it does not involve random sampling), but it provides a representative view of the nation's waters in its coverage and scope. Together, the 51 study units monitored between 1991 and 2001 include the aquifers and watersheds that supply more than 60% of the nation's drinking water and water used for agriculture and industry (NRC, 2002). NAWQA monitors the occurrence of chemicals such as pesticides, nutrients, volatile organic compounds (VOCs), trace elements, and radionuclides, and the condition of aquatic habitats and fish, insects, and algal communities (Hamilton et al., 2004).

Monitoring of study units occurs in stages. Between 1991 and 2001, approximately one-third of the study units at a time were studied intensively for a period of three to five years, alternated with a period of less intensive research and monitoring that lasted between five and seven years. Thus, all participating study units rotated through intensive assessment in a ten-year cycle (Leahy and Thompson, 1994). The first ten-year cycle was called "Cycle 1." Summary reports are available for the 51 study units that underwent intensive monitoring in Cycle 1 (USGS, 2001). Cycle 2 monitoring is scheduled to proceed in 42 study units from 2002 to 2012 (Hamilton et al., 2004).

VOC National Synthesis

Through a series of National Synthesis efforts, the USGS NAWQA program is preparing comprehensive analyses of data on topics of particular concern. These data are aggregated from the individual study units and other sources to provide a national overview.

The VOC National Synthesis began in 1994. The most comprehensive VOC National Synthesis reports to date are one random survey and one focused survey funded by the American Water Works Association Research Foundation (AwwaRF) and carried out by USGS in collaboration with the Metropolitan Water District of Southern California and the Oregon Health & Science University. The random survey (Grady, 2003) targeted surface and ground waters used as source water by community water systems (CWSs). Samples were taken from the source waters of 954 CWSs in 1999 and 2000. The random survey was designed to be nationally representative of CWS source water. In the focused survey (Delzer and Ivahnenko, 2003), 134 CWS source waters were monitored for VOCs between 1999 and 2001. These surface and ground waters were chosen because they were suspected or known to contain methyl tertiary butyl ether (MTBE). The focused survey was designed to provide insight into temporal variability and anthropogenic factors associated with VOC occurrence. Details of the monitoring plan for these two studies are provided by Ivahnenko and colleagues (2001).

Additional products of the VOC National Synthesis include a compilation of historical VOC monitoring data from multiple studies (Squillace et al., 1999). The data, collected from 2948 wells between 1985 and 1995 by local, state, and federal agencies, were reviewed to ensure they met data quality criteria. Most of the data were from early study unit monitoring. The samples represent both urban and rural areas, and both drinking water and non-drinking water wells. A full analysis of 10 years of study unit monitoring data has not yet been performed by the VOC National Synthesis.

4.2.2 Results

Random and Focused VOC Surveys

The national random survey and focused survey both found no detections of 1,3-dichloropropene at the reporting level of 0.2 µg/L (Grady, 2003; Delzer and Ivahnenko, 2003). Even when evaluating occurrence at levels as low as method detection limits (0.024 µg/L for *cis*-1,3-dichloropropene and 0.026 µg/L for *trans*-1,3-dichloropropene), the focused survey found no detections of *cis*- or *trans*-1,3-dichloropropene (Delzer and Ivahnenko, 2003).

Compilation of Historical VOC Monitoring Data

Multiple investigators collected *cis*-1,3-dichloropropene samples from 349 urban wells and 2138 rural wells, and *trans*-1,3-dichloropropene samples from 347 urban wells and 2039 rural wells. At a reporting level of 0.2 µg/L, there were no detections of either *cis*- or *trans*-1,3-dichloropropene (Squillace et al., 1999).

4.3 Drinking Water Occurrence

4.3.1 UCM Rounds 1 and 2

4.3.1.1 Data Sources and Methods

In 1987, EPA initiated the UCM program to fulfill a 1986 SDWA Amendment that required monitoring of specified unregulated contaminants to gather information on their occurrence in drinking water for future regulatory decision-making purposes. EPA implemented the UCM program in two phases or rounds. The first round of UCM monitoring generally extended from 1988 to 1992 and is referred to as UCM Round 1 monitoring. The second round of UCM monitoring generally extended from 1993 to 1997 and is referred to as UCM Round 2 monitoring.

UCM Round 1 monitored for 34 volatile organic compounds (VOCs), including 1,3-dichloropropene (52 FR 25720, July 8, 1987). UCM Round 2 monitored for the same 34 VOCs, plus 13 synthetic organic compounds (SOCs) and sulfate (57 FR 31776, July 17, 1992).

The UCM Round 1 database contains contaminant occurrence data from 38 states, Washington, DC, and the U.S. Virgin Islands. The UCM Round 2 database contains data from 34 states and several tribes. Due to incomplete state data sets, national occurrence estimates based on raw (unedited) UCM Round 1 or Round 2 data could be skewed to low-occurrence or high-occurrence settings (e.g., some states only reported detections). To address potential biases in the data, EPA developed national cross-sections from the UCM Round 1 and Round 2 State data using an approach similar to that used for EPA's 1999 Chemical Monitoring Reform (CMR), the first Six Year Review, and the first CCL Regulatory Determinations. This national cross-section approach was developed to support occurrence analyses and was supported by scientific peer reviewers and stakeholders. Because UCM Round 1 and Round 2 data represent different time periods and include occurrence data from different states, EPA developed separate national cross-sections for each data set.

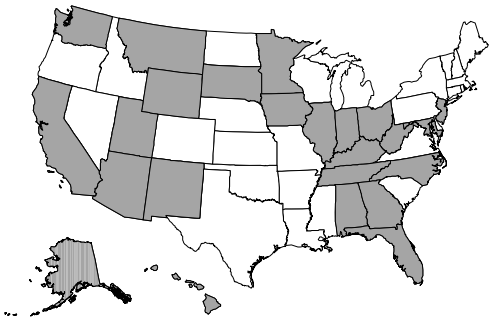
The UCM Round 1 national cross-section consists of data from 24 states, with approximately 3.3 million total analytical data points from approximately 22,000 unique PWSs. The UCM Round 2 national cross-section consists of data from 20 states, with approximately 3.7 million analytical data points from slightly more than 27,000 unique PWSs. The two national cross-sections represent significantly large samples of national occurrence data. Within each cross-section, the number of systems and analytical records for each contaminant varies.

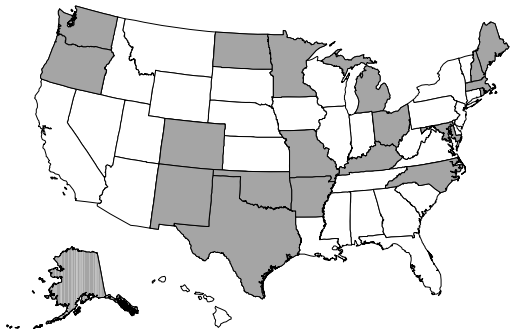
EPA constructed the national cross-sections in a way that provides a balance and range of states with varying pollution potential indicators, a wide range of the geologic and hydrologic conditions, and a very large sample of monitoring data points. While EPA recognizes that some limitations exist, the Agency believes that the national cross-sections do provide a reasonable estimate of the overall distribution and the central tendency of contaminant occurrence across the United States. See Figure 4-1 for a listing of states in each national cross-section. Further

details on the UCM program and the construction of cross-sections can be found in other documents (U.S. EPA, 2000f, and others currently in preparation).

Figure 4-1 Cross-section States for Round 1 (24 States) and Round 2 (20 States)

Round 1		Round 2	
Alabama	Minnesota*	Alaska*	New Hampshire
Alaska*	Montana	Arkansas	New Mexico*
Arizona	New Jersey	Colorado	North Carolina*
California	New Mexico*	Kentucky*	North Dakota
Florida	North Carolina*	Maine	Ohio*
Georgia	Ohio*	Maryland*	Oklahoma
Hawaii	South Dakota	Massachusetts	Oregon
Illinois	Tennessee	Michigan	Rhode Island
Indiana	Utah	Minnesota*	Texas
Iowa	Washington*	Missouri	Washington*
Kentucky*	West Virginia		
Maryland*	Wyoming		





* cross-section state in both Round 1 and Round 2

4.3.1.2 Derivation of the Health Reference Level

To evaluate the systems and populations exposed to 1,3-dichloropropene through PWSs, the monitoring data were analyzed against the Minimum Reporting Level (MRL) and a benchmark value for health that is termed the Health Reference Level (HRL). Two different approaches were used to derive the HRL, one for chemicals that cause cancer and exhibit a linear response to dose and the other applies to noncarcinogens and carcinogens evaluated using a non-linear approach.

The oral cancer slope factors calculated from chronic dietary, gavage and inhalation data ranged from 5×10^{-2} to $1 \times 10^{-1}(mg/kg/day)^{-1}$. Additional detail regarding the cancer assessment for 1,3-dichloropropene may be found in Section 8. Due to uncertainties in the delivered doses

in some studies, EPA (IRIS) recommended using the oral slope factor of 1×10^{-1} $(mg/kg/day)^{-1}$ from an NTP (1985) study. The HRL is based on the concentration in drinking water equivalent to a one-in-a million risk (10^{-6}) of cancer above background calculated as follows:

Concentration at 10^{-6} Risk = (Risk x Body Weight)/(Slope Factor x Drinking Water Intake)

= (0.000001 x 70 kg)/(0.1 $(mg/kg/day)^{-1}$-x 2 L/day)

= 3.5×10^{-4} mg/L (0.4 µg/L rounded to one significant figure)

4.3.1.3 Results

1,3-Dichloropropene monitoring results from UCM Rounds 1 and 2 may have been compromised by the widespread use of sodium sulfate and sodium thiosulfate as dechlorinating agents. Before it was recognized that sodium sulfate and sodium thiosulfate degrade 1,3-dichloropropene in analytical samples, the two compounds were commonly used to preserve drinking water samples for VOC testing. Hence, older drinking water surveys, like UCM Rounds 1 and 2, likely underestimate actual 1,3-dichloropropene occurrence. (This concern does not apply to the ambient 1,3-dichloropropene monitoring described above. USGS's ambient monitoring typically does not involve a dechlorination step. In rare cases when dechlorination is necessary, USGS employs ascorbic acid as the dechlorinating agent.)

With the caveat that UCM occurrence estimates are likely underestimates, it is still instructive to analyze the occurrence data collected. Tables 4-1 and 4-2 show the results from the Round 1 and Round 2 cross-sections. Results are analyzed at the level of simple detections (at or above the minimum reporting level, or MRL), exceedances of the health reference level (>HRL, or >0.4 µg/L), and exceedances of one half the value of the HRL (>½HRL or >0.2 µg/L). MRLs for 1,3-dichloropropene were not uniform. They varied from 0.02 to 10 µg/L in the first Round, and from 0.08 to 1 µg/L in the second Round. The modal (most common) MRL in both Rounds was 0.5 µg/L. Because the MRL was often higher than the HRL and ½HRL, it is likely that the sampling failed to capture some ½HRL and HRL exceedances at the participating systems, and that the ½HRL and HRL analyses underestimate actual 1,3-dichloropropene occurrence.

In Round 1 cross-section states, 1,3-dichloropropene was detected at approximately 0.16% of PWSs, affecting 0.86% of the population served, equivalent to approximately 1.8 million people nationally. All of these detections were at concentrations higher than the HRL. This is not surprising, since the most common MRL, 0.5 µg/L, is higher than the HRL.

When all Round 1 results are included in the analysis, including results from states with incomplete or less reliable data, 1,3-dichloropropene detection frequencies appear to be slightly higher than the cross-section data indicate. Detections affect 0.20% of PWSs and 0.95% of the population served; exceedances of the HRL (and ½HRL) affect 0.19% of PWSs and 0.94% of the population served.

In Round 2 cross-section states, 1,3-dichloropropene was detected at 0.35% of PWSs, affecting 0.55% of the population served, equivalent to approximately 1.2 million people nationally. The ½HRL benchmark was exceeded in 0.30% of PWSs, affecting 0.42% of the population served, equivalent to approximately 0.9 million people nationally. The HRL benchmark was exceeded in 0.23% of PWSs, affecting 0.33% of the population served, equivalent to approximately 0.7 million people nationally. Compared with Round 1, Round 2 shows greater occurrence of 1,3-dichloropropene across the board, and shows a greater proportion of detections at low levels that do not exceed the health-related benchmarks. Both of these phenomena are at least partly explained by the fact that the analytical detection methods used in Round 2 were generally more sensitive.

When all Round 2 results are included in the analysis, 1,3-dichloropropene occurrence results appear to be slightly lower than those observed for the cross-section data. Detections affect 0.31% of PWSs and 0.47% of the population served; ½HRL exceedances affect 0.27% of PWSs and 0.36% of the population served; and HRL exceedances affect 0.20% of PWSs and 0.27% of the population served.

Table 4-1 Summary UCM Occurrence Statistics for 1,3-Dichloropropene (Round 1)

Frequency Factors	24 State Cross-Section[1]		All Reporting States[2]		National System & Population Numbers[3]	
Total Number of Samples	31,104		31,973		--	
Percent of Samples with Detections	0.06%		0.09%		--	
99th Percentile Concentration (all samples)	< MRL		< MRL		--	
Health Reference Level (HRL)	0.4 µg/L		0.4 µg/L		--	
Minimum Reporting Level (MRL) - Range - (modal value)[4]	0.02 - 10 µg/L (0.5 µg/L)		0.02 - 10 µg/L (0.5 µg/L)		--	
Maximum Concentration of Detections	2.0 µg/L		17.0 µg/L		--	
99th Percentile Concentration of Detections	2.0 µg/L		15.6 µg/L		--	
Median Concentration of Detections	1.0 µg/L		1.0 µg/L		--	
Total Number of PWSs Number of GW PWSs Number of SW PWSs	9,164 8,303 898		9,307 8,401 947		65,030 59,440 5,590	
Total Population Population of GW PWSs Population of SW PWSs	50,917,006 24,660,968 29,271,833		52,879,061 26,106,876 29,867,090		213,008,182 85,681,696 127,326,486	
Occurrence by System	**Number**	**Percentage**	**Number**	**Percentage**	**National Extrapolation[5]**	
					Cross-Section	**All States**
PWSs with detections (≥ MRL) Range across States GW PWSs with detections SW PWSs with detections	15 0 - 7 10 5	0.16% 0 - 1.75% 0.12% 0.56%	19 0 - 7 14 6	0.20% 0 - 100% 0.17% 0.63%	106 N/A 72 31	133 N/A 99 35
PWSs > 1/2 HRL Range across States GW PWSs > 1/2 HRL SW PWSs > 1/2 HRL	15 0 - 7 10 5	0.16% 0 - 1.75% 0.12% 0.56%	18 0 - 7 13 6	0.19% 0 - 100% 0.15% 0.63%	106 N/A 72 31	126 N/A 92 35
PWSs > HRL Range across States GW PWSs > HRL SW PWSs > HRL	15 0 - 7 10 5	0.16% 0 - 1.75% 0.12% 0.56%	18 0 - 7 13 6	0.19% 0 - 100% 0.15% 0.63%	106 N/A 72 31	126 N/A 92 35
Occurrence by Population Served						
Population served by PWSs with detections Range across States Pop. Served by GW PWSs with detections Pop. Served by SW PWSs with detections	436,223 0 - 225,630 146,155 290,068	0.86% 0 - 6.12% 0.59% 0.99%	500,486 0 - 225,630 210,418 342,118	0.95% 0 - 100% 0.81% 1.15%	1,825,000 N/A 508,000 1,262,000	2,016,000 N/A 691,000 1,458,000
Population served by PWSs > 1/2 HRL Range across States Pop. Served by GW PWSs > 1/2 HRL Pop. Served by SW PWSs > 1/2 HRL	436,223 0 - 225,630 146,155 290,068	0.86% 0 - 6.12% 0.59% 0.99%	497,246 0 - 225,630 207,178 342,118	0.94% 0 - 100% 0.79% 1.15%	1,825,000 N/A 508,000 1,262,000	2,003,000 N/A 680,000 1,458,000
Population served by PWSs > HRL Range across States Pop. Served by GW PWSs > HRL Pop. Served by SW PWSs > HRL	436,223 0 - 225,630 146,155 290,068	0.86% 0 - 6.12% 0.59% 0.99%	497,246 0 - 225,630 207,178 342,118	0.94% 0 - 100% 0.79% 1.15%	1,825,000 N/A 508,000 1,262,000	2,003,000 N/A 680,000 1,458,000

1. Summary Results based on 24-State Cross-Section, UCM Round 1 data.
2. Summary Results based on All Reporting States, UCM Round 1 data.
3. Total PWS and population numbers are from EPA March 2000 Water Industry Baseline Handbook, 2nd Edition.
4. Because several different analytical methods were used, MRLs were not uniform. The modal value is the most common MRL.
5. National extrapolations are generated by multiplying the system/population percentages and the national Baseline Handbook system/population numbers.

Abbreviations:
PWS = Public Water Systems; GW = Ground Water; SW = Surface Water; N/A = Not Applicable; Total Number of Samples = total number of samples on record for the contaminant; 99th Percentile Concentration = the concentration in the 99th percentile sample (out of either all samples or just samples with detections); Median Concentration of Detections = the concentration in the median sample (out of samples with detections); Total Number of PWSs = the total number of PWSs for which sampling results are available; Total Population Served = the total population served by PWSs for which sampling results are available; PWSs with Detections, PWSs >½HRL, or PWSs >HRL = PWSs with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark, respectively; Population Served by PWSs with Detections, by PWSs >½HRL, or by PWSs >HRL = population served by PWSs with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark, respectively.

Notes:
-Only results at or above the MRL were reported as detections. Concentrations below the MRL are considered non-detects.
-Because some systems were counted as both ground water and surface water systems and others could not be classified, GW and SW figures might not add up to totals.
-Due to differences between the ratios of GW and SW systems with monitoring results and the national ratio, extrapolated GW and SW figures might not add up to extrapolated totals.
-Due to MRL variability, it is likely that the sampling failed to capture some ½HRL and HRL exceedances at the participating systems, and the ½HRL and HRL analyses underestimate actual contaminant occurrence..

Table 4-2 Summary UCM Occurrence Statistics for 1,3-Dichloropropene (Round 2)

Frequency Factors	20 State Cross-Section[1]		All Reporting States[2]		National System & Population Numbers[3]	
Total Number of Samples	70,631		79,388		--	
Percent of Samples with Detections	0.11%		0.10%		--	
99th Percentile Concentration (all samples)	< MRL		< MRL		--	
Health Reference Level (HRL)	0.4 µg/L		0.4 µg/L		--	
Minimum Reporting Level (MRL) - Range - (modal value)[4]	0.08 - 1 µg/L (0.5 µg/L)		0.08 - 1 µg/L (0.5 µg/L)		--	
Maximum Concentration of Detections	39 µg/L		39 µg/L		--	
99th Percentile Concentration of Detections	39 µg/L		25 µg/L		--	
Median Concentration of Detections	0.5 µg/L		0.5 µg/L		--	
Total Number of PWSs Number of GW PWSs Number of SW PWSs	16,787 15,178 1,609		18,944 17,098 1,846		65,030 59,440 5,590	
Total Population Population of GW PWSs Population of SW PWSs	45,951,052 17,423,030 28,528,022		55,713,623 21,446,615 34,267,008		213,008,182 85,681,696 127,326,486	
Occurrence by System	**Number**	**Percentage**	**Number**	**Percentage**	**National Extrapolation[5]**	
					Cross-Section	**All States**
PWSs with detections (≥ MRL) Range across States GW PWSs with detections SW PWSs with detections	58 0 - 43 48 10	0.35% 0 - 2.91% 0.32% 0.62%	59 0 - 43 48 11	0.31% 0 - 2.91% 0.28% 0.60%	225 N/A 188 35	203 N/A 167 33
PWSs > 1/2 HRL Range across States GW PWSs > 1/2 HRL SW PWSs > 1/2 HRL	50 0 - 35 41 9	0.30% 0 - 2.36% 0.27% 0.56%	51 0 - 35 41 10	0.27% 0 - 2.36% 0.24% 0.54%	194 N/A 161 31	175 N/A 143 30
PWSs > HRL Range across States GW PWSs > HRL SW PWSs > HRL	38 0 - 23 29 9	0.23% 0 - 1.55% 0.19% 0.56%	38 0 - 23 29 9	0.20% 0 - 1.55% 0.17% 0.49%	147 N/A 114 31	130 N/A 101 27
Occurrence by Population Served						
Population served by PWSs with detections Range across States Pop. Served by GW PWSs with detections Pop. Served by SW PWSs with detections	252,643 0 - 209,261 197,066 55,577	0.55% 0 - 5.78% 1.13% 0.19%	260,157 0 - 209,261 197,066 63,091	0.47% 0 - 5.78% 0.92% 0.18%	1,171,000 N/A 969,000 248,000	995,000 N/A 787,000 234,000
Population served by PWSs > 1/2 HRL Range across States Pop. Served by GW PWSs > 1/2 HRL Pop. Served by SW PWSs > 1/2 HRL	192,870 0 - 149,488 141,275 51,595	0.42% 0 - 4.13% 0.81% 0.18%	200,384 0 - 149,488 141,275 59,109	0.36% 0 - 4.13% 0.66% 0.17%	894,000 N/A 695,000 230,000	766,000 N/A 564,000 220,000
Population served by PWSs > HRL Range across States Pop. Served by GW PWSs > HRL Pop. Served by SW PWSs > HRL	151,553 0 - 108,171 99,958 51,595	0.33% 0 - 2.99% 0.57% 0.18%	151,553 0 - 108,171 99,958 51,595	0.27% 0 - 2.99% 0.47% 0.15%	703,000 N/A 492,000 230,000	579,000 N/A 399,000 192,000

1. Summary Results based on 20-State Cross-Section, UCM Round 2 data.
2. Summary Results based on All Reporting States, UCM Round 2 data.
3. Total PWS and population numbers are from EPA March 2000 Water Industry Baseline Handbook, 2nd Edition.
4. Because several different analytical methods were used, MRLs were not uniform. The modal value is the most common MRL.
5. National extrapolations are generated by multiplying the system/population percentages and the national Baseline Handbook system/population numbers.

Abbreviations:
PWS = Public Water Systems; GW = Ground Water; SW = Surface Water; N/A = Not Applicable; Total Number of Samples = total number of samples on record for the contaminant; 99th Percentile Concentration = the concentration in the 99th percentile sample (out of either all samples or just samples with detections); Median Concentration of Detections = the concentration in the median sample (out of samples with detections); Total Number of PWSs = the total number of PWSs for which sampling results are available; Total Population Served = the total population served by PWSs for which sampling results are available; PWSs with Detections, PWSs >½HRL, or PWSs >HRL = PWSs with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark, respectively; Population Served by PWSs with Detections, by PWSs >½HRL,or by PWSs >HRL = population served by PWSs with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark, respectively.

Notes:
-Only results at or above the MRL were reported as detections. Concentrations below the MRL are considered non-detects.
-Due to differences between the ratios of GW and SW systems with monitoring results and the national ratio, extrapolated GW and SW figures might not add up to extrapolated totals.
-Due to MRL variability, it is likely that the sampling failed to capture some ½HRL and HRL exceedances at the participating systems, and the ½HRL and HRL analyses underestimate actual contaminant occurrence.

Regional Patterns

Each of the following maps focuses on a somewhat different aspect of the geographical distribution of 1,3-dichloropropene occurrence. Figure 4-2 identifies all states with at least one PWS with a detection of 1,3-dichloropropene in Round 1 or Round 2. All states are included in this analysis, including both cross-section states with reliable data and non-cross-section states with less reliable data, in order to provide the broadest assessment of possible 1,3-dichloropropene occurrence. Figure 4-3 presents the same information (identifying states with detections, regardless of whether they were included in the cross-sections) separately for Round 1 (1988-1992) and Round 2 (1993-1997), to reveal temporal trends.

Figure 4-4 illustrates the geographic distribution of states with different detection frequencies (percentage of PWSs with at least one detection), and Figure 4-5 illustrates the geographic distribution of different HRL exceedance frequencies (percentage of PWSs with at least one HRL exceedance). Only cross-section states, which have the most complete and reliable occurrence data, are included in these two analyses. In each figure, Round 1 data are presented in the upper map and Round 2 data are presented in the lower map to reveal temporal trends.

In each map, two color categories represent states with no data. Those in white do not belong to the relevant Round or cross-section, and those in the lightest category of shading were included in the Round or cross-section but have no data for 1,3-dichloropropene. The darker shades are used to differentiate occurrence findings in states with 1,3-dichloropropene data.

These maps reveal no clear geographic or temporal patterns of 1,3-dichloropropene occurrence. States with PWSs with detections are distributed from the east to the west coast, and from the Canadian to the Mexican borders. Even the states with the highest proportion of PWSs with detections are generally distributed across the United States.

Figure 4-2 Geographic Distribution of 1,3-Dichloropropene Detections in Both Cross-Section and Non-Cross-Section States (Combined UCM Rounds 1 and 2)

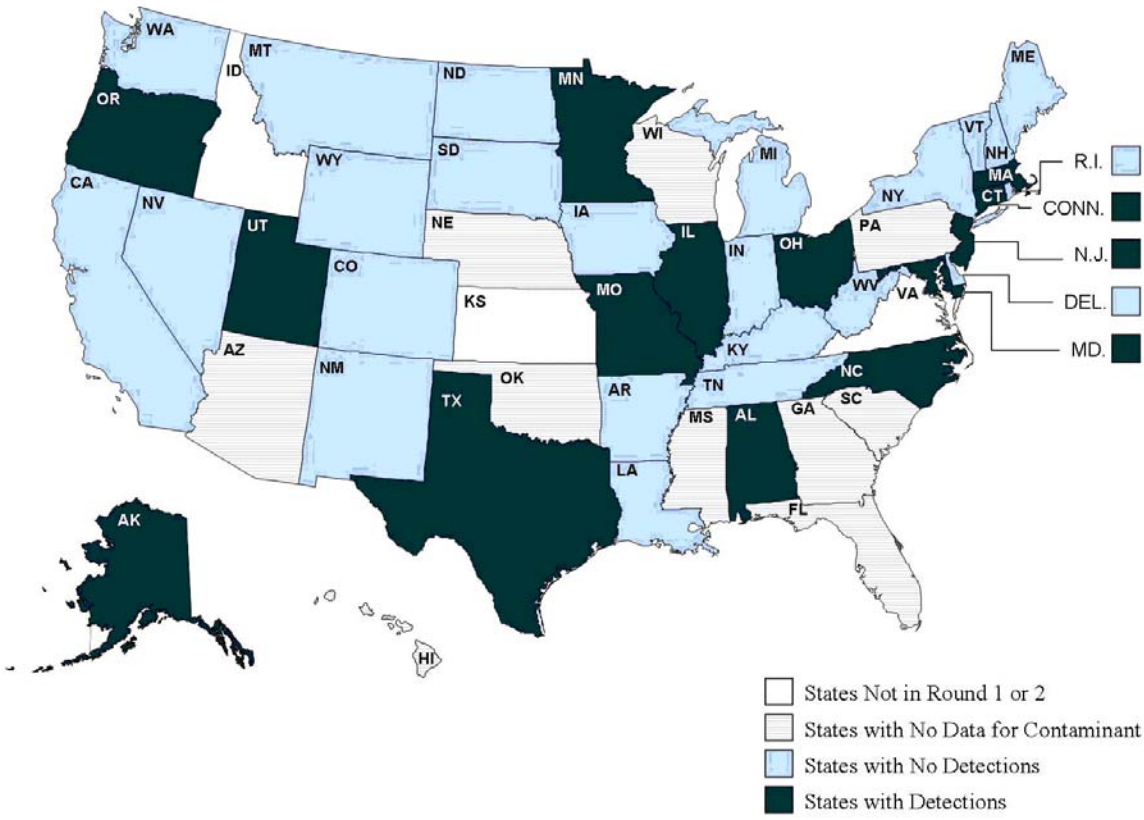
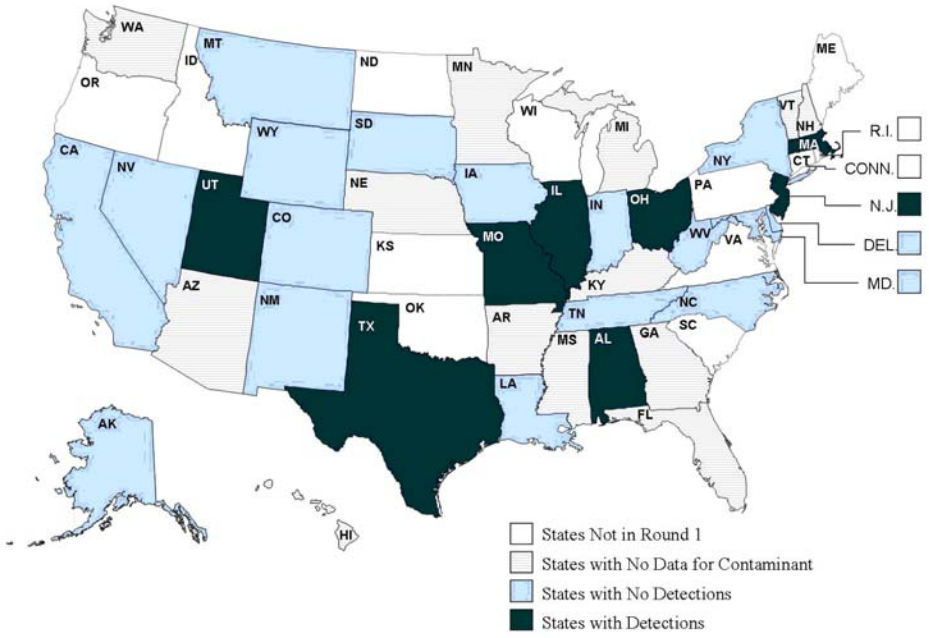


Figure 4-3 Geographic Distribution of 1,3-Dichloropropene Detections in Both Cross-Section and Non-Cross-Section States (Above: UCM Round 1; Below: UCM Round 2)



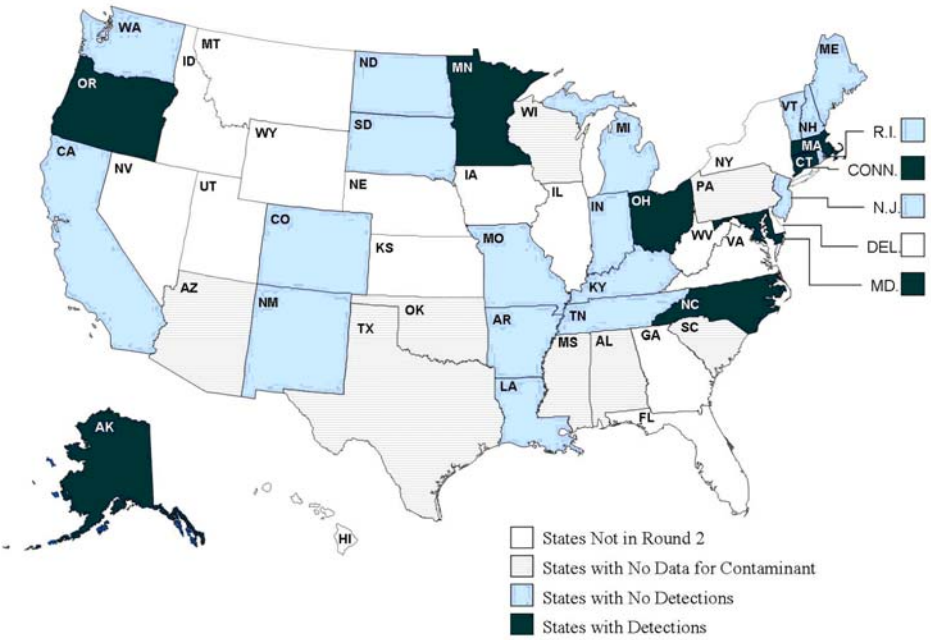
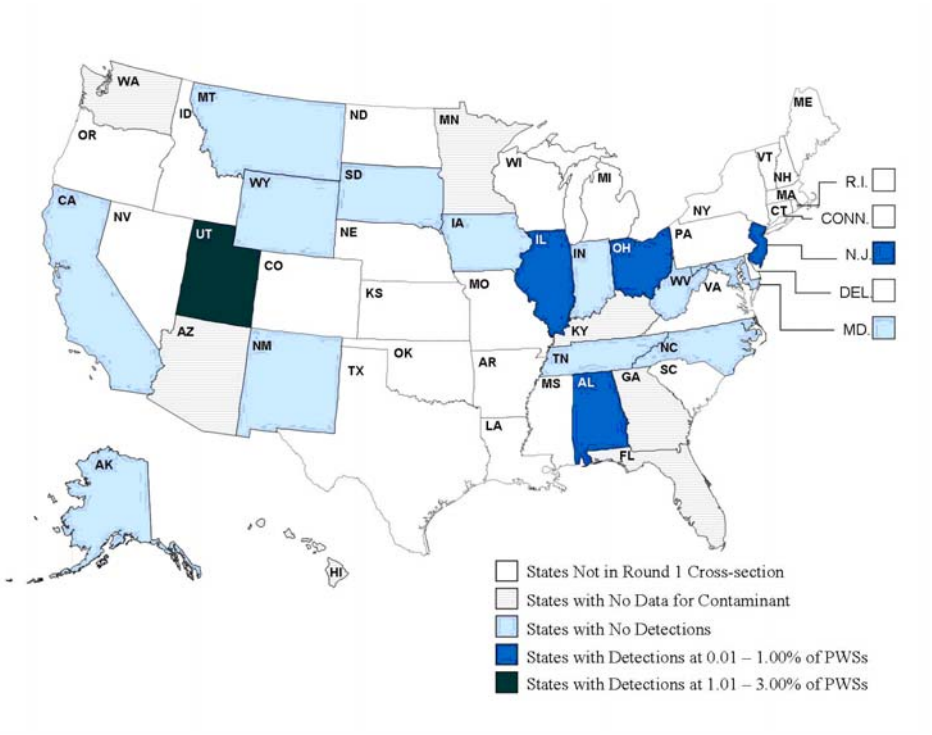


Figure 4-4 Geographic Distribution of 1,3-Dichloropropene Detection Frequencies in Cross-Section States (Above: UCM Round 1; Below: UCM Round 2)



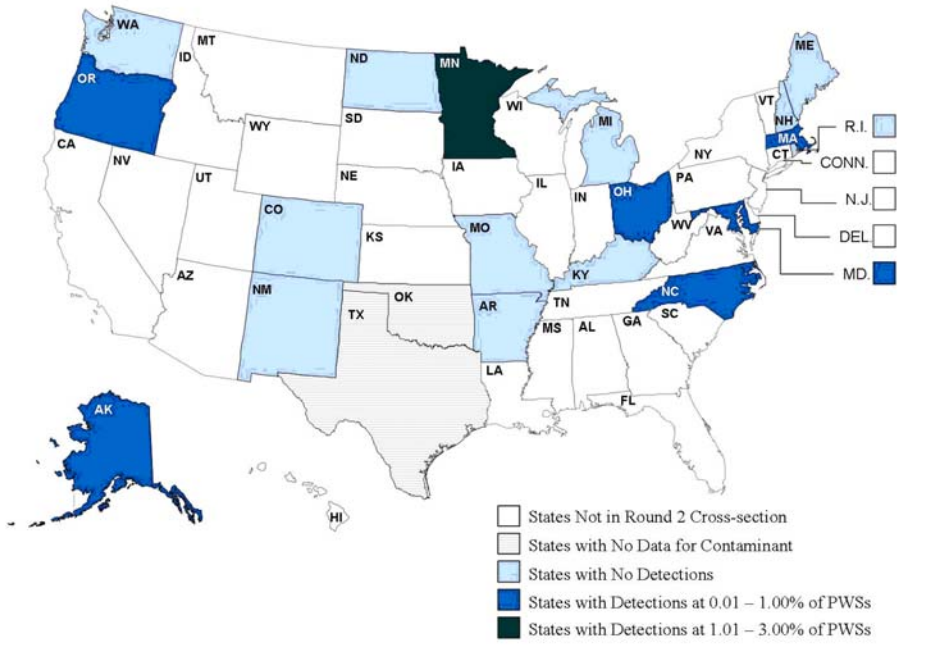
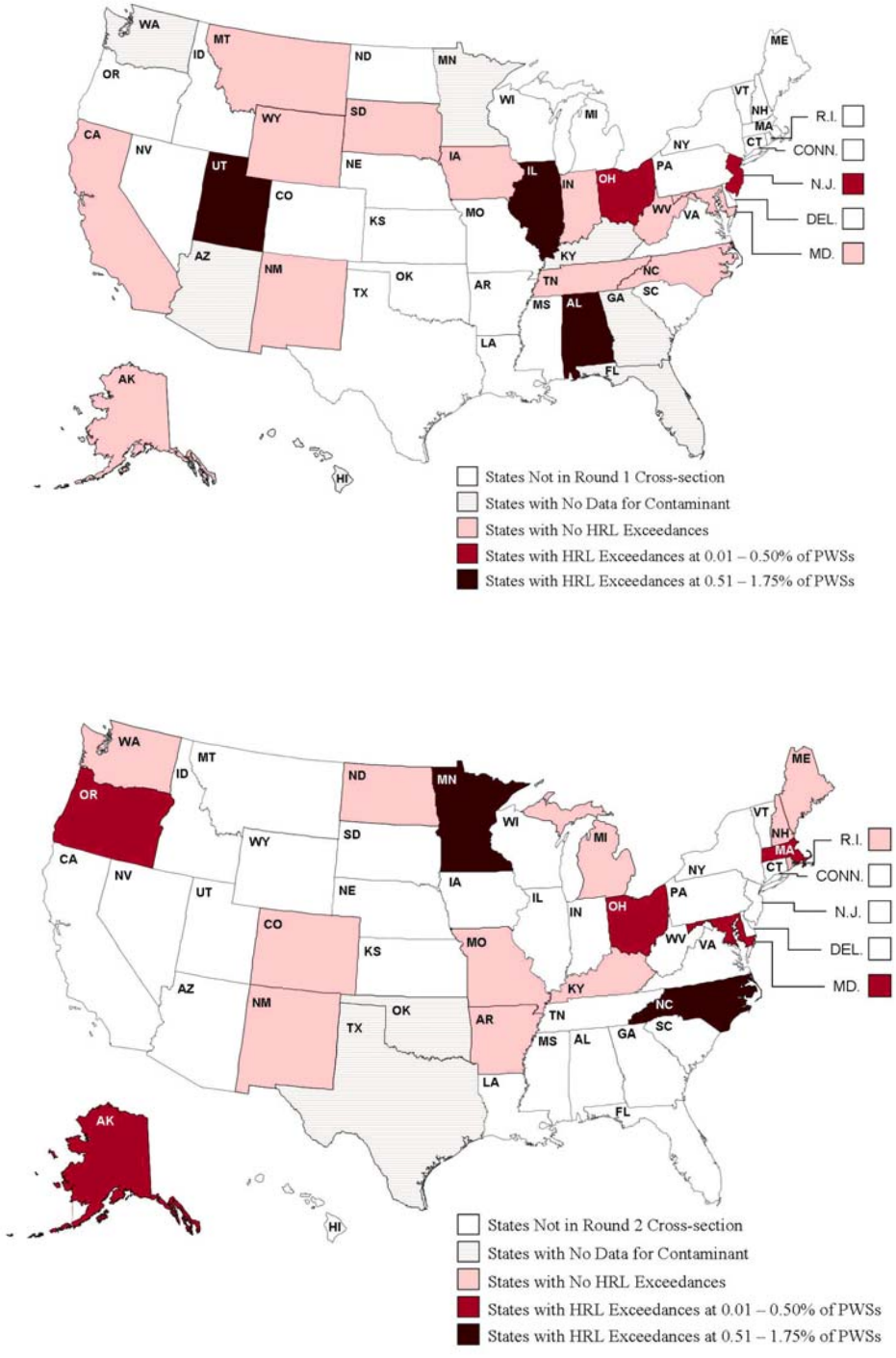


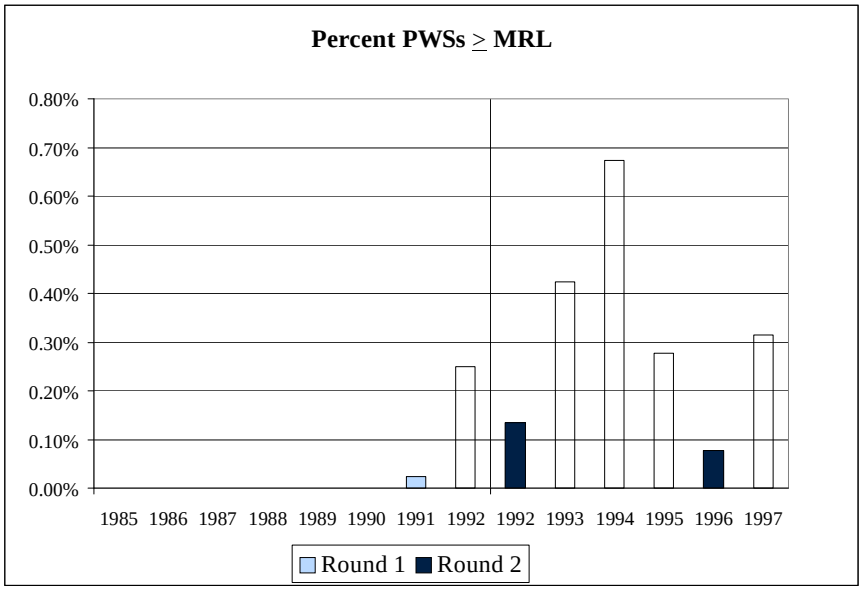
Figure 4-5 Geographic Distribution of 1,3-Dichloropropene HRL Exceedance Frequencies in Cross-Section States (Above: UCM Round 1; Below: UCM Round 2)

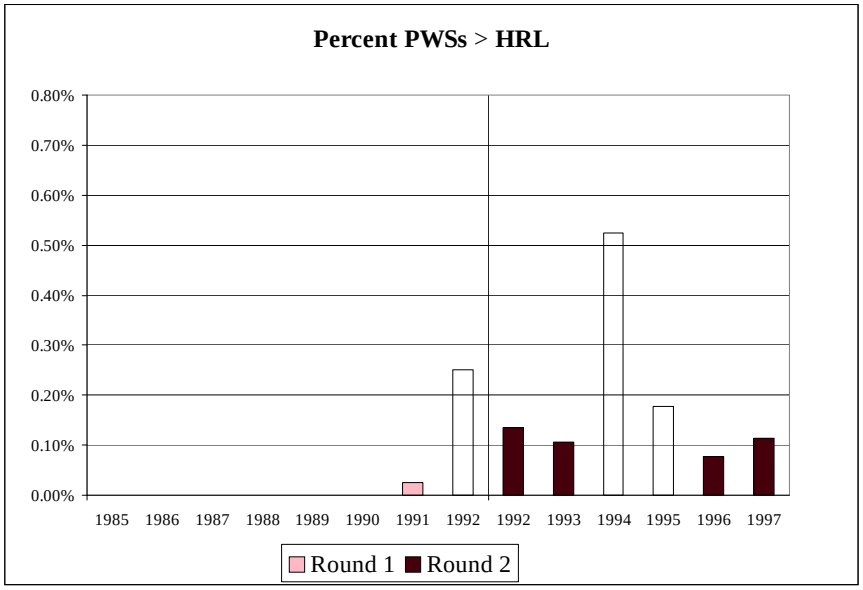


Temporal Patterns

Eight states (Alaska, Kentucky, Maryland, Minnesota, North Carolina, New Mexico, Ohio, and Washington) contributed 1,3-dichloropropene data to both the Round 1 and Round 2 cross-sections. While these states are not necessarily nationally representative, they enable a preliminary assessment of temporal trends in 1,3-dichloropropene occurrence. Figures 4-6 and 4-7 indicate that both detections and HRL exceedances began in 1991 and peaked in 1994, and that by far the state with the highest rate of detections, among the eight, was Minnesota.

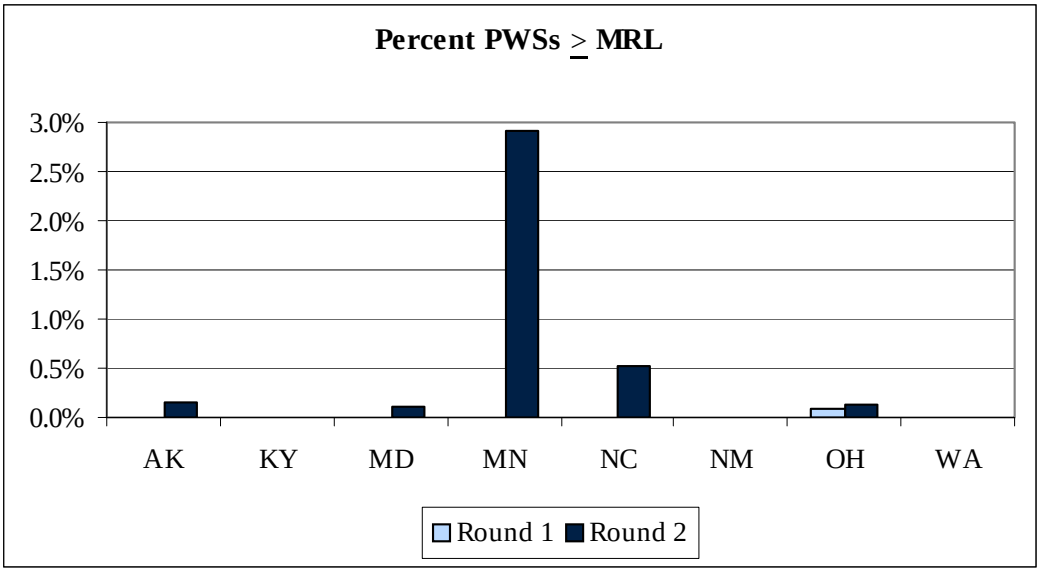
Figure 4-6 Annual Frequency of 1,3-Dichloropropene Detections (above) and HRL Exceedances (below), 1985 - 1997, in Select Cross-Section States

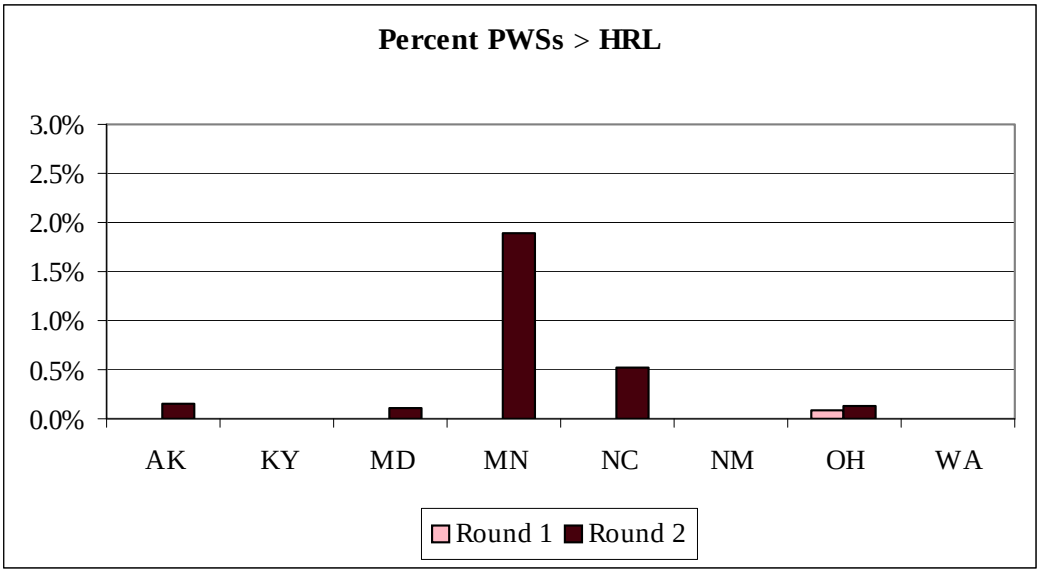




Note: Data are from AK, KY, MD, MN, NC, NM, OH, and WA.
Both Round 1 and Round 2 have data for 1992.
The HRL for 1,3-dichloropropene is 0.4 µg/L.

Figure 4-7 Distribution of 1,3-Dichloropropene Detections (above) and HRL Exceedances (below) Among Select Cross-Section States





4.3.2 UCMR 1 Monitoring

4.3.2.1 Data Sources and Methods

In 1999, EPA developed the UCMR 1 program in coordination with the CCL and the National Drinking Water Contaminant Occurrence Database to provide national occurrence information on unregulated contaminants. With the exception of transient non-community systems and systems that purchase 100% of their water, EPA required all large PWSs (systems serving more than 10,000 people), plus a statistically representative national sample of 800 small PWSs (systems serving 10,000 people or fewer) to conduct assessment monitoring. Approximately one-third of the participating small systems were scheduled to monitor for these contaminants during each calendar year from 2001 through 2003. Large systems could conduct 1 year of monitoring at any time during the 2001-2003 UCMR 1 period. EPA specified a quarterly monitoring schedule for surface water systems and a twice-a-year, 6-month interval monitoring schedule for ground water systems. Although UCMR 1 monitoring was conducted primarily between 2001 and 2003, some results from large systems were not collected and reported until as late as 2006.

The objective of the UCMR 1 sampling approach for small systems was to collect contaminant occurrence data from a statistically selected, nationally representative sample of small systems. The small system sample was stratified and population weighted and included some other sampling adjustments, such as allocating a selection of at least two systems from each state. Although 1,3-dichloropropene was not officially a UCMR 1 contaminant, EPA collected 1,3-dichloropropene data from UCMR 1 small system samples alongside the regular List 1 contaminants, using an appropriate analytical method that does not involve sodium sulfate or sodium thiosulfate. The surface water and ground water systems were selected to be representative of small systems nationwide

4.3.2.2 Results

A total of 3,719 samples from 796 systems were analyzed for *cis*- and *trans*-1,3-dichloropropene. Neither isomer was detected in any sample. The reporting limit for each isomer was 0.50 µg/L (Table 4-3).

Table 4-3 Summary UCMR 1 Occurrence Statistics for 1,3-Dichloropropene in Small Systems

Frequency Factors	UCMR Data - Small Systems		National System & Population Numbers[1]
Total Number of Samples	3,719		--
Percent of Samples with Detections	0.00%		--
99th Percentile Concentration (all samples)	< MRL		--
Health Reference Level (HRL)	0.4 µg/L		--
Minimum Reporting Level (MRL)	0.50 µg/L		--
99th Percentile Concentration of Detections	< MRL		--
Median Concentration of Detections	< MRL		--
Total Number of PWSs	796		60,414
Number of GW PWSs	589		56,072
Number of SW PWSs	207		4,342
Total Population	2,758,082		45,414,590
Population of GW PWSs	1,937,327		36,224,336
Population of SW PWSs	820,755		9,190,254
Occurrence by System	**Number**	**Percentage**	**National Extrapolation[2]**
PWSs (GW & SW) with Detections (≥ MRL)	0	0.00%	0
PWSs (GW & SW) > 1/2 HRL	0	0.00%	0
PWSs (GW & SW) > HRL	0	0.00%	0
Occurrence by Population Served			
Population Served by PWSs with Detections	0	0.00%	0
Population Served by PWSs > 1/2 HRL	0	0.00%	0
Population Served by PWSs > HRL	0	0.00%	0

1. Total PWS and population numbers are from EPA September 2004 Drinking Water Baseline Handbook, 4th edition.
2. National extrapolations are generated separately for each population-served size stratum and then added to yield the national estimate of GW PWSs with detections (and population served) and SW PWSs with detections (and population served). For intermediate calculations at the level of individual strata, see EPA's UCMR 1 Occurrence Report, entitled "The Analysis of Occurrence Data from the First Unregulated Contaminant Monitoring Regulation (UCMR 1) in Support of Regulatory Determinations for the Second Drinking Water Contaminant Candidate List."

Abbreviations:
PWS = Public Water Systems; GW = Ground Water; SW = Surface Water; N/A = Not Applicable; Total Number of Samples = the total number of samples on record for the contaminant; 99th Percentile Concentration = the concentration in the 99th percentile sample (out of either all samples or just samples with detections); Median Concentration of Detections = the concentration in the median sample (out of samples with detections); Total Number of PWSs = the total number of PWSs for which sampling results are available; Total Population Served = the total population served by PWSs for which sampling results are available; PWSs with detections, PWSs > ½HRL, or PWSs > HRL = PWSs with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark, respectively; Population Served by PWSs with detections, by PWSs >½HRL, or by PWSs >HRL = population served by PWSs with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark, respectively.

Notes:
-Small systems are those that serve 10,000 persons or fewer.
-Only results at or above the MRL were reported as detections. Concentrations below the MRL are considered non-detects.
-Due to differences between the ratio of GW and SW systems with monitoring results and the national ratio, extrapolated GW and SW figures might not add up to extrapolated totals.

4.4 Summary

Both a national random survey and a focused survey of ambient occurrences of 1,3-dichloropropene, conducted by the NAWQA program between 1991 and 2001, found no

detections of 1,3-dichloropropene at the reporting level of 0.2 µg/L. In addition, there were no occurrences at the method detection limits (0.024 µg/L for *cis*-1,3-dichloropropene and 0.026 µg/L for *trans*-1,3-dichloropropene) during the focused survey. No detections of either *cis*- or *trans*-1,3-dichloropropene were found at a reporting level of 0.2 µg/L in multiple investigations of urban and rural wells.

The UCM Round 1 and Round 2 data should be interpreted with caution, since some samples may have been compromised by interference with sample preservatives, detection limits were not uniform, and in many cases the methods used were not sensitive enough to detect concentrations as low as the HRL. For example, in both rounds, the most common detection level for 1,3-dichloropropene was 0.5 µg/L, as compared to the HRL of 0.4 µg/L. Nevertheless, the data appear to show a decline in the number of people exposed to ½ the HRL and the HRL between Round 1 (1988-1992) and Round 2 (1993-1997). The Round 1 estimate for exposure above the HRL was approximately 1.8 million people, compared to about 700,000 people in Round 2. Similarly, the estimated population exposed at greater than ½ the HRL in Round 1 was also 1.8 million people, as compared to the approximately 900,000 suggested by Round 2 data. The decline in the populations exposed to ½ the HRL and the HRL is supported by the ambient data for 1,3-dichloropropene that show no detections at reporting levels from 0.024 to 0.2 µg/L between 1991 and 2001.

UCMR 1 monitoring, conducted from 2001 to 2003 from UCMR 1 small systems nationwide, detected no *cis*- nor *trans*-1,3-dichloropropene in any sample using a reporting limit for each isomer of 0.50 µg/L.

5.0 EXPOSURE FROM MEDIA OTHER THAN WATER

5.1 Exposure from Food

5.1.1 Concentration in Non-Fish Food Items

1,3-Dichloropropene is a fumigant applied to soils before planting to control for nematodes. It is classified as a non-food use pesticide by the EPA, and, thus, does not have any food tolerances. Exposure through foods is not expected, as studies developed for its re-registration do not show residues of 1,3-dichloropropene in crops grown in treated soils (U.S. EPA, 1998c).

Only one study was identified that examined the concentration of 1,3-dichloropropene in food items. Daft (1989) analyzed 231 ready-to-eat foods for the U.S. Food and Drug Administration's Market Basket Survey, for 22 fumigants and industrial residues. 1,3-Dichloropropene was not detected in any food samples at a detection limit of 1 ppb.

5.1.2 Concentrations in Fish and Shellfish

Monitoring data regarding the presence of 1,3-dichloropropene in fish and shellfish were not located in the available literature. Information on 1,3-dichloropropene concentrations in surface waters to estimate concentrations that may bioconcentrate in fish tissues also was not located in the literature.

5.1.3 Intake of 1,3-Dichloropropene from Food

Non-Fish Food Dietary Intake

1,3-Dichloropropene was not detected in food samples in the United States, as reported by Daft (1989), and is not anticipated to be a typical route of exposure to 1,3-dichloropropene (U.S. EPA, 1998c). Thus, intake of 1,3-dichloropropene from non-fish food items is assumed, on average, to be zero.

A high-end, conservative estimate of dietary exposure to 1,3-dichloropropene may be made using a non-fish food concentration of one-half the detection limit reported in Daft (1989) of 1 ppb. This estimate assumes that 1,3-dichloropropene may exist in food items at concentrations below the 1 ppb detection limit. Assuming a concentration of 0.5 ppb (5×10^{-7} mg/kg) in non-fish food items, and an intake rate of 1.305 kg food/day (U.S. EPA, 1988), the total estimated daily intake of 1,3-dichloropropene for a 70 kg adult (U.S. EPA, 1988) is 9.3×10^{-9} mg/kg-day. For a 10-kg child, with an intake rate of 0.84 kg food/day (U.S. EPA, 1988), the total estimated daily intake of 1,3-dichloropropene in food is 4.2×10^{-8} mg/kg-day.

5.2 Exposure from Air

5.2.1 Concentration of 1,3-Dichloropropene in Air

1,3-Dichloropropene is not a widely occurring atmospheric pollutant (Shah and Heyerdahl, 1989), although it is a volatile compound and may enter into the atmosphere after its application to soils (Krijgsheld and Van der Gen, 1986). Concentration data for 1,3-dichloropropene in air have primarily been reported for workplaces, although several studies have measured ambient concentrations.

Ambient air samples analyzed for *cis*-1,3-dichloropropene were collected during the period of 1970-1987 from urban areas throughout the United States. The median urban atmospheric concentration of *cis*-1,3-dichloropropene in 148 samples was 0.0239 ppmV (parts per million by volume) (0.11 mg/m^3). Information on rural, suburban, source-dominated, or indoor air concentrations of *cis*- or *trans*-1,3-dichloropropene were not available from this study (Shah and Heyerdahl, 1989).

Ambient concentrations of 1,3-dichloropropene may be elevated near sources or in source-dominated areas. High ambient air concentrations of 1,3-dichloropropene were detected in 1990 near a fumigation area in California, prompting a four-year suspension of Telone II® use (California Department of Food and Agriculture, 1990).

Woodruff et al. (1998) reported ambient air concentrations of 1,3-dichloropropene based on a hazard ratio (estimated outdoor concentration divided by a benchmark concentration) for census tracts in the United States. Outdoor ambient air concentrations of hazardous air pollutants (HAPs) were estimated from stationary and mobile source emission data for 1990 using an atmospheric dispersion model (Assessment System for Population Exposure Nationwide [ASPEN]). Cancer and chronic non-cancer hazard ratios were calculated using a one-in-a million cancer risk and EPA's inhalation reference concentrations (RfC) as benchmark concentrations, as reported in Caldwell et al. (1998). The estimated median cancer hazard ratio of 1,3-dichloropropene for the 60,083 census tracts was between 1 and 2, corresponding to modeled ambient concentrations of 4.7×10^{-5} to 5.3×10^{-5} ppm (2.16×10^{-4} to 2.43×10^{-4} mg/m^3). Chronic toxicity hazard ratios were below 0.1 for all census tracts, with a median of approximately 0.003. This median ratio corresponds to an average modeled ambient concentration of 1.3×10^{-5} ppm (6×10^{-5} mg/m^3). In the revised, final report for this study, the mean concentration of 1,3-dichloropropene in ambient air for all census tracts was estimated as 1.2×10^{-5} ppm (5.6×10^{-6} mg/m^3) (SAIC, 1999). While the ambient concentrations simulated by this study are much lower than those reported by Shah and Heyerdahl (1989), Woodruff et al. (1998) note that modeled concentrations have a tendency to underestimate actual ambient HAP concentrations.

In a more recent study, Lee et al. (2002) used ambient 1,3-dichloropropene air data collected by the California Air Resources Board (CARB) in 1990, 1996, and 2000 to estimate airborne inhalation risks to California communities. In 2000, data were collected from two rural monitoring locations. The first monitoring location, denoted as 2000a, had high use of 1,3-

dichloropropene (mean ± SD = 2.7±13) and secondary use of methyl bromide; the second monitoring location, denoted as 2000b, had high use of methyl bromide and secondary use of 1,3-dichloropropene (mean ± SD = 0.2±0.59). Using non-cancer reference doses (RfDs)[1] from various agencies as benchmark concentrations, non-cancer hazard quotients (HQ) (intake divided by the reference dose) were calculated. 1,3-Dichloropropene had estimated HQs greater than one for both adults and children (≤12-years old) for subchronic exposures, using the 1990 data, as follows: for the 50th percentile of risk, the HQ was 1.6; for the 75th percentile of risk, the HQ was 3.5; and for the 95th percentile of risk, the HQ was 11.5. All other HQs (other subchronic, all chronic and acute) were less than one.

Lifetime cancer risks (intake multiplied by the PF) were estimated using cancer potency factors. Calculated lifetime cancer risks for 1,3-dichloropropene in 1990 reached or exceeded 1 x 10^{-6} for an estimated 25 to 50% of the population.

As mentioned above, 1,3-dichloropropene use permits were suspended in California in 1990 after high concentrations were found in community air. Accordingly, exposures and calculated non-cancer and cancer risks for 1,3-dichloropropene were reduced for the subsequent monitoring years (1996 and 2000), with the exception of the 95th percentile of non-cancer risk (adults and children) using the 2000a air monitoring data (HQ of 15.5).

5.2.2 Intake of 1,3-Dichloropropene from Air

Assuming an ambient concentration of 0.0239 ppmV (0.11 mg/m^3) (the median urban atmospheric concentration of *cis*-1,3-dichloropropene from the National Ambient Volatile Organic Compounds Database), a compilation of published and unpublished air monitoring data from 1970 for 148 samples collected from representative locations (Shah and Heyerdahl, 1989), and an inhalation rate of 20 m^3/day (U.S. EPA, 1988), the average estimated daily intake of 1,3-dichloropropene for a 70-kg adult is 3.15 x 10^{-2} mg/kg-day. The estimated average daily intake of 1,3-dichloropropene in air for a 10 kg child is 1.65 x 10^{-1} mg/kg-day, based on an inhalation rate of 15 m^3/day (U.S. EPA, 1988). Persons working in treated fields shortly after fumigant treatment may have slightly higher inhalation exposures than the general population.

5.3 Exposure from Soil

5.3.1 Concentration of 1,3-Dichloropropene in Soil

Agricultural uses of compounds containing 1,3-dichloropropene contribute to soil exposures. After application of 1,3-dichloropropene as a fumigant, soil concentrations of 1,3-dichloropropene are dependent upon its volatilization into soil air and the surrounding air, degradation, and movement with the soil water (Yon et al., 1991).

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[1]The authors state that the term "RfD" is used to indicate all non-cancer reference values cited from various sources, avoiding the use of multiple terms developed by various agencies, such as reference concentration, minimum risk level, or reference exposure level. Reference values that are shown in air concentration units of milligrams per cubic meter, rather than milligrams per kilogram body weight, are based on portal-of-entry effects.

Laboratory experiments and model simulations approximate that 2-77% of 1,3-dichloropropene volatilizes from the soil after subsurface injection (McKenry and Thomason, 1974; Leistra and Frissel, 1975; Basile, et al., 1986; Chen et al., 1995). Field studies report volatilization losses of 1,3-dichloropropene of up to 50% from upper soil layers, depending on soil type, soil moisture, and humidity (Yon et al., 1991). McKenry and Thomason (1974) found volatilization into soil air to be a major route of dilution of 1,3-dichloropropene in soil. A study conducted in Holland reported soil air concentrations of up to 1420 µg/m^3 immediately after soil injection (California State Water Resources Board, Toxic Substances Control Program, 1983). Eight to eleven days after injection, soil air concentrations had dropped to 0.2-11 µg/m^3 (Yon et al., 1991). Field and laboratory studies on 1,3-dichloropropene degradation approximate its half life in soil to range from 4-25 days (Van der Pas and Leistra, 1987; Van Dijk, 1974).

Despite its high volatility and degradation processes, Leistra (1970) and Williams (1968) reported 1,3-dichloropropene in soils several months after its application (Yang, 1986). Roberts and Stoydin (1976) found that 12 weeks after being applied to soil and stored in sealed containers approximately 18-19% of 1,3-dichloropropene remained in sandy loam soils. For medium loam soils, 10-22% of the 1,3-dichloropropene remained. After 20 weeks, sandy and medium loam soils contained 4-5% and 3-14% of the initial 1,3-dichloropropene, respectively (Yang, 1986).

Chung et al. (1999) reported 1,3-dichloropropene concentrations for surface soil (0-15 cm) samples from a farm in Florida after treatment with Telone II®. Application of 1,3-dichloropropene at 1.56 kg/ha resulted in initial soil concentrations of 16 µg/g. After 5 days, soil concentrations were reduced to 13 ug/g, and were not detected in surface soils after 10 days.

5.3.2 Intake of 1,3-Dichloropropene from Soil

Due to its rapid dissipation in soil, the general population is not likely to be exposed to 1,3-dichloropropene via soil, and intakes are typically expected to be zero. An estimate of maximum exposures to 1,3-dichloropropene from soil, occurring around the time of application, can be made based upon the maximum soil concentration reported by Chung et al. (1999) of 16 µg/g. The total daily intake of 1,3-dichloropropene from soil for a 70 kg adult, with a daily intake of 50 mg/day (U.S. EPA, 1997a) would be approximately 1.1 x 10^{-5} mg/kg-day. For a 10 kg child exposed to the same soil concentrations, and an intake rate of 100 mg/day (U.S. EPA, 1997a), the total daily intake would be approximately 1.6 x 10^{-4} mg/kg-day.

5.4 Other Residential Exposures

1,3-Dichloropropene is not a naturally occurring product (IARC, 1986). However, it is a chemical component of reclaimed asphalt pavement (RAP) as either one of several organic components of asphalt, or a chemical that has become associated with asphalt pavement (in the same manner as oil and brake dust) during its use. RAP poses the potential for environmental exposures when it is landfilled or stockpiled before being milled into new asphalt. Brantley and Townsend (1999) examined the leaching of 1,3-dichloropropene, among other chemicals, from RAP from six sites in Florida. Two sample sites contained RAP from specific milling projects,

whereas the remaining four sample stockpiles were from various RAP sources. Batch test results for 1,3-dichloropropene were below GC/MS detection limits of 1 µg/L. Column leaching tests, simulating leachate generated under both landfilling and rainfall conditions, also were below GC/MS detection limits of 1 µg/L. RAP is not anticipated to be a major route of environmental exposure to 1,3-dichloropropene. Intake of 1,3-dichloropropene from RAP is typically expected to be zero.

Additional data about the presence of 1,3-dichloropropene in other media that could be associated with potential residential exposures were not located in the available literature.

5.5 Occupational (Workplace) Exposures

5.5.1 Description of Industries and Workplaces

Exposures to 1,3-dichloropropene may occur for workers during its handling and application as a soil fumigant, or during its manufacture. The National Occupational Exposure Survey (NOES) conducted between 1981 and 1983 by the National Institute of Occupational Safety and Health (NIOSH), estimated that 1779 workers were potentially exposed to 1,3-dichloropropene. This survey did not report concentrations, frequency, or durations of exposures (NIOSH, 1989).

5.5.2 Types of Exposure (Inhalation, Dermal, Other)

Occupational exposures are most likely to occur by inhalation and dermal contact at workplaces where 1,3-dichloropropene and/or compounds containing 1,3-dichloropropene are produced or used as soil fumigants (ATSDR, 1994).

5.5.3 Concentrations of 1,3-Dichloropropene in the Work Environment

Several studies have reported exposures to 1,3-dichloropropene during its handling and application as a soil fumigant (Albrecht, 1987; Albrecht et al., 1986; Markovitz and Crosby, 1984; Nater and Gooskens, 1976; Osterloh et al., 1984, 1989a,b; Schenker and McCurdy, 1986; van Joost and Jong, 1988; Wang, 1984). Albrecht (1987) determined that workers applying Telone II® to pineapple fields in Hawaii were exposed to 1,3-dichloropropene at concentrations predominantly below 1 ppm (4.61 mg/m^3).

Monsanto Agricultural Products Company conducted laboratory studies that simulated the concentration of 1,3-dichloropropene that would occur in workplace air during its manufacture. Under simulated workplace conditions, 1,3-dichloropropene ranged from 0.4-4.0 ppm (1.84-18.43 mg/m^3) (Leiber and Berk, 1984).

Monitoring data pertaining to dermal exposures to 1,3-dichloropropene were not located in the available literature (ATSDR, 1994).

5.6 Summary

Concentration and estimated intake values for 1,3-dichloropropene in media other than water are summarized in the table below. Most exposure to 1,3-dichloropropene appears to occur through air.

Table 5-1 Concentration/Estimated Intake Values for 1,3-Dichloropropene in Media Other than Water

Parameter	Medium					
	Food[1]		Air[2]		Soil[3]	
	Adult	Child	Adult	Child	Adult	Child
Concentration in medium (based on available data, as discussed in Chapter 5)	Non-Fish (NF) average: 0 mg/kg Non-Fish (NF) high-end: 5×10^{-7} mg/kg		0.11 mg/m^3		16 mg/kg	
Estimated daily intake (mg/kg-day) (assuming 70 kg adult body weight and 10 kg child body weight)	NF: (average) 0 NF: (high-end) 9.3×10^{-9}	NF: (average) 0 NF: (high-end) 4.2×10^{-8}	3.15×10^{-2}	1.65×10^{-1}	1.1×10^{-5}	1.6×10^{-4}

1. Since food is not anticipated to be a typical route of exposure to 1,3-dichloropropene, the average intake of 1,3-dichloropropene from non-fish food items is assumed to be zero. Using a non-fish food concentration of one-half the detection limit of 1 ppb for food samples in the United States, as reported by Daft (1989), and an intake rate of 1.305 kg food/day for adults and an intake rate of 0.84 kg food/day for children.
2. Estimated using an ambient air concentration of 0.11 mg/m^3 (the median urban atmospheric concentration of *cis*-1,3-dichloropropene from the National Ambient Volatile Organic Compounds Database, Shah and Heyerdahl, 1989), and using standard rates of inhalation.
3. Estimated based on maximum soil concentration reported by Chung et al. (1999) of 16 µg/g, and adult daily intake of 50 mg/day and child daily intake rate of 100 mg/day.

6.0 TOXICOKINETICS

The toxicokinetics of 1,3-dichloropropene are similar in humans and in rodents. Inhalation and oral studies with both humans and animals have shown that 1,3-dichloropropene is absorbed rapidly, and in its major metabolic pathway, is conjugated with glutathione (GSH) via glutathione S-transferase (GST), and rapidly excreted in the urine as N-acetyl-(S-3-chloroprop-2-enyl) cysteine (3CNAC), the mercapturic acid metabolite (Fisher and Kilgore, 1988a; U.S. EPA, 2000e), accounting for up to 84% of the administered dose for the *cis*-isomer (Hutson et al., 1971; Climie et al., 1979). Urinary excretion was the predominant route of elimination during 48 hours after dosing, accounting for 51%–61% of the administered dose in rats and 63%–79% in mice (Dietz et al., 1984). Thus, the major metabolic pathway for 1,3-dichloropropene leads to its detoxification and excretion. In addition, it is unlikely to accumulate in the body. Some studies have found that epoxidation of 1,3-dichloropropene is a minor metabolic pathway. Formation of carbon dioxide from 1,3-dichloropropene also is another possible route of metabolism in rats and mice; Dietz et al. (1985) reported that up to 24% of the trans- isomer was recovered in expired air. Figure 6-1 presents the metabolic pathways for 1,3-dichloropropene, with the primary metabolic pathway of GSH conjugation shown below the box containing the 1,3-dichloropropene formula.

6.1 Absorption

Absorption data are available only for oral and inhalation exposure. No studies were located regarding absorption following dermal exposure in humans or animals.

Oral Exposure

No studies were located regarding absorption following oral exposure in humans. However, in F344 rats, Stott et al. (1998) demonstrated that the pharmacokinetics of 1,3-dichloropropene orally administered in a microencapsulated starch-sucrose shell are similar to that of neat 1,3-dichloropropene (i.e., 1,3-dichloropropene alone). Female rats were co-administered ^{13}C-1,3-dichloropropene and microencapsulated 1,3-dichloropropene (25 mg/kg each) suspended in corn oil, via gavage. Blood concentrations of total or *cis*- and *trans*- isomers of 1,3-dichloropropene in treated rats were measured at various intervals by gas chromatography/mass spectrometry (GC/MS). The absorption half life of neat 1,3-dichloropropene was 2.5 minutes for the *cis*-isomer and 2.7 minutes for the *trans*- isomer, while the absorption half life for encapsulated 1,3-dichloropropene was 1.3 minutes for the *cis*-isomer and 2.3 minutes for the *trans*- isomer.

Inhalation Exposure

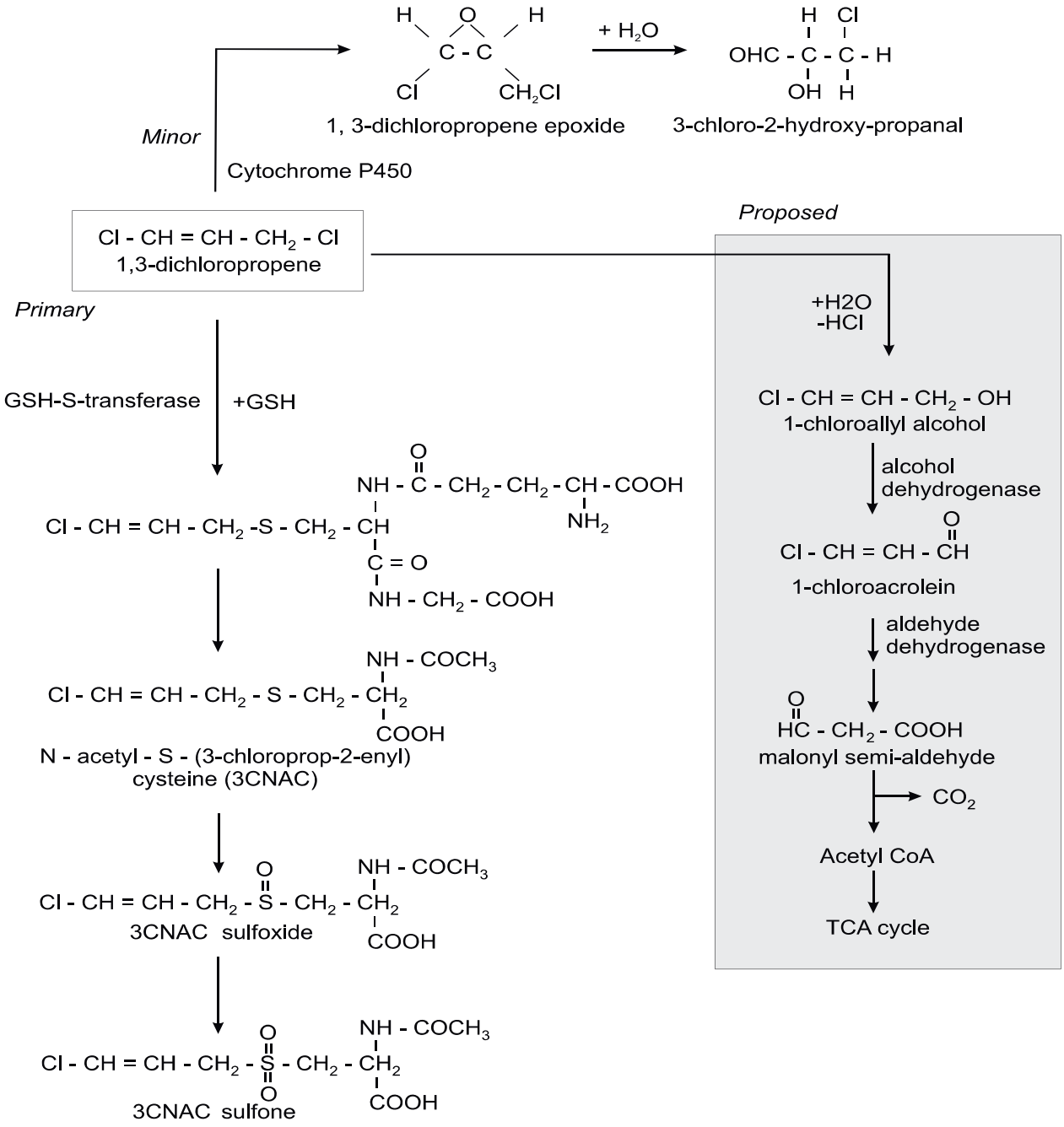
The detection of the N-acetyl-cysteine, a conjugate of 1,3-dichloropropene, in the urine of four men 24 hours after field application of Telone II® indicates that 1,3-dichloropropene is absorbed in humans after inhalation exposure (Osterloh et al., 1984).

Waechter et al. (1992) also reported the absorption of 1,3-dichloropropene by humans after inhalation exposure. Six male volunteers were exposed to 1 ppm commercial Telone II®

(50.6% *cis*-isomer, 45.2% *trans*-isomer) for 6 hours. The absorption of *cis*-1,3-dichloropropene was 72-80% while the absorption of *trans*-1,3-dichloropropene was 77-82%.

Stott and Kastl (1986) reported the absorption of 1,3-dichloropropene by rats after inhalation exposure. Male Fisher 344 (F344) rats were exposed to 30, 90, 300, or 900 ppm of technical grade 1,3-dichloropropene (mixture of *cis*- and *trans*-isomers) for 3 hours. The uptake was 82, 65, 66, or 62%, respectively. A decrease in the respiratory rate was observed in rats exposed to 90 ppm or more. Saturation of metabolism for 1,3-dichloropropene was observed at 300 ppm or more, which could account for the decrease in uptake at these concentrations.

Figure 6-1 Metabolic Pathways for 1,3-Dichloropropene



Sources: Waechter and Kastl (1988); Schneider et al. (1998a)

6.2 Distribution

Data are available only for distribution in animals following oral exposure. No studies were located regarding distribution following oral, inhalation, or dermal exposure in humans.

In rats and mice after oral administration, Deitz et al. (1985) reported that 1,3-dichloropropene is distributed primarily to the forestomach, glandular stomach, kidney, liver, and bladder, as compared to the fat, skin, and blood. Male F344 rats and B6C3F1 mice were administered one single oral dose of ^{14}C-1,3-dichloropropene (l or 50 mg/kg to rats and 1 or 100 mg/kg to mice). Forty-eight hours after administration, in the 1-mg/kg dose group, the forestomach and bladder had the highest ^{14}C-activities in both species, followed by the liver, kidney, and glandular stomach. ^{14}C-activity in the remaining tissues was much less. At the high dose, the forestomach and kidney had the highest ^{14}C-activities in both species. In rats, these were followed by the glandular stomach, liver, and bladder; in mice they were followed by the liver, fat, bladder, and glandular stomach. Due to the rapid metabolism and excretion of 1,3-dichloropropene, the ^{14}C-activities measured 48 hours after the single doses actually represent metabolized 1,3-dichloropropene rather than the parent compound (Deitz et al., 1985).

Analysis of the distribution of radioactivity 48 hours after gavage administration of ^{14}C-*cis*/*trans*- 1,3-dichloropropene (not specified whether a *cis*/*trans* mixture or isomers were tested separately) to rats revealed essentially equal distribution of 1,3-dichloropropene or its metabolites to most organs and tissues (Waechter and Kastl, 1988). The highest concentrations of radioactivity were found in the nonglandular stomach and the urinary bladder. Lower concentrations of radioactivity were also found in blood, bone, brain, fat, heart, kidney, liver, lung, skeletal muscle, skin, spleen, ovaries, and testes.

6.3 Metabolism

Overview of Metabolic Pathways

Studies have shown that 1,3-dichloropropene is primarily metabolized by GSH conjugation after inhalation or oral exposures in animals and humans (illustrated as the "primary" pathway in Figure 6-1) (Climie et al., 1979; Osterloh et al., 1984; Deitz et al., 1985; Fisher and Kilgore, 1989; Waechter et al., 1992). Orally administered 1,3-dichloropropene results in the metabolism of 1,3-dichloropropene to 3CNAC. Although the major metabolic pathway of 1,3-dichloropropene is conjugation by GSH, Schneider et al. (1998a) found that epoxidation of 1,3-dichloropropene is a minor metabolic pathway in mouse liver at doses equal to or exceeding the reported LD_{50} of this compound in mice (illustrated as the "minor" pathway in Figure 6-1). The two isomers of 1,3-dichloropropene appear to be metabolized at different rates. Metabolism of 1,3-dichloropropene by GSH conjugation appears to occur in the nasal tissue, kidney, and liver, after inhalation exposure in rats and primarily in the forestomach, glandular stomach, and liver, after oral exposure in rats and mice (Deitz et al., 1982; Deitz et al., 1985; Stott and Kastl, 1986). In addition, an alternate pathway occurs in which bacteria biodegrade 1,3-dichloropropene in soil (Belser and Castro, 1971) (illustrated as the "proposed" pathway in Figure 6-1).

Studies of 1,3-Dichloropropene Metabolism in Humans

For inhalation exposures, Osterloh et al. (1984) reported the detection of the N-acetyl-cysteine (3CNAC) metabolite of *cis*-1,3-dichloropropene in the urine of four men occupationally exposed to Telone II®, indicating that glutathione conjugation is a metabolic pathway in humans. This metabolite was the major urinary metabolite, and a significant correlation was observed between exposure levels of 1,3-dichloropropene and excretion of the metabolite. Similar findings were reported by Waechter et al. (1992) for humans after inhalation exposure to Telone II®.

Animal Studies of 1,3-Dichloropropene Metabolism

Fisher and Kilgore (1989) reported that 1,3-dichloropropene was rapidly metabolized to 3CNAC in rats after inhalation exposure to Telone II®. Climie et al. (1979) reported that following the oral administration of ^{14}C-labeled *cis*-1,3-dichloropropene to rats, urine collected for 24 hours yielded 82-84% of the radioactivity as 3CNAC. Similarly, Deitz et al. (1985) reported that after oral administration of *cis*- and *trans*-1,3-dichloropropene to male F344 rats and B6C3F1 mice, the major metabolites in urine were 3CNAC and its sulfone derivative in both species.

Plateau blood levels of the *cis*- and *trans*- isomers were 0.085±0.024 and 0.12±0.03 μg/mL, respectively, in rats exposed to 30 ppm Telone II® for 1 hour, and 0.2±0.04 and 0.26±0.03 μg/mL, respectively, in rats exposed to 90 ppm Telone II® for 1 hour. Plateau blood levels reached after 2 to 3 hours in rats exposed to 300 ppm were 0.89±0.2 and 1.87±0.27 μg/mL for the *cis*- and *trans*- isomers, respectively (Stott and Kastl, 1986). *In vitro* studies using a rat liver enzyme preparation revealed that the *cis*-isomer was metabolized four to five times faster than the *trans*- isomer (Climie et al., 1979).

Metabolism of 1,3-dichloropropene by GSH conjugation appears to occur in the nasal tissue, kidney, and liver, after inhalation exposure in rats and primarily in the forestomach, glandular stomach, and liver, after oral exposure in rats and mice (Deitz et al., 1982; Deitz et al., 1985; Stott and Kastl, 1986). Stott and Kastl (1986) reported that nonprotein sulfhydryl glutathione (used in the GSH conjugation of 1,3-dichloropropene) levels decreased in the nasal tissues, kidney, and liver of rats after inhalation exposure to Telone II®. In a study to determine the effect of 1,3-dichloropropene on glutathione levels in rodents, Deitz et al. (1982) observed the decrease of glutathione in the forestomach, glandular stomach, liver, and kidney in mice following a single gavage administration of 50 mg/kg *cis*- and *trans*-1,3-dichloropropene. In a subsequent study, Deitz et al. (1985) reported that after single gavage doses of 0, 1, 5, 25, 50, or 100 mg/kg ^{14}C-1,3-dichloropropene to male F344 rats and B6C3F1 mice, significant depression of glutathione levels occurred in the forestomach and the glandular stomach of rats and mice at the 25 to 100 mg/kg doses. Depression of glutathione levels also occurred in the liver for both species, but it was less than that observed in the forestomach and glandular stomach. No statistically-significant changes in glutathione levels were observed in the kidney or urinary bladder of either rats or mice (Deitz et al., 1985).

Although the major metabolic pathway of 1,3-dichloropropene is conjugation by GSH, Schneider et al. (1998a) found that epoxidation of 1,3-dichloropropene is a minor metabolic

pathway ("minor" pathway in Figure 6-1) in mouse liver at doses equal to or exceeding the reported LD_{50} of this compound in mice. Schneider et al. (1998a) administered either 350 mg/kg of individual isomers or 700 mg/kg of combined *cis*/*trans*-1,3-dichloropropene to male Swiss-Webster mice by intraperitoneal injection and then measured epoxide formation in the liver at various times up to 150 minutes later. The GC/MS measurements revealed that 1,3-dichloropropene concentrations in the liver peaked about 10 minutes after treatment and then decayed with apparent first-order kinetics with half-lives of 36 minutes for the *cis*-isomer and 50 minutes for the *trans*- isomer. Epoxide concentrations were approximately two orders of magnitude lower than the parent compound at less toxic doses of 100 or 700 mg/kg. Bartels et al. (2000) followed up this experiment to examine the potential for epoxidation of 1,3-dichloropropene in rats and mice at doses lower than the LD_{50} levels. Only very low levels of the epoxidation metabolite (1,3-dichloropropene oxide) were seen following intraperitoneal administration of 700 mg/kg of 1,3-dichloropropene; acute toxicity also was noted at this level. Oral administration of 100 mg/kg resulted in no formation of the metabolite. In *in vitro* experiments, Schneider et al. (1998a) demonstrated that conjugation of 1,3-dichloropropene with GSH decreases epoxide formation in mouse liver.

6.4 Excretion

Excretion data are available only for oral and inhalation exposure. No studies were located regarding excretion following dermal exposure in humans or animals.

Oral Exposure

Studies have shown that following oral exposure, 1,3-dichloropropene is excreted as the mercapturic acid primarily in the urine, with lesser amounts being excreted in feces and expired air in humans and animals (Hutson et al., 1971; Climie et al., 1979; Deitz et al., 1984). Both Hutson et al. (1971) and Climie et al. (1979) reported the significant recovery of ^{14}C-labeled 1,3-dichloropropene in urine from rats after oral exposure. In both studies, 82-84% of the administered *cis*-isomer was recovered as the mercapturic acid conjugate of 1,3-dichloropropene in a 24-hour collection of urine. However, only 55-60% of the *trans*- isomer was recovered as the mercapturic acid conjugate in the urine (Hutson et al., 1971). A significant portion of the *trans*- isomer was recovered as $^{14}CO_2$ (22-25%). A smaller percentage of each isomer was recovered in the feces: 2-3% of the *cis*-isomer and 2% of the *trans*- isomer. Less than 2% of either compound remained in the carcass after 4 days (Hutson et al., 1971). Similar results were reported by Deitz et al. (1984). Following the oral administration of ^{14}C-labeled 1,3-dichloropropene to male rats and mice, 51-61% and 63-79%, respectively, of the administered dose were recovered in the urine. Feces and expired carbon dioxide contained about 18% and 5%, respectively of the administered dose in rats, and 15% and 14%, respectively, of the administered dose in mice. Only 2-6% of the original dose remained in the carcass at the end of 48 hours (Deitz et al., 1984).

Inhalation Exposure

Following inhalation exposures, urinary excretion of 1,3-dichloropropene occurs in two phases: a rapid initial phase followed by a slower elimination phase (Stott and Kastl, 1986; van Welie et al., 1991; Waechter et al., 1992). The initial phase of elimination primarily represents the redistribution of 1,3-dichloropropene from blood to tissues while the second phase of elimination is determined by the rate of metabolism (Stott and Kastl, 1986). In addition, there is a dose-dependent relationship between exposure to 1,3-dichloropropene and excretion of the urinary mercapturic acids, *cis*- and *trans*-3CNAC (Fisher and Kilgore, 1988b; Osterloh et al., 1989a; Osterloh et al., 1989b; van Welie et al., 1991).

In a human study by Waechter et al. (1992), the urinary excretion of 1,3-dichloropropene was an apparent first-order process at an inhalation exposure of 4.54 mg/m^3 for 6 hours. The elimination half-lives for the initial phase were 4.2±0.8 hours (*cis*-isomer) and 3.2±0.8 hours (*trans*- isomer), while the half lives for the terminal phase were 12.3±2.4 hours (*cis*-isomer) and 17.1±6 hours (*trans*- isomer). Similar results were reported by van Welie et al. (1991). Twelve male workers exposed to 0.3 to 18.9 mg/m^3 *cis*- and *trans*-l ,3-D during 1 to 11 hour shifts excreted 3CNAC in their urine in a pattern that followed first order elimination kinetics. The elimination half-lives of 3CNAC were 5.0±1.2 hours for the *cis*-isomer and 4.7±1.3 hours for the *trans*- isomer (van Welie et al, 1991). Van Welie et al. (1991) also reported that a dose-response relationship exists between respiratory occupational exposure to 1,3-dichloropropene and excretion of the *cis*- and *trans*-3CNAC. They observed that *cis*-1,3-dichloropropene yielded three times more 3CNAC than *trans*-l,3-D, which is consistent with differences in the rate of metabolism between the isomers. In an evaluation similar in design to van Welie et al. (1991), Osterloh et al. (1989a) concluded that excretion of urinary 3CNAC in humans is correlated with 1,3-dichloropropene exposures.

Stott and Kastl (1986) exposed F344 male rats to 136, 409, 1363, and 4086 mg/m^3 1,3-dichloropropene for 3 hours. A pronounced rapid elimination phase was observed in all rats exposed to 1363 mg/m^3 or less. In this initial phase, the half life of *cis*-1,3-dichloropropene was calculated at 3-5 minutes for animals exposed to $\leq$1363 mg/m^3 and increased to more than 14 minutes for animals exposed to 4086 mg/m^3. Rats exposed to *trans*-1,3-dichloropropene had a longer first phase elimination half-life averaging 6 minutes for those exposed to 1363 mg/m^3 or less and 27 minutes in those exposed to 4086 mg/m^3. Following this first phase, both *cis*- and *trans*-1,3-dichloropropene exhibited a second slower and longer phase of elimination in rats exposed to 1363 mg/m^3 or 4086 mg/m^3, roughly 25 to 43 minutes, independent of isomer or exposure concentrations.

In a study to evaluate the dose-dependency of GSH metabolism, Fisher and Kilgore (1988b) exposed male Sprague-Dawley rats to technical grade 1,3-dichloropropene vapors for 1 hour at concentrations up to 789 ppm (3582 mg/m^3). The 24-hour urine collection (to measure *cis*-3CNAC) indicated a concentration-dependent increase of *cis*-3CNAC in the urine of rats exposed from 0 to 284 ppm (1289 mg/m^3) 1,3-dichloropropene.

7.0 HAZARD IDENTIFICATION

The purpose of Section 7.0 is to assess and summarize the health hazards caused by exposure to 1,3-dichloropropene. Included in this section are summaries of relevant toxicological and epidemiological studies, other key data important for understanding health effects, information on potentially sensitive subpopulations, and an evaluation of the evidence for carcinogenicity. Section 7.0 concludes with syntheses of the non-carcinogenic and carcinogenic health effects of 1,3-dichloropropene.

7.1 Human Effects

This section will summarize the health effects observed in humans following exposure to 1,3-dichloropropene. Case reports, both for the general population, as well as for workers, are presented in Section 7.1.1. Several long-term studies, in both the general population and in occupational settings, are presented in Section 7.1.2.

7.1.1 Short-Term Studies

No short-term human studies were identified for 1,3-dichloropropene. However several case reports documenting the health effects in humans following acute and subacute exposures to 1,3-dichloropropene were identified and are presented.

Intentional and Accidental Acute Ingestion

Hernandez et al. (1994) presented the details of a case report in which a young man died 40 hours after accidentally ingesting 1,3-dichloropropene. A 27-year-old male that accidentally drank an unknown quantity of dichloropropene presented himself to the emergency department 2 hours after ingestion with acute gastrointestinal distress, sweating, tachypnea (rapid, shallow respiratory rate), tachycardia (rapid heart rate), hypovolemic disturbance, and lividity (blackish-bluish discoloration) on both legs. Over the next several hours, the patient developed adult respiratory distress syndrome, as well as hemodynamic, gastrointestinal, liver, and kidney deterioration. Death from multiple organ failure occurred 38 hours following admission to the hospital. Toxicological identification of the ingested compound by GC/MS confirmed that Telone II (*cis*- and *trans*-l,3-D) was the cause of death (Hernandez et al., 1994).

Acute and Short-Term Inhalation Exposure

About 80 people were exposed to 1,3-dichloropropene vapors after a truck accident. Signs and symptoms included headaches, irritation of mucous membranes, dizziness, and chest discomfort, and three individuals became unconscious. Forty-one exposed individuals were tested; 11 had slightly elevated serum glutamic oxaloacetic transaminase and/or glutamic pyruvic transaminase values. Values returned to normal in 8 people after 48 to72 hours, but some still had slightly elevated serum glutamic oxaloacetic transaminase (Hayes, 1982).

Humans exposed to 1,3-dichloropropene (not otherwise specified) after a tank truck spill complained of mucous membrane irritation, chest pain, coughing, and breathing difficulties (Flessel et al., 1978; Markovitz and Crosby, 1984).

Markovitz and Crosby (1984) described a case report in which 9 firefighters were exposed to 1,3-dichloropropene during the cleanup of a tanker truck. Initial signs and symptoms included headache, nausea, and breathing difficulties. Six years following the incident, two of the firemen developed histiocytic lymphoma and died. As of the date of the publication, none of the other men had developed malignancies (Markovitz and Crosby, 1984).

A case report identified a farmer in good health who developed pain in the right ear, nasal mucosa, and pharynx after applying 1,3-dichloropropene to his fields for 30 days. Hospital examination revealed a red and painful external ear, hyperemia, superficial ulcerations of the nasal mucosa, and inflammation of the pharynx. The hose containing 1,3-dichloropropene had a small leak which sprayed the chemical near his face. Over the following year, the man developed leukemia; subsequently, he died of pneumonia (Markovitz and Crosby, 1984). In another case of an accidental exposure of a farmer to 1,3-dichloropropene, Corazza et al. (2003) described immediate contact dermatitis in all the body areas that had come into direct contact with the chemical. Three weeks later, even without direct contact with the chemical, the individual again reported an acute allergic contact dermatitis, indicating the sensitizing potential of 1,3-dichloropropene. Another report of skin effects that persisted for several days included symptoms such as a severe burning feeling, reddening of the skin, edema, and blisters (Meulenbelt and de Vries, 1997). Skin sensitization to l,3-D was noted in a 26-year-old male exposed during the manufacture of the soil fumigant DD-92®. Skin contact produced an itchy rash in this subject (Van Joost and de Jong, 1988).

Bousema et al. (1991) reported the findings of a case report in which a male process operator at a pesticide plant had developed an acute bullous dermatitis on his feet following dermal exposure to DD-95® (a nematocide containing 95% 1,3-dichloropropene). The operator had soiled his shoes with DD-95® about 10 days before he developed the dermatitis in August 1988 and again 1 day before the dermatitis reappeared in September 1989. The patient was patch-tested with DD-95® at 2%, 1 %, 0.5%, 0.1 %, 0.03%, and 0.005% and responded positively to all concentrations up to three days later. A control group of 20 volunteers was similarly tested at a concentration of 0.05% DD-95®, but none showed any positive symptoms. The authors suggest that there is a small but distinct subgroup of individuals working with pesticides who develop an allergic reaction upon dermal contact with DD-95® and other pesticides containing mainly 1,3-dichloropropene (Bousema et al., 1991).

7.1.2 Long-Term Studies

Long-term studies include studies of general population exposures to airborne agricultural pesticides, and occupational studies of workers involved in spraying soil fumigants containing telone.

Epidemiological Studies

Two studies that focused on community exposures to pesticides in California were identified. One study (Clary and Ritz, 2003) examined the incidence of pancreatic cancer mortality and its relationship to the use of pesticides in high pesticide use areas. Deaths from pancreatic cancer from 1989 to 1996 were compared with a random sample of non-cancer deaths

in three agricultural counties. Among long-term residents, pancreatic cancer mortality was elevated for areas with the highest use of four pesticides from 1972 to 1989, including 1,3-dichloropropene. The analysis showed an increased risk for those residents who had lived in one of the three counties for at least 20 years and whose residence at the time of death was in areas of the highest quartile of 1,3-dichloropropene application in comparison to the lower three quartiles. Several other pesticides exhibited similar size risk increases, but none of the 95% confidence intervals excluded the null value. In addition, only 1,3-dichloropropene and dieldrin had been classified by the EPA as either possible, probable, or known human carcinogens. The authors noted that dieldrin was removed from the market in 1987, while 1,3-dichloropropene is still in use.

A second study (Lee et al., 2002) calculated inhalation risks due to airborne agricultural pesticides using ambient air data. Exposure estimates greater than or equal to non-cancer reference values occurred for 50% of the exposed population for several exposures, including 1,3-dichloropropene subchronic exposures (using 1990 data and previously established toxicity values). Lifetime cancer risks of one-in-a-million or greater were estimated for 50% of the exposed population for 1,3-dichloropropene.

Nater and Gooskens (1976) reported the results of a study using patch tests on previously exposed workers to determine whether occupational dermatitis resulting from direct contact with 1,3-dichloropropene was due to an allergic or a primary irritant reaction. Three cases of occupational skin contact with a common nematocide soil fumigant, D-D® mixture, were examined. The mixture contained 1,3-dichloropropene, 1,2-dichloropropene, and epichlorohydrin. Patient 1 received two l-week exposures l year apart and developed itching erythematous rash. Patient 2 developed the rash after a single exposure. Patient 3 was employed spraying pesticides on a daily basis for 10 years between September and January. After 7 years, he developed dermatitis on his arms, face, and ears, which subsided upon avoidance of the nematocide. Patch testing was performed on the three subjects with D-D®, other preparations of 1,3-dichloropropene, and 1,2-dichloropropene at 1% in acetone (a concentration producing no reaction in five volunteers), and with the 20 standard allergens of the International Contact Dermatitis Research Group. Patch testing of all 1,3-dichloropropene preparations produced allergic reactions in patient 1 (with spongiosis, lymphocyte infiltration, and migration), but not in patients 2 or 3. No patients reacted positively to 1,2-dichloropropene. The results indicate that 1,3-dichloropropene is a primary irritant (as demonstrated by the occupational dermatitis in patients 2 and 3), but also that 1,3-dichloropropene can cause a contact allergic reaction, as demonstrated by the positive patch test in patient 1 (Nater and Gooskens, 1976).

Brouwer et al. (1991) performed a prospective study to examine the liver and kidney effects of subchronic exposure to 1,3-dichloropropene in employees of the Dutch flower bulb industry. Venous blood and spot urine samples were collected from the 14 commercial applicators who used 1,3-dichloropropene in soil fumigation operations at the start of the bulb culture season in July and after the season ended in October. Possible hepatotoxicity was assessed by determining serum activities of alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, γ-glutamyltranspeptidase, alkaline phosphatase, and total serum bilirubin. Kidney function was evaluated by measuring serum β_2-microglobulin and

creatinine, urinary albumin, retinal binding protein, β-galactosidase, and alanine aminopeptidase. Blood GSH concentration and erythrocyte GST activity were determined to evaluate the effect on blood GSH conjugation capacity.

Data from the environmental monitoring study indicated that the fumigators were exposed to time weighted average (TWA) concentrations of 1.9-18.9 mg/m^3 1,3-dichloropropene. The Dutch standard of 5 mg/m^3 was exceeded about 30% of the exposure time. The only parameter of liver function to be significantly affected by 1,3-dichloropropene was a significant decrease in serum total bilirubin concentration. For kidney function, urine albumin and retinol binding protein concentrations were significantly increased and serum creatinine concentration was significantly decreased by the end of the spraying season. Blood GSH concentration and erythrocyte GST activity also were significantly decreased. The authors concluded that a subclinical nephrotoxic effect due to exposure to 1,3-dichloropropene over a spraying season could not be ruled out. The authors also mentioned that changes in serum chemistry and urine analysis parameters may have been adaptive responses to detoxification and elimination of 1,3-dichloropropene. The serum chemistry and urine analysis parameters of the exposed workers were not subsequently evaluated to assess whether the observed alterations returned to normal values. The decrease in GSH and GST values indicate that GSH conjugation is involved in 1,3-dichloropropene elimination and likely detoxification (Brouwer et al., 1991).

Verplanke et al. (2000) examined 13 commercial application workers exposed to *cis*-dichloropropene for 117 days, and 22 matched control workers. The geometric mean exposure (time-weighted average) of the workers was 2.7 mg/m^3 with a range of 0.1 to 9.5 mg/m^3. Biological monitoring data were collected to investigate kidney and liver function before, during, and after the fumigation season. No differences were found between the values of the renal effect variables or the liver variables except for a lower urinary ratio of 6-β-hydroxycortisol to free cortisol used to monitor hepatic cytochrome P-450IIIA isoenzyme activity) in the exposed group (however, this parameter was not considered to be related to the exposures).

7.2 Animal Studies

This section addresses the health effects observed in animal studies following exposure to 1,3-dichloropropene. Animal studies focusing on acute toxicity, subchronic toxicity, neurotoxicity, developmental/reproductive toxicity, chronic toxicity, and carcinogenicity are summarized in the following sections.

7.2.1 Acute Toxicity (Oral, Dermal, Inhalation)

Acute toxicity studies generally examine one-time or very short-term exposures. Acute oral and dermal animal studies often determine the lethal dose for 50% of the animals (LD_{50}), while acute inhalation animal studies determine the lethal air concentration for 50% of the animals (LC_{50}).

Oral Exposure

Several studies have reported oral LD_{50} values for various formulations of 1,3-dichloropropene in the Fischer 344 rat. The oral LD_{50} for M-3993 was 713 mg/kg in males and 470 mg/kg in females (Lichy and Olson, 1975). The LD_{50} for Telone C-17® was 519 mg/kg in males and 304 mg/kg in females (Mizell et al., 1988a). The LD_{50} for Telone II was 300 mg/kg in males and 224 mg/kg in females (Jeffrey et al., 1987). For the *cis*-isomer of 1,3-dichloropropene, LD_{50} values of 121 mg/kg, 126 mg/kg, and 117 mg/kg were determined for male and female rats combined, male rats, and female rats, respectively (Jones, 1988a).

In a rat LD_{50} study, a single oral administration of Telone II® induced dose-related respiratory effects, which included lung congestion (75 mg/kg/day) and lung hemorrhage (250 mg/kg/day) (Jones and Collier, 1986a). Abnormally red and hemorrhagic lungs were observed in rats that received a single oral dose (110 mg/kg/day) of *cis*-1,3-dichloropropene in an LD_{50} study (Jones, 1988a).

1,3-Dichloropropene may cause gastrointestinal effects following oral exposure. Histological examination of the stomach revealed several raised white patches on the mucosal surface of rats that received a single gavage dose of 75 mg/kg Telone II®a, a commercial formulation of 1,3-dichloropropene (Jones and Collier, 1986a). Rats that received a single oral dose of 110 mg/kg *cis*-1,3-dichloropropene or more developed ulcerations of the glandular stomach and hemorrhage of the small intestine (Jones, 1988a). Mizell et al. (1988a) reported that a single gavage dose of 100 mg/kg Telone C-17® induced hyperkeratosis of the nonglandular stomach in the rat.

Inhalation Exposure

LC_{50} values for inhalation exposure to 1,3-dichloropropene have been determined in rats (Cracknell et al., 1987; Streeter et al., 1987; Streeter and Lomax, 1988). The LC_{50} for female rats exposed to Telone II®a for 4 hours was 904 ppm (Streeter et al., 1987). The LC_{50} for male rats was 855-1035 ppm for 1,3-dichloropropene. Telone C-17® appears to be more toxic than Telone II®a; the LC_{50} for rats after a 1-hour exposure to Telone C-17® was 253 ppm (Streeter and Lomax, 1988). Six of 10 rats died after a 4-hour exposure to 676 ppm Telone II®a. In the same study, no rats died after a 4-hour exposure to 595 ppm or less of Telone II®a (Cracknell et al., 1987).

Acute exposures of rats to various formulations of 1,3-dichloropropene induce respiratory effects (Cracknell et al., 1987; Streeter et al., 1987; Streeter and Lomax, 1988). Gross pathological examination revealed atelectasis (partial lung collapse), emphysema, and/or edema in rats exposed to 206 ppm of Telone C-17® for 1 hour. Atelectasis was still present in animals surviving the 2-week observation period (Streeter and Lomax, 1988). As noted for death, Telone C-17® also appears to be more toxic than Telone II®a after acute exposure. No respiratory effects were noted in rats after a 4-hour exposure to 582 ppm of Telone II®a; however, swollen lungs were observed in rats after a 4-hour exposure to 595 ppm (Cracknell et al., 1987). In the same study, rats exposed to 676 ppm Telone II® had lung congestion, tracheal congestion, and fluid in the thoracic cavity (Cracknell et al., 1987). Streeter et al. (1987) observed multifocal lung hemorrhage in rats exposed for 4 hours to 1035 ppm of Telone II®a.

Rabbits exposed by inhalation to 300 ppm Telone II® during gestation days 6-18 developed ataxia and died. The cause of death was not determined, although lung congestion and edema were noted on necropsy (Kloes et al., 1983).

Dermal Exposure

The acute dermal LD_{50} values for *cis*-1,3-dichloropropene were 794 mg/kg, 758 mg/kg, and 841 mg/kg in male and female rats combined, male rats, and female rats, respectively (Jones, 1988b). The acute dermal LD_{50} for Telone II®a in rats was 1200 mg/kg (Jones and Collier, 1986b). The acute dermal LD_{50} in rabbits for M-3993 was 713 mg/kg in males and 407 mg/kg for females (Lichy and Olson, 1975). In a similar study, the dermal LD_{50} for Telone II®a in rabbits was 333 mg/kg (Jeffrey et al., 1987b). Six of 10 rabbits died or were submitted to pathology in a moribund condition within 4 days after receiving a dermal application of 500 mg/kg Telone C-17® (Mizell et at. 1988b).

Gross necropsy revealed abnormally red lungs in rats that died after dermal application of 800 mg/kg *cis*-1,3-dichloropropene (Jones, 1988b). Rats that received a single dermal application of 500 mg/kg Telone II®a developed lung congestion, and at 800 mg/kg, lung hemorrhage (Jones and Collier, 1986b).

Acute dermal application of dilute or full strength Telone II®a or M-3993 (doses ranging from 0.1 mL to 0.5 mL of a 10% solution) rapidly produced erythema (redness of the skin) and edema in rats, rabbits, and guinea pigs (Lichy and Olson, 1975; Carreon and Wall, 1983; Jones and Collier, 1986b; Jeffrey, 1987b; Mizell, 1988). At concentrations of 200 mg/kg Telone II® or more, necrosis and subcutaneous/skeletal muscle were observed in rabbits and in rats (Jones and Collier, 1986b; Mizell, 1988; Mizell et al., 1988b).

Severe conjunctival irritation, corneal injury, and corneal opacity were observed after instillation of 0.1 mL Telone II®a or M-3993 into the conjunctival sacs of rabbits (Jeffrey, 1987a; Lichy and Olsen, 1975).

7.2.2 Short-Term Studies

No short term studies were identified for 1,3-dichloropropene.

7.2.3 Subchronic Studies

Oral and inhalation subchronic studies in animals are available. No subchronic studies were identified for dermal exposure in animals for 1,3-dichloropropene.

Oral Exposure

Telone II® (96% 1,3-dichloropropene) was administered to Fischer 344 rats (10/sex/group) at dietary levels of 0, 5, 15, 50, or 100 mg/kg/day for 13 weeks. No clinical signs of toxicity were noted at any dose level. The body weights and organ weights were significantly reduced in males (6-16%) ingesting $\geq$5 mg/kg/day and in females (5-11%) ingesting $\geq$15 mg/kg/day. In addition, a majority of the rats (both sexes) ingesting $\geq$15 mg/kg/day Telone II®

developed a slight basal cell hyperplasia and those ingesting ≥50 mg/kg/day Telone II® developed hyperkeratosis in the nonglandular portion of the stomach (Haut et al., 1996).

In a subchronic study, Telone II® (96% 1,3-dichloropropene) was administered to B6C3F1 mice (10/sex/group) at dietary levels of 0, 15, 50, 100, or 175 mg/kg/day for 13 weeks. No clinical signs of toxicity were noted at any dose level. Body weights of male and female mice ingesting dosages of ≥15 mg/kg/day were depressed in a dose-related manner at the end of the study by 5-15% and 5-13%, respectively (Haut et al., 1996).

In order to determine its potential toxicologic effects in dogs, Stebbins et al. (1999) administered 1,3-dichloropropene (equal mixtures of *cis* and *trans*) to beagle dogs (4/sex/group) at dietary levels of 0, 5, 15, or 41 mg/kg/day for 13 week. At the end of this study, body weights were lower than the control group in males at 15 and 41 mg/kg/day (3% and 28%, respectively) and in females at 5, 15, or 41 mg/kg/day (4.5%, 12%, and 25%, respectively). The higher doses caused a regenerative hypochromic microcyte anemia (depressed erythrocyte counts, hemoglobin concentrations, and hematocrit values) in both sexes, which worsened over the exposure period in the 41-mg/kg/day group and remained constant over the exposure period in the 15-mg/kg/day group. A partial reversal of the anemia (only erythrocyte counts were equivalent in dosed and control groups) occurred in the high dose animals during the 5-week recovery period following the dosing regimen (Stebbins et al., 1999).

Inhalation Exposure

In a 30-day inhalation study, Fischer 344 rats (10/sex/group), were exposed to Telone II® ("production grade" - no percentage of 1,3-dichloropropene presented) at concentrations of 0, 3, 10, or 30 ppm (equivalent to 0, 13.6, 45.4, and 136.2 mg/m^3, respectively). The exposure duration was 6 hours/day, 5 days/week for 4 weeks. There was no mortality at any dose level. At the end of this study, body weights of male rats at all concentrations were similar to that of the control group. Females exhibited a slight decrease in body weights. There was an increase in the incidence of enlarged peribronchial lymph nodes in males at 13.6 and 45.4 mg/m^3, but not at 136.2 mg/m^3. The incidences were 1, 5, 6, and 2 at 0, 13.6,45.4, and 136.2 mg/m^3, respectively (Coate et al., 1978).

In a subchronic toxicity study, Fischer 344 rats (28/sex/group) were exposed to DD® (25% *cis*- 1,3-dichloropropene, 27% *trans*-1,3-dichloropropene, and 29%-1,2-dichloropropene) at concentrations of 0, 5, 15, or 50 ppm (equivalent to 0, 22.7, 68.1, and 227 mg/m^3, respectively), 6 hours/day, 5 days/week for either 6 (10/sex/group) or 12 (19/sex/group) weeks. No clinical signs of toxicity were observed. After 12 weeks of exposure to 227 mg/m^3, the females exhibited a significant increase in relative kidney weights, and the males exhibited a significant increase in relative liver weights. Histologic, serum chemistry, and urinalysis parameters, however, were either transiently altered and/or showed no changes that were dose-related outside normal ranges (Parker et al., 1982).

In a subchronic toxicity study, Fischer 344 rats (10/sex/group) were exposed to Telone II® (90.9% 1,3-dichloropropene) at concentrations of 0, 10, 30, 90, or 150 ppm (equivalent to 0, 45.4, 136.2, 408.6, and 681 mg/m^3, respectively). The exposure duration was 6 hours/day, 5

days/week for 13 weeks. Both sexes exhibited a significant decrease in body weights at 408.6 and 681 mg/m^3. Rats exposed to 136.2, 408.6, and 681 mg/m^3 showed treatment-related histopathological lesions in the nasal turbinates (Stott et al., 1984).

In a subchronic toxicity study, B6C3F1 mice (10/sex/group) were exposed to Telone II® (90.9% 1,3-dichloropropene) at concentrations of 0, 10, 30, 90, or 150 ppm (equivalent to 0, 45.4, 136.2, 408.6, and 681 mg/m^3, respectively). The exposure duration was 6 hours/day, 5 days/week for 13 weeks. Both sexes exhibited a significant decrease in body weights, while females showed epithelial degeneration and hyperplasia of the nasal turbinates at 408.6 and 681 mg/m^3 (Stott et al., 1984). Hyperplasia of the transitional epithelium of the urinary bladder was observed in female mice exposed to > 409 mg/m^3 technical-grade 1,3-dichloropropene for 13 weeks (Stott et al., 1988).

In a 30-day inhalation study, CD-1 mice (10/sex/group), were exposed to Telone II® ("production grade") at concentrations of 0, 3, 10, or 30 ppm (equivalent to 0, 45.4, 136.2, 408.6, and 681 mg/m^3, respectively). The exposure duration was 6 hours/day, 5 days/week for 4 weeks. There was no mortality at any dose level or any treatment related findings at any dose (Coate et al., 1978).

In a subchronic toxicity study, CD-l mice (28/sex/group) were exposed to D-D® (25% *cis*-l,3-dichloropropene, 27% *trans*-l,3-dichloropropene, and 29% *trans*-1,2-dichloropropene) at concentrations of 0, 5, 15, or 50 ppm (equivalent to 0, 22.7, 68.1, and 227 mg/m^3, respectively). The exposure duration was 6 hours/day, 5 days/week for either 6 (10/sex/group) or 12 (19/sex/group) weeks. No clinical signs of toxicity were observed. After 12 weeks of exposure, white blood cell counts were significantly decreased at 12 weeks in male mice exposed to 15 ppm (68.1 mg/m^3) and in female mice exposed to 50 ppm (227 mg/m^3). Glutamic pyruvic transaminase activity was significantly decreased in the 68.1 and 227 mg/m^3 groups of female mice at 12 weeks. Other histologic, serum chemistry, and urinalysis parameters were either transiently altered and/or showed no changes that were dose-related or outside normal ranges. In male mice, statistically-significant decreases were observed in relative testis weight at 6 weeks, but not at 12 weeks in the 50-ppm group. Absolute and relative liver weight increases were statistically significant at 12 weeks in both the 5- and 50-ppm groups, but not in the 15-ppm group. After 6 weeks, there was an increased incidence of enlarged peribronchial lymph nodes in all exposed mice without any accompanying histopathological changes. The only treatment-related histopathology was a slight to moderate diffuse hepatocyte enlargement in both sexes (12/21 treated vs. 4/18 controls for males and 6/18 treated vs. 1/18 controls for females) exposed to 50 ppm D-D®. No treatment related gross pathology or histopathology was observed in the respiratory tracts in any of the exposed animals (Parker et al., 1982).

7.2.4 Neurotoxicity

As described in the following section, neurotoxicity has been observed in acute animal studies, however, longer-term inhalation studies have not resulted in neurological changes.

Oral Exposure

Clinical signs of neurotoxicity were observed at 1 and 4 hours after a single oral dose (75 mg/kg/day) of 1,3-dichloropropene in rats (Jones, 1988a). The observations included hunched posture, pilo-erection, lethargy, ptosis, ataxia, and decreased respiratory rate. More sensitive tests for neurological effects were not used (ATSDR, 1992).

Inhalation Exposure

Ataxia of the hind limbs and loss of the righting reflex was observed in pregnant rabbits exposed to 300 ppm of Telone II® during gestation days 6-18. No neurological signs of toxicity were observed in rabbits exposed to 50 or 150 ppm or in rats exposed to 300 ppm (Kloes et al., 1983).

No clinical signs of neurotoxicity were observed in rats, guinea pigs, rabbits, or dogs after inhalation exposure to 3 ppm Telone II® a for 6 months (Torkelson and Oyen, 1977). This was the same in rats or mice exposed to up to 150 ppm Telone II® a for 13 weeks (Coate 1979a; Stott et al., 1988), or to 60 ppm Telone II® b for 6-24 months (Lomax et al., 1989). The absence of clinical signs is supported by histological examinations of brain and spinal cords in rats and mice that revealed no lesions attributable to 1,3-dichloropropene exposure (Coate 1979b; Stott et al., 1988; Lomax et al., 1989). More sensitive tests for neurological effects, however, were not included in these studies (ATSDR, 1992).

Dermal Exposure

Rats that received single dermal applications of 500 mg/kg *cis*-1,3-dichloropropene or more were lethargic and had increased salivation (Jones, 1988b). At 800 mg/kg or more, ptosis, hunched posture, pilo-erection, lethargy, and decreased respiration rate were noted. Ataxia was observed in this study at dose levels of 1300 mg/kg and 2000 mg/kg (Jones, 1988b). Rats that received a single dermal application of 1300 mg/kg or more of Telone II®a became ataxic and lost the righting reflex, indicating neurological deficits (Jones and Collier, 1986b). Several studies of 1,3-dichloropropene (Jones and Collier, 1986b; Jeffrey et al., 1987b; Mizell et al., 1988b), reported clinical signs in rats and rabbits that possibly indicate a neurological effect of 1,3-dichloropropene after dermal application. These signs included lethargy, salivation, lacrimation, and labored respiration (ATSDR, 1992).

7.2.5 Developmental/Reproductive Toxicity

No evidence of developmental or reproductive effects have been observed in oral or inhalation animal studies, as summarized in the following sections. No studies were-located regarding developmental/reproductive effects after dermal exposure to 1,3-dichloropropene.

Oral Exposure

Histological evaluation of reproductive organs and tissues from rats and mice that received oral doses of Telone II®a (0, 25, or 50 mg/kg for rats and 0, 50, or 100 mg/kg for mice) for 2 years revealed no lesions attributable to the exposure (NTP, 1985). More sensitive tests for reproductive effects, however, were not performed in this study (ATSDR, 1992).

Inhalation Exposure

Linnett et al. (1988) studied the subchronic reproductive toxicity of D-D®, which is a mixture of 1,3-dichloropropene (57%) and 1,2-dichloropropene (% not specified). Wistar rats (30 males/group and 24 females/group) were exposed by inhalation to 0, 10, 30, or 90 ppm (equivalent to 0, 45.4, 136, and 409 mg/m^3, respectively) D-D®. The exposure duration was 6 hours/day, 5days/week for 10 weeks. Selected male rats from each exposure group (n=20) were mated with unexposed virgin females during week 3, 5, 8, and 10 of exposure. After the 10-week exposure period, selected females from each exposure group (n=15) were mated with unexposed males. The remaining males and females from each treatment group were sacrificed immediately after the exposure period for standard toxicological evaluation. No treatment-related effects were observed in any of the mating, fertility, fecundity, and reproductive pathology/histopathology endpoints, including sperm morphology and estrus cycling at any of the doses tested (Linnett et al., 1988).

In a two-generation rat study, Breslin et al. (1989) exposed Fischer 344 rats (30/sex/group) to 0, 10, 30, or 90 ppm 1,3-dichloropropene (0, 42, 124, or 373 mg/m^3). The animals in the F0 and Fl generations were exposed 6 hours/day, 5 days/week for 10 and 12 weeks, respectively, before breeding. They then were exposed 7 days/week during breeding, gestation, and lactation. No adverse exposure-related effects were found on reproductive and neonatal parameters.

In a developmental study, Fischer 344 rats and New Zealand white rabbits were exposed to 90.1% *cis*- and *trans*-1,3-dichloropropene at concentrations of 0, 50, 150, or 300 ppm (equivalent to 0, 82, 245, and 490 mg/m^3, respectively). The exposure duration was 6 hours/day during gestation days 6-15 for rats and 6-18 for rabbits. No evidence of teratogenicity was observed. Maternal effects in rats included decreases in weight gain and food consumption at all exposure levels. In rabbits, decreased weight gain was observed in the animals exposed to 60 and 100 ppm (Hanley et al., 1987).

In a second developmental study, Fischer 344 rats and New Zealand white rabbits were exposed to 90.1% *cis*- and *trans*-1,3-dichloropropene at concentrations of 0, 50, 150, or 300 ppm (equivalent to 0, 204, 613, and 1226 mg/m^3, respectively). The exposure duration was 6 hours/day during gestation days 6-15 for rats and 6-18 for rabbits. Irritation, as evidenced by nasal exudate and red, crusty material around the eyes, was observed in the rat dams exposed to 300 ppm. Teratogenic effects were not observed in either the rats or the rabbits in any exposure group, but embryotoxocity (decreased number of fetuses per litter and increased resorptions) was observed in rats exposed to 300 ppm. Decreased body weight gains were observed in rat dams in all exposure groups and significant maternal weight loss was reported at the two highest exposure levels. In the rabbits exposed to 300 ppm, severe maternal neurotoxicity (ataxia of hind limbs and loss of the righting reflex) was observed, therefore, embryotoxicity could not be assessed (Kloes et al., 1983).

7.2.6 Chronic Toxicity

Several chronic oral and inhalation animal toxicity studies are available, and are summarized below. A single chronic dermal animal study was identified.

Oral Exposure

In a study reported by the National Toxicological Program (NTP) in 1985, Telone II® (89% 1,3-dichloropropene) was administered in corn oil by gavage to Fischer 344 rats (52/sex/group). They were given doses of 0, 25, or 50 mg/kg/day three times a week for 104 weeks. At the end of the study, body weights of the high-dose male rats were depressed 5% relative to those for low-dose and/or control male rats. In both sexes, there were increased incidences of basal cell or epithelial hyperplasia of the forestomach at both treatment levels, and edema of the urinary bladder at the highest treatment level. In females, nephropathy occurred at both treatment levels (NTP, 1985).

NTP (1985) also studied B6C3F1 mice (50/sex/group) administered the commercial grade formulation of Telone II® (89.0% 1,3-dichloropropene) in corn oil by gavage at doses of 0, 50, or 100 mg/kg/day three times per week for 104 weeks. In female mice, there were increased incidences of hyperplasia of the forestomach at the high dose, and a dose-related increase in hydronephrosis. In both sexes at 50 and 100 mg/kg/day, there was a dose-related increased incidence of epithelial hyperplasia of the urinary bladder (NTP, 1985). Carcinogenic effects observed in this study are discussed in Section 7.2.7.

Male and female Fischer rats (60/sex/dose) were administered a microencapsulated formulation of Telone II® (96% 1,3-dichloropropene) in the diet at doses of 0, 2.5, 12.5, or 25 mg/kg/day for 24 months. At 12 months 10 animals/sex/dose were sacrificed. Body weight gains were decreased in males (8% and 21%) and females (15 and 25%) at 12.5 and 25 mg/kg/day, respectively, compared to controls at 24 months. Food consumption also was decreased in males at 12.5 and 25 mg/kg/day and in females at 25 mg/kg/day at 24 months. There was an increased incidence of basal cell hyperplasia of the nonglandular mucosa of the stomach of both sexes at the 12- and 24-month sacrifice at 12.5 and 25 mg/kg/day. Males also had an increase in liver masses and nodules at 12.5 and 25 mg/kg/day. No other clinical signs of toxicity were observed (Stott et al., 1995).

Fischer 344 rats were administered 1,3-dichloropropene in their diets for up to two years, at dose levels of 0, 2.5, 12.5, or 25 mg/kg/day (Stebbins et al., 2000). Rats given 12.5 or 25 mg/kg/day had decreased body weights and body weight gains. Rats also exhibited basal cell hyperplasia of the nonglandular mucosa of the stomach in the 12.5- and 25-mg/kg/day groups at 12 months (not significantly different from controls). This also occurred at 24 months (males: 20/50 at 12.5 mg/kg/day and 30/50 at 25 mg/kg/day; females: 20/50 at 12.5 mg/kg/day and 37/50 at 25 mg/kg/day). All treated rats also exhibited an increased incidence of eosinophilic foci of altered cells in the liver at 24 months, although this is a common spontaneous occurrence in aged Fischer 344 rats.

In a two-year toxicity/carcinogenicity study in B6C3F1 mice (50/sex/group), Telone II® (95.8% 1,3-dichloropropene) was administered as microcapsules by dietary administration at levels of 0, 2.5, 25, or 50 mg/kg/day. There were no effects on clinical signs, mortality, ophthalmology, hematology parameters, organ weights, macroscopic pathology, or microscopic pathology at any dose (Redmond et al., 1995). However, there was a significant decrease in body weights and body weight gains in the 25- and 50-mg/kg/day groups.

B6C3F1 mice were administered 1,3-dichloropropene in their diets for up to two years, at dose levels of 0, 2.5, 25, or 50 mg/kg/day (Stebbins et al., 2000). Mice in the 25 and 50 mg/kg/day dose groups had decreased body weights and body weight gains. The only histologic change in mice was decreased size of hepatocytes in males at 50 mg/kg/day for 12 months. This was consistent with decreased cytoplasmic glycogen content and decreased liver weights, however, this effect was not present at 24 months.

In a chronic toxicity study, beagle dogs (4/sex/dose) were administered approximately 0, 0.5, 2.5, or 15 mg/kg/day 1,3-dichloropropene, as Telone II®, in their diets for 1 year. Body weights of males given 15 mg/kg/day were 5-12% lower than the control group during the first 13 weeks of the study and 13-19% lower than the control group during the remaining 9 months. Body weights of females given 15 mg/kg/day were 5-14% lower than the control group during the majority of the dosing period. Both sexes ingesting a dose of 15 mg/kg/day experienced a regenerative, hypochromic microcytic anemia characterized by decreased hematocrit, hemoglobin concentrations, and size of erythrocytes, which remained relatively constant in severity between 3 and 12 months of treatment. Histopathologic alterations associated with the anemia in the high dose groups consisted of increased hematopoiesis of the bone marrow and increased extramedullary hematopoiesis of the spleen (Stebbins et al., 1999).

Inhalation Exposure

Fischer 344 rats (50/sex/group) were exposed to Telone II® (49.5% *cis*- and 42.6% *trans*-1,3-dichloropropene) at 0, 5, 20, or 60 ppm (equivalent to 0, 23, 84, and 251 mg/m^3, respectively). The exposure duration was 6 hours/day, 5 days/week for 2 years. An ancillary group of 10 animals/sex/group was similarly exposed to duration-adjusted exposures of 0, 3.7, 14.9, or 44.6 mg/m^3 for 6 or 12 months. No clinical signs of toxicity or significant differences in survival were observed in the exposed rats as compared to controls. However, histopathological examination revealed exposure-related effects in the nasal tissues of both male and female rats exposed to 60 ppm for 24 months. These effects included unilateral or bilateral decreased thickness of the olfactory epithelium due to degenerative changes, erosions of the olfactory epithelium, and fibrosis beneath the olfactory epithelium (Lomax et al., 1989).

In a chronic study, B6C3F1 mice (50/sex/group) were exposed to Telone II® (49.5% *cis*- and 42.6% *trans*-l,3-dichloropropene) at 0, 5, 20, or 60 ppm (equivalent to 0, 23, 84, and 251 mg/m^3, respectively). The exposure duration was 6 hours/day, 5 days/week for 2 years. An ancillary group of 10 animals/sex/group was similarly exposed to duration-adjusted exposures of 0, 3.7, 14.9, or 44.6 mg/m^3 for 6 or 12 months. No clinical signs of toxicity or significant differences in survival were observed in the exposed mice compared to controls. In both sexes, there were dose-related incidences of bladder hyperplasia which were statistically significant for

both sexes at 60 ppm and for females at 20 ppm. Both sexes of mice (20 ppm males and 60 ppm females) also had compound-related hypertrophy and hyperplasia of the respiratory epithelium. Some groups also had degeneration of the olfactory epithelium, which was statistically significant at 60 ppm for both sexes and at 20 ppm for females. In males exposed to 60 ppm, there was a statistically-significant increase in the incidence of benign lung tumors and hyperplasia and hyperkeratosis in the forestomach (Lomax et al., 1989).

In a chronic toxicity/carcinogenicity study, B6C3F1 mice were exposed by whole-body inhalation to Telone II® (92.1% 1,3-dichloropropene) at aerosol concentrations of 0, 5, 20, or 60 ppm (0, 23, 84, or 251 mg/m^3). The number of animals exposed were 50/sex/group, plus 10/sex/group in 6- and 12- month exposure groups. The exposure duration was 6 hours/day, 5 days/week for a total of 510 days over a 2-year period. There was no effect on survival (at least 80% in each group). There was a statistically-significant decrease in body weight gain in 60 ppm males (3-9%) and females (2-11%). Urinary bladder effects were noted primarily in females at 20 and 60 ppm. Slight, moderate, or marked roughened, irregular and opaque surfaces were reported in 20/50 females at 20 ppm and 30/49 at 60 ppm compared with 3/50 in the control group. Hypertrophy and hyperplasia of the nasal respiratory mucosa (very slight/slight) were observed in both sexes at 60 ppm and in female mice at 20 ppm. Degeneration of olfactory epithelium (very slight/slight) was noted in both sexes at 60 ppm. Hyperplasia of the epithelial lining of the nonglandular portion of the stomach was observed in a higher incidence compared to the control group in males and to a lesser extent in females at 60 ppm (Dow, 1987).

7.2.7 Carcinogenicity

Carcinogenicity of 1,3-dichloropropene has been studied in animals using oral, inhalation, and dermal exposures, as summarized in the following sections.

Oral Exposure

In a study reported by the NTP (1985), Fischer 344 rats (52/sex/group) were gavaged with Telone II® (89.0% 1,3-dichloropropene) in corn oil at doses of 0, 25, and 50 mg/kg/day, 3 times/week for 104 weeks. No increased mortality occurred in the treated animals. Elevated incidences of the following tumors (single and combined) were observed at the highest dose tested: 1) forestomach squamous cell papillomas in males and females (mostly benign) in the 50-mg/kg/day groups, which developed within one year of exposure; 2) combined forestomach squamous cell papillomas and carcinomas (24 months after exposure began), which were significant for males in the 50-mg/kg/day group; and 3) liver neoplastic nodules, which were statistically significant only in males in the 25- and 50-mg/kg/day groups (24 months after exposure began). The increased incidence of forestomach tumors was accompanied by a positive trend for forestomach basal cell hyperplasia in male and female rats of both treated groups (25 and 50 mg/kg/day). The incidence of adrenal gland pheochromocytomas in males of the low-dose group was significantly elevated when compared with vehicle controls. Thyroid follicular cell adenomas and carcinomas occurred with a statistically-significant positive trend in low-dose female rats. However, the increased incidence of thyroid tumors in low-dose male rats was not statistically significant (NTP, 1985).

NTP (1985) also studied B6C3F1 mice (50/sex/group). Telone II® (89.0% 1,3-dichloropropene) was administered in corn oil by gavage at doses of 0, 25, or 50 mg/kg/day, 3 times/week for 104 weeks. Due to excessive mortality in control male mice from myocardial inflammation approximately 1 year after the initiation of the study, the study in males was not considered to be adequate. Elevated incidences of the following tumors (single and combined) were observed either at the highest dose level tested or at both dose levels tested: 1) forestomach squamous cell papillomas or combined papillomas and carcinomas in males and females and squamous cell carcinomas in females; 2) urinary bladder transitional cell carcinomas in both sexes; and 3) lung adenomas and combined lung adenomas and carcinomas in both sexes. NTP concluded that there was a "clear evidence of carcinogenicity" for female mice, since the administration of Telone II® had caused an increased incidence of transitional cell carcinomas of the urinary bladder, as well as an increased incidence of alveolar /bronchial adenomas of the lung and of squamous cell papillomas and carcinomas of the forestomach in female mice (NTP, 1985).

In a chronic toxicity/carcinogenicity study, Stott et al. (1995) administered Telone II® (96% 1,3-dichloropropene) as microcapsules by dietary administration to Fischer 344 rats at levels of 0, 2.5, 12.5, or 25 mg/kg/day for two years. The number of animals exposed were 60/sex/group with 10/sex/group sacrificed at 12 months. At the end of the study, there was evidence of carcinogenicity. As previously discussed (Section 7.2.6, Chronic Toxicity, Oral Exposure) the incidence of nonneoplastic forestomach hyperplasia at 24 months was statistically increased at 12.5 and 25 mg/kg/day. No statistically-significant incidence of malignancies was observed in rats of either sex. The results indicated an increased incidence of benign liver cell tumors (hepatocellular adenomas) in both sexes of rats at 24 months in males at 25 mg/kg/day. The incidences of rats with primary hepatocellular adenomas were increased in males at the two highest doses (6/50 and 9/50 for 12.5 mg/kg and 25 mg/kg, respectively) and in females at the highest dose (4/50). The highest dose tested was considered adequate to assess the carcinogenic potential of 1,3-dichloropropene in rats (U.S. EPA, 1998c).

Fischer 344 rats were administered 1,3-dichloropropene in their diets for 24 months, at dose levels of 0, 2.5, 12.5, or 25 mg/kg/day (Stebbins et al., 2000). A significantly increased number of hepatocellular adenomas (benign) were observed only in males at 25 mg/kg/day (significantly increased incidence of 9/50); non-significant increases were observed in males at 12.5 mg/kg/day (6/50) and in females at 25 mg/kg/day (4/50). There were no significant increases of hepatocellular carcinomas (malignant) in any dose groups.

Redmond et al. (1995) reported there was no evidence of carcinogenicity from a two-year study in which B6C3F1 mice were administered 0, 2.5, 25, or 50 mg/kg Telone II® (95.8% 1,3-dichloropropene) as microcapsules in their diet. This is in direct contrast with the observations of carcinogenicity made in the NTP study (1985). EPA (2000e) concludes that the NOAEL/LOAEL for cancer in this study may be uncertain, because it is uncertain whether the loaded microcapsules were stable during use. EPA (2000e) notes, however, that the incidences of lung tumors (combined bronchoalveolar adenoma and carcinoma) in the two studies are similar for the 50 mg/kg groups (for males, 13/50 in NTP [1985] and 11/50 in Redmond et al. [1995] and for females, 4/50 in NTP [1985] and 5/50 in Redmond et al. [1995]).

Inhalation Exposure

Lomax et al. (1987) reported that there was no evidence of carcinogenicity from a two-year study in which Fischer 344 rats were exposed to Telone II® (92.1% 1,3-dichloropropene) at aerosol concentrations of 0, 5, 20, or 60 ppm (0, 22.7, 90.8, 272.4 mg/m^3, respectively). The exposure frequency was 6 hours/day, 5 days/week for a total of 509 days.

In a chronic toxicity/carcinogenicity study, Dow (1987) exposed B6C3F1 mice (50/sex/group plus 10/sex/group for 6- and 12-month exposure groups) to Telone II® (92.1% 1,3-dichloropropene at aerosol concentrations of 0, 5, 20, or 60 ppm (0, 22.7, 90.8, 272.4 mg/m^3, respectively) 6 hours/day, 5 days/week for a total of 510 days over a 2-year period. At the end of the study period, there was evidence of carcinogenicity. Bronchoalveolar adenomas appeared in a higher incidence in 60-ppm males only when compared with the control group. Although the lung tumors noted in this mouse inhalation study were benign, the tumor induction was dose dependent (9/50, 6/50, 13/50, and 22/50 for 0, 5, 20, 60 ppm, respectively), the tumor incidence was outside the range of historical controls, and the tumor type also was seen in the mouse oral bioassay.

In a chronic toxicity/oncogenicity study in which Fischer 344 rats and B6C3F1 mice were exposed to 0, 5, 20, or 60 ppm Telone II® via inhalation for 2 years, Lomax et al. (1989) reported that there was a statistically-significant increase in the incidence of bronchoalveolar adenomas in male mice exposed to 60 ppm Telone II® for 24 months. An increased incidence of this benign lung tumor was not observed in female mice or in male or female rats exposed to Telone II® under the same protocol (Lomax et al., 1989). Similar results were reported by Lomax et al. (1987) and Dow (1987).

Dermal Exposure

1,3-Dichloropropene did not induce skin papilloma formation in mice after dermal application of 122 mg per mouse three times weekly for 74 weeks (Van Duuren et al., 1979).

7.3 Other Key Data

7.3.1 Mutagenicity/Genotoxicity Effects

Genotoxicity studies of 1,3-dichloropropene in *in vitro* test systems are summarized in Table 7-2 at the end of this chapter. The studies summarized below have conflicting results regarding the genotoxicity of 1,3-dichloropropene.

Several groups have reported that 1,3-dichloropropene is mutagenic *in vitro* with and without metabolic activation in the Ames *Salmonella* test (De Lorenzo et al., 1977; Neudecker et al., 1977; Stolzenberg and Rine, 1980; Vithayathil et al., 1983; Creedy et al., 1984; Neudecker and Henschler, 1986). In contrast, 1,3-dichloropropene purified on silic acid columns was not mutagenic (Talcott and King, 1984). Silic acid removes polar impurities, which when added back to the purified 1,3-dichloropropene, restore mutagenic activity (Talcott and King, 1984). Watson et al. (1987) confirmed the findings that purified 1,3-dichloropropene is not mutagenic in the Ames *Salmonella* test. Watson et al. (1987) also found that the impurities alone were

mutagenic. Thus, the weight of evidence of these data suggests that the mutagenic activity of 1,3-dichloropropene preparations in earlier bacterial tests was likely due to mutagenic polar impurities and not to 1,3-dichloropropene.

Although purified 1,3-dichloropropene was not directly mutagenic, Watson et al. (1987) observed mutagenic activity in the presence of S9 fraction or washed microsomes from rat liver. Watson et al. (1987) have suggested that *cis*-1,3-dichloropropene undergoes mono-oxygenase-dependent bioactivation to mutagenic metabolites only in the absence of GSH. Thus, mutagenicity was abolished when the concentration of GSH was adjusted to normal physiological concentrations (5 mM). These findings are consistent with the results of Creedy et al. (1984), which showed that GSH eradicated the microbial mutagenicity of both isomers of 1,3-dichloropropene after it was adjusted to normal physiological concentrations. These results suggest that normal physiological concentrations of GSH provide efficient protection against the mutagenic activity of 1,3-dichloropropene and associated trace impurities.

Schneider et al. (1998b) also reported that conjugation of 1,3-dichloropropene with GSH decreases epoxide formation. The authors showed that *cis*- and *trans*-epoxides are mutagenic in the *Salmonella* TA100 assay. The addition of GSH to the assay, with or without GST, diminished the mutagenicity of *cis*-1,3-dichloropropene epoxide, the most potent isomer, and obliterated the mutagenicity of *trans*-l,3-dichloropropene epoxide. The investigators postulated that the epoxides or their decomposition products (i.e., 3-chloro-2-hydroxypropanal) are responsible for the mutagenicity of 1,3-dichloropropene in the presence of liver enzymes.

Neudecker and Henschler (1986) used enzyme inhibitors to determine whether rat liver enzymes (i.e., S9) metabolize allylic chloropropenes, such as 1,3-dichloropropene, via epoxidation or via cleavage of the allylic chlorine, which then forms the allylic chloroalcohol, the aldehyde, and then acrylic acid. The investigators distinguished these pathways by measuring mutagenicity in *Salmonella* TA100. Addition of SKF525, an inhibitor of microsomal oxygenase which prevents formation of 1,3-dichloropropene epoxide, had no effect on mutagenicity. Also, 1,1,1-trichloropropene-2,3-oxide, an inhibitor of epoxide hydrolase that prevents metabolism of the epoxide, had no effect on mutagenicity. However, addition of cyanamide, an inhibitor of aldehyde dehydrogenase that prevents metabolism of the aldehyde activates 1,3-dichloropropene by hydrolysis to chloroalcohols that subsequently oxidize to 3-chloroacrolein (hydrolytic-oxidative pathway) and then to the respective acrylic acid.

In mammalian test systems, 1,3-dichloropropene triggered unscheduled DNA synthesis in Hela cells (Eder et al., 1987; Schiffmann et al., 1983); sister chromatid exchange in Chinese hamster V79 cells (van der Hude et al., 1987) and Chinese hamster ovary cells (Loveday et al., 1989); mitotic aberrations in Chinese hamster lung cells (Sasaki et al., 1988); and DNA fragmentation in Chinese hamster V79 cells (Martelli et al., 1993).

Van der Hude et al. (1987) assessed the genotoxicity of several halogenated short-chain hydrocarbons, including *cis*- and *trans*-1,3-dichloropropene, using the *in vitro* sister chromatid exchange (SCE) test in the Chinese hamster V79 cell line. Without S9 activation, 0.1-0.4 mM 1,3-dichloropropene showed a dose-dependent increase in the frequency of SCE. Higher

concentrations were required to induce significant SCE frequencies with 1,3-dichloropropene compared with other short-chain chlorinated hydrocarbons tested. The observed increase in SCE was abolished by the addition of rat liver S9 mix. These results are inconsistent with those of Watson et al. (1987), which showed mutagenic activity of purified 1,3-dichloropropene after the addition of S9, but not without S9. Moreover, van der Hude et al. (1987) used a formulation purified by gas chromatography, and as established by Watson et al. (1987), impurities due to such "purification" have mutagenic activity. Thus, the positive response to 1,3-dichloropropene in this assay was probably caused by mutagenic impurities rather than 1,3-dichloropropene.

Martelli et al. (1993) investigated the cytotoxicity and genotoxicity of 1,3-dichloropropene in cultured Chinese hamster lung, i.e., V79 cells, and in hepatocytes from male Sprague-Dawley rats. DNA fragmentation was significantly increased in a dose-dependent manner in V79 cells, which cannot metabolize 1,3-dichloropropene, after 1-hour incubation with subtoxic concentrations (1.8-5.6 mM) of 1,3-dichloropropene. This result is inconsistent with the *Salmonella* assays that showed no genotoxic activity without metabolic activation (Talcott and King, 1984; Watson et al., 1987); however, this result is consistent with other *Salmonella* assays. During an experiment to determine the time course for DNA repair, DNA lesions in V79 cells were only partially repaired 24 hours after removal of 1,3-dichloropropene. Subtoxic concentrations (0.18-0.56 mM) did not produce DNA fragmentation after a 20-hour incubation. Thus, in V79 cells, it appears that DNA fragmentation due to subtoxic concentrations of 1,3-dichloropropene was repaired successfully. However, rat hepatocytes, which have an intact metabolizing system, were more sensitive to DNA fragmentation. DNA fragmentation produced by 0.18-1 mM 1,3-dichloropropene in rat hepatocytes was reduced by both GSH and inhibition of cytochrome P450 activity with metapyrone. This experiment showed that the protective effect of GSH in mutagenicity assays (Watson et al., 1987; Creedy et al., 1984; Neudecker and Henschler, 1986) also applies to mammalian cells. It also contradicts the finding of Neudecker and Henschler (1986) that metabolism by cytochrome P450 has no role in the mutagenicity of 1,3-dichloropropene.

Ghia et al. (1993) examined the genotoxic activity of 1,3-dichloropropene using a battery of short-term *in vivo* tests. Male Sprague-Dawley rats were administered doses of 1,3-dichloropropene ranging from 62.5 mg/kg to 250 mg/kg by either a single oral gavage or a single intraperitoneal injection. Animals were pre-treated with either buthionine-sulfoximine (BSO) or diethyl-maleate (DEM) to reduce GSH levels, or with methoxsalen (MS) to inhibit cytochrome P450. A dose-dependent increase in DNA fragmentation was most pronounced in the liver (the site for tumors at 25 mg/kg/day in Stott et al. [1995] and at 50 mg/kg in NTP [1985]) and the stomach mucosa (the site for tumors at 50 mg/kg in NTP [1985]) and occurred to a lesser extent in the kidney. No DNA fragmentation occurred in the lung, bone marrow, or brain. Partial repair was observed after 24 hours. Reduction of GSH levels with BSO or DEM pretreatment did not affect DNA fragmentation in the liver, but that was explained by the fact that neither BSO nor DEM increased depletion of liver GSH over that caused by dichloropropene alone. The inhibition of cytochrome P450 with MS reduced the frequency of DNA fragmentation in the liver as shown by Martelli et al. (1993) in rat hepatocytes. Despite the fact that the 125 mg/kg dose administered was 5 times higher than that of Stott et al. (1995) and 2.5 times higher than that of NTP (1985), there was no evidence of DNA repair induction in

UDS assays. In addition, no statistically-significant increases in micronucleated polychromatic erythrocytes (PCE) in bone marrow (consistent with the absence of DNA fragmentation) and spleen or in micronucleated hepatocytes were observed at the same dose.

The authors concluded that DNA fragmentation *in vivo* correlated well with 1,3-dichloropropene carcinogenic activity in the rat liver and stomach mucosa observed by Stott et al. (1995) and NTP (1985), respectively. However, the doses used by Ghia et al. (1993) were at least 2.5 times that producing liver tumors in Stott et al. (1995) and 1.25 times that producing forestomach tumors in NTP (1985). In addition, even at the high doses used by Ghia et al. (1993), the genotoxicity results of the rat hepatocyte DNA repair assay and the MN assay of bone marrow, spleen, and liver cells were negative.

Kevekordes et al. (1996) tested a number of pesticides for clastogenic and aneugenic properties in 1) an *in vivo* mouse bone marrow MN test, and 2) an *in vitro* sister chromatid exchange (SCE) assay using human lymphocytes in the presence or absence of rat liver S9. 1,3-Dichloropropene by gavage significantly increased the frequency of micronucleated polychromatic erythrocytes (PCE) in the bone marrow cells of female mice at the two highest doses tested (187 and 234 mg/kg), whereas no increase in PCE was observed in male mice at doses up to 280 mg/kg/day. With and without S9 activation, the frequency of SCE in cultured human lymphocytes was statistically increased compared with the control group, but only at the highest dose tested (100 μM). In the discussion of these findings, the authors point out that 1,3-dichloropropene formulations are likely to contain a number of mutagenic impurities (Kevekordes et al., 1996). Therefore, the mutagenic activity cannot necessarily be attributed to 1,3-dichloropropene.

1,3-Dichloropropene does not produce dominant lethal mutations in Wistar or F344 rats or New Zealand white rabbits, as evidenced by the absence of embryonic or fetal deaths in inhalation studies by Hanley et a1. (1987) and Linnett et al. (1988).

7.3.2 Immunotoxicity

Gross and histological examinations were done on the thymus and lymph nodes of rats and mice exposed to 150 ppm or less of Telone II®a for 13 weeks (Stott et al., 1988), 60 ppm Telone II®b for 6-24 months (Lomax et al., 1989), or to 50 ppm of DD® for 6-12 weeks (Parker et al., 1982). No lesions were attributable to 1,3-dichloropropene exposure. However, more sensitive tests for immune system function were not used (ATSDR, 1992).

7.3.3 Hormonal Disruption

No studies were identified regarding hormonal disruption following exposure to 1,3-dichloropropene.

7.3.4 Physiological or Mechanistic Studies

Stott et al. (1997a) conducted a series of studies to elucidate the potential mechanisms of tumorigenicity of 1,3-dichloropropene in male B6C3F1 mice and F344 rats. The selection of dose, sex, species, and route of administration was based on the tumors seen in 2-year oral and inhalation bioassays with rats and mice, including: Stott et al. (1995), in which hepatocellular adenomas were observed in male rats fed 25 mg/kg/day 1,3-dichloropropene; NTP (1985), in which urinary bladder tumors were noted in female mice gavaged with 50 mg/kg 1,3-dichloropropene three times/week and in male mice at 100 mg/kg; NTP (1985), in which nonneoplastic bladder effects were observed at 25 mg/kg; and Lomax et al. (1989), in which bronchoalveolar adenomas were observed in male mice exposed to 272 mg/m^3 by inhalation.

Stott et al. (1997a) gavaged male rats with 0, 5, 12.5, 25, or 100 mg/kg/day 1,3-dichloropropene for 3 days, 12 days (5 days/week), or 26 days (5 days/week). In addition, male mice were exposed to whole-body inhalation concentrations of 0, 10, 30, 60, or 150 ppm (equivalent to 0, 45.4, 136.2, 272, or 681 mg/m^3, respectively) for 6 hours/day for 3 days, 12 days (5 days/week), or 26 days (5 days/week). The following mechanistic endpoints were evaluated: 1) GSH levels in rat liver and mouse lung; 2) levels of DNA replication as determined by increased regenerative cell proliferation in rat liver and mouse epithelia from urinary bladder and bronchiole; 3) rates of apoptosis in rat liver and mouse epithelia from urinary bladder and bronchiole; and 4) adduct formation in rat liver and mouse lung measured by the ^{32}P-Post-Labeling assay.

Results from the Stott et al. (1997b) study included a dose-dependent decrease in tissue GSH levels. While liver GSH levels increased back to control levels by the end of the exposure period (26 days), GSH levels in mouse lung did not. Both tissues showed a rebound (greater than control levels) in GSH levels when animals exposed for 11 days were tested 24 hours after dosing was terminated. No changes were noted in either cell proliferation or apoptosis rates in rat liver or in mouse lung or urinary bladder epithelia. In addition, no unique DNA adduct formation or increase in the incidence of normally occurring adducts was found in rat liver or mouse lung.

The authors concluded that these studies provide scientific support to a weight-of-evidence conclusion that tumorigenesis associated with high-dose ingestion or inhalation of 1,3-dichloropropene is nongenotoxic in etiology and is not dependent on 1) enhanced cell proliferation; 2) depressed rates of apoptosis; or 3) increased or unique DNA adduct formation. However, these mechanistic studies did not identify a mechanism of action for tumor formation. Neither the genotoxic nor the nongenotoxic mechanisms tested elicited positive results. The studies showed that 1,3-dichloropropene, at doses used in chronic bioassays, depletes GSH in target organs. They were consistent with GSH protection against cytotoxicity and tumorigenicity by conjugating with 1,3-dichloropropene. Bacterial assays (Watson et al., 1987; Creedy et al., 1984; Neudecker and Henscher, 1986) and *in vitro* mammalian assays (Martelli et al., 1993) also have shown that GSH protects against genotoxic effects (Stott et al., 1997a).

1,3-Dichloropropene was not a tumor initiator in mice treated with a single application of 122 mg per mouse, followed by repeated applications of the tumor promoter, phorbol myristic acid, for 58 weeks (Van Duuren et al., 1979).

7.3.5 Structure-Activity Relationship

A study by Neudecker and Henschler (1986) was focused on the class of allylic chloropropenes. Neudecker and Henschler (1986) used enzyme inhibitors to determine whether rat liver enzymes (i.e., S9) metabolize allylic chloropropenes, such as 1,3-dichloropropene, via epoxidation or cleavage of the allylic chlorine, which then forms the allylic chloroalcohol, the aldehyde, and then acrylic acid. The investigators distinguished these pathways by measuring mutagenicity in *Salmonella* TA100. Addition of SKF525, an inhibitor of microsomal oxygenase that prevents formation of 1,3-dichloropropene epoxide, had no effect on mutagenicity. Also, 1,1,1-trichloropropene-2,3-oxide, an inhibitor of epoxide hydrolase that prevents metabolism of the epoxide, had no effect on mutagenicity. However, addition of cyanamide, an inhibitor of aldehyde dehydrogenase that prevents metabolism of the aldehyde activates 1,3-dichloropropene by hydrolysis to chloroalcohols that subsequently oxidize to 3-chloroacrolein (hydrolytic-oxidative pathway) and then to the respective acrylic acid.

7.4 Hazard Characterization

7.4.1 Synthesis and Evaluation of Non-Cancer Effects

The primary effect noted in humans after repeated occupational exposure to 1,3-dichloropropene is dermatitis (Bousema et al., 1991; Nater and Gooskens, 1976). Exposure to high concentrations, as may occur in chemical spills, can produce severe toxicity manifested by a dose-related range of acute neurotoxic symptoms (Flessel et al., 1978; Hayes, 1982; Markovitz and Crosby, 1984), and accidental ingestion of large quantities of 1,3-dichloropropene has been fatal (Hernandez et al., 1994). The quantity and concentrations at which these severe effects occurred are not reported.

In a general population study in California near agricultural areas where 1,3-dichloropropene is commonly used, an increased incidence of pancreatic cancer was observed, but concurrent exposures to other agricultural chemicals could have been a confounder (Clary and Ritz, 2003). Actual exposure concentrations were unknown; the surrogate for exposure in this study was pesticide usage.

In chronic and subchronic high-dose animal studies, histopathologic changes have been noted in target organs along the portals of entry (e.g., forestomach for oral administration; nasal mucosa and lung for inhalation) and/or in organs involved in the metabolism (liver) and excretion of conjugated metabolites (e.g., urinary bladder and kidney). The table below shows the lowest observed effect level for subchronic and chronic studies for various adverse effects observed in rats, mice, and dogs.

Table 7-1 Lowest Observed Effect Levels of Non-neoplastic Histopathologic Changes for Cited Studies

Species	Route of Administration	Histopathologic Changes	Lowest Observed Effect Level	Reference
SUBCHRONIC - ORAL				
Dogs	Oral	No histopathologic changes noted	Not available (NA)	Stebbins et al. (1999)
Rats	Oral	Basal cell hyperplasia of forestomach (both sexes)	15 mg/kg/day	Haut et al. (1996)
Mice	Oral	No histopathologic changes noted	NA	Haut et al. (1996)
SUBCHRONIC - INHALATION				
Rats	Inhalation	No treatment-related histopathologic changes noted	Not available (NA)	Coate et al. (1978)
Rats	Inhalation	No histopathologic changes noted	NA	Parker et al. (1982)
Rats	Inhalation	Lesions in nasal turbinates (both sexes)	30 ppm	Stott et al. (1984)
Mice	Inhalation	No histopathologic changes noted	NA	Coate et al. (1978)
Mice	Inhalation	Hepatocyte enlargement (both sexes)	50 ppm	Parker et al. (1982)
Mice	Inhalation	Epithelial degeneration and hyperplasia of nasal turbinates (females)	90 ppm	Stott et al. (1984)
Mice	Inhalation	Hyperplasia of the transitional epithelium of the urinary bladder (females)	>90 ppm	Stott et al. (1988)
CHRONIC - ORAL				
Dogs	Oral	Hematopoiesis of the bone marrow and extramedullary hematopoiesis of the spleen (both sexes)	15 mg/kg/day	Stebbins et al. (1999)
Rats	Oral	Basal cell or epithelial hyperplastic lesions of forestomach (both sexes)	25 mg/kg/day (10.7 mg/kg/day when averaged over 7 days)	NTP (1985)

Species	Route of Administration	Histopathologic Changes	Lowest Observed Effect Level	Reference
Rats	Oral	Basal cell hyperplasia of nonglandular mucosa of stomach (both sexes) Eosinophilic foci of altered cells in liver (both sexes)	12.5 mg/kg/day	Stebbins et al. (2000)
Rats	Oral	Basal cell hyperplasia of nonglandular mucosa of stomach (both sexes) Increase in liver masses and nodules (males)	12.5 mg/kg/day	Stott et al. (1995)
Mice	Oral	Epithelial hyperplasia of urinary bladder (both sexes)	50 mg/kg/day (21.4 mg/kg/day when averaged over 7 days)	NTP (1985)
Mice	Oral	No histopathologic changes noted	NA	Redmond et al. (1995)
Mice	Oral	Decreased size of hepatocytes at 12 months (males); this effect was not present at 24 months	50 mg/kg/day	Stebbins et al. (2000)
CHRONIC - INHALATION				
Rats	Inhalation	Nasal tissue effects (both sexes)	60 ppm	Lomax et al. (1989)
Mice	Inhalation	Slight, moderate, or marked roughened, irregular and opaque surfaces of the bladder Hypertrophy and hyperplasia of nasal respiratory epithelium	20 ppm (females)	Dow (1987)
Mice	Inhalation	Bladder hyperplasia Hypertrophy and hyperplasia of respiratory epithelium Degeneration of the olfactory epithelium	20 ppm (females)	Lomax et al. (1989)

Neither reproductive nor developmental toxicity was observed in a two-generation study in rats or in developmental studies in rats and rabbits after maternal inhalation of concentrations up to 376 mg/m^3 1,3-dichloropropene (Hanley et al., 1988; Linnett et al., 1988; Breslin et al., 1989). Even concentrations that produced parental toxicity (i.e., decreased body weight and/or nasal histopathology) did not produce reproductive or developmental effects (Hanley et al., 1988; Breslin et al., 1989).

7.4.2 Synthesis and Evaluation of Carcinogenic Effects

Limited evidence associating carcinogenicity in humans to 1,3-dichloropropene exposures arises from case studies in which two firemen and one farmer were accidentally exposed to acute high doses and subsequently developed blood cancers (non-Hodgkin's lymphoma and leukemia) (Markovitz and Crosby, 1984). Such case reports lack quantitative rigor and are often highly selective. Nevertheless, they may identify an association when there are unique features such as uncommon tumors. These case studies do not provide a sound basis for inferring a causal association between exposure to 1,3-dichloropropene and blood cancers since the possibility of confounding factors has not been considered or ruled out.

In an early chronic laboratory animal study (NTP, 1985), oral gavage was employed as the means of administration, and a formulation of 1,3-dichloropropene containing epichlorohydrin was used as the test substance. 1,3-Dichloropropene produced forestomach hyperplasia in rats and mice, as well as forestomach squamous cell papillomas and carcinomas in rats. Other target organs observed in this study included the mouse urinary bladder (epithelial hyperplasia), rat liver (neoplastic nodule formation), and mouse kidney (hydronephrosis). The lowest observed effect level for these endpoints was 25 mg/kg/day in both species.

When the method of oral administration of 1,3-dichloropropene was changed to feeding (Stott et al., 1995; Haut et al., 1996), forestomach lesions occurred in rats, but when compared with the NTP (1985) study, the severity of hyperplasia was reduced. Other targets identified in the NTP gavage study (mouse forestomach, urinary bladder, kidney, and rat liver) exhibited no histopathologic changes in the feeding studies (Redmond et al., 1995; Stott et al., 1995). Differences in histopathology between the NTP (1985) and the feeding studies may be due to the method of administration (daily dietary exposure vs. concentrated bolus dosing). Other investigators have observed that oral gavage increases blood levels of toxicant and toxicity compared with the same dose administered by gastric infusion over two hours (Sanzgiri et al., 1995). The decrease in the number of target organs in the feeding studies also may be due to the absence of epichlorohydrin in the feeding formulation. In the mouse dietary study (Redmond et al., 1995), there is uncertainty as to whether the mice received the intended dose, as reflected by the absence of cancer (urinary bladder tumors) and non-cancer effects (urinary bladder hyperplasia, forestomach hyperplasia, and hydronephrosis) previously observed in the NTP (1985) study. However, the incidences of lung tumors (combined bronchoalveolar adenoma and carcinoma) in the two studies are similar at similar doses. For the 50-mg/kg groups, lung tumor rates for males were 13/50 (NTP, 1985) and 11/50 (Redmond et al., 1995) and, for females, lung tumor rates were 4/50 (NTP, 1985) and 5/50 (Redmond et al., 1995). The other major toxic effect in the feeding studies was reduced body weight at the higher doses in both rats and mice.

The two-year animal bioassays clearly establish that 1,3-dichloropropene is carcinogenic at relatively high doses. Rodent feeding studies by Stott et al. (1995) observed a late-onset increase in the incidence of benign hepatocellular adenomas (with one hepatocarcinoma) in male rats at the highest dose tested, 25 mg/kg/day. No treatment-related tumors were observed in female rats or in male or female mice fed up to 50 mg/kg/day. The Stebbins et al. (2000) feeding study found an increased incidence of hepatocellular adenomas in rats administered 12.5 or 25 mg/kg/day for 24 months, but no oncogenic response in mice. An increased incidence of eosinophilic foci of altered cells in the liver was also noted, but was considered a spontaneous occurrence in the livers of aged F344 rats.

The gavage study by NTP (1985) found significant incidences of bronchoalveolar, forestomach, and urinary bladder tumors in mice at 50 mg/kg, and forestomach and liver tumors in rats at 25 mg/kg. With the exception of the urinary bladder tumors in mice, most tumors were benign. In 50-mg/kg rats, four carcinomas were observed in forestomach and one in the liver. In mice, eight carcinomas in urinary bladder and three in bronchoalveolar areas were observed at 50 mg/kg, while two were observed in the forestomach at 100 mg/kg. Although the NTP study was rejected for RfD development by the EPA (U.S. EPA, 2000e) because the thrice weekly, high-dose gavage regime was not well-designed to study chronic toxicity, the data established that 1,3-dichloropropene is a carcinogen at relatively high bolus doses. Current test guidelines recommend seven times weekly gavage, but indicate that five times/week is acceptable (U.S. EPA, 1998d). NTP acknowledged that the epichlorohydrin used as a stabilizer in Telone II may be partially responsible for the squamous cell papillomas and carcinomas, at least in rat forestomach since hyperplasia, papilloma, and carcinoma were found in the forestomachs of rats in an epichlorohydrin drinking water study (Konishi et al., 1980). The chronic feeding study by Stott et al. (1995), which did not include epichlorohydrin, found forestomach hyperplasia in rats, but no carcinomas or papillomas.

In chronic inhalation bioassays, a statistically-significant increase in the incidence of benign lung adenomas was observed in male mice only at the highest exposure of 272 mg/m^3, but no malignancies were observed (Lomax et al., 1989). The tumors occurred with late onset as they were only observed after 24 months of exposure, but not after 6 or 12 months. No tumors were reported for female mice or for male or female rats.

Most animals exposed to 272 mg/m^3 for 6, 12 or 24 months exhibited nasal histopathology. For the 24-month exposures, the incidence of nasal histopathology was significant in female mice at 90.8 mg/m^3 and in male mice at 272 mg/m^3 1,3-dichloropropene. Despite the dose-dependent hypertrophy and hyperplasia of the nasal respiratory epithelium and/or degeneration of the olfactory epithelium in rats at the highest exposure of 272 mg/m^3, no animals developed tumors in the nasal mucosa. Mice that exhibited these effects had cases that were graded as “slight” histopathologic changes, involving approximately 10% or less of the total respective epithelium, and the changes did not progress in severity or distribution from one exposure duration to the next.

The lack of tumorigenesis in the rat nasal mucosa may be due to the relatively low vapor uptake of this tissue (Stott and Kastl, 1986) and the protective action of GSH. Uptake is much

greater in the rat lung than in the nasal mucosa. Additionally, whereas GSH is depleted in a dose-dependent manner in the nasal mucosa, it appears to be dose-independent in the lung. Decreases of up to70% of control values are maintained across a wide range of dose levels (Fisher and Kilgore, 1988a). The relatively low uptake and rapid detoxification of inhaled 1,3-dichloropropene by GSH in the nasal mucosa appear to be sufficient to protect against carcinogenicity, but not toxicity, along the primary portal of entry. In the rat lung, neither toxicity nor carcinogenicity was observed.

The mutagenicity and toxicity of 1,3-dichloropropene have been extensively studied in both *in vitro* and *in vivo* assays. Early bacterial studies demonstrated that 1,3-dichloropropene was mutagenic in a variety of test systems in the absence of metabolic activation (De Lorenzo et al., 1977; Neudecker et al., 1977; Stolzenberg and Hine, 1980; Creedy et al., 1984; Neudecker and Henschler, 1986). Although later studies showed that these findings were due to mutagenic impurities in the 1,3-dichloropropene formulation (Talcott and King, 1984; Watson et al., 1987), even purified 1,3-dichloropropene caused mutations in the presence of S9 (Watson et al., 1987). Genetic reversions in bacteria were prevented, however, by the addition of physiological concentrations of GSH (Creedy et al., 1984; Watson et al., 1987).

In the absence (verified or assumed) of mutagenic impurities, 1,3-dichloropropene has produced mixed results in mammalian *in vitro* and *in vivo* genotoxicity studies. Although the positive studies indicate that 1,3-dichloropropene can be mutagenic, the relevance of these studies to mammalian tumor formation is uncertain due to the high concentrations or doses used. The lowest concentrations used in *in vitro* studies, on the order of 0.1 mM, are still two orders of magnitude higher than that found in rat blood after high, acute doses of 1,3-dichloropropene. The peak blood level detected after a 3-hour exposure of rats to 409 mg/m^3 1,3-dichloropropene was 0.004 mM 1,3-dichloropropene (Stott and Kastl, 1986). The highest concentration in the 2-year chronic bioassay by Lomax et al. (1989) was 227 mg/m^3. The peak blood level detected in rats after a 25 mg/kg gavage with 1,3-dichloropropene (highest dietary dose administered by Stott et al., 1995) was approximately 0.0027 mM 1,3-dichloropropene (Stott et al., 1998). Even the lowest doses used in *in vivo* genotoxicity tests (62.5 mg/kg in rats by Ghia et al., 1993) were more than twice those used in formation in chronic rodent bioassays is uncertain due to the lack of information about the relative sensitivity of the test systems. However, the weight-of-evidence from short-term studies suggests that 1,3-dichloropropene is mutagenic.

7.4.3 Mode of Action and Implications in Cancer Assessment

Although the major metabolic pathway of 1,3-dichloropropene is conjugation by GSH and subsequent excretion in the urine, Schneider et al. (1998b) found that epoxidation of 1,3-dichloropropene occurs as a minor metabolic pathway in mouse liver at about LD_{50} doses. The doses administered were 3.5-7 times the maximum dose administered to mice in the NTP (1985) study and 7-14 times those administered to mice in the feeding study of Redmond et al., (1995). Schneider et al. (1998b) observed that the epoxides were mutagenic in bacterial assays and that the mutagenicity was decreased (*cis*-epoxide) or abolished (*trans*-epoxide) by the addition of GSH. The investigators also demonstrated that conjugation of 1,3-dichloropropene with GSH decreases epoxide formation in mouse liver. The authors postulated that the epoxides

or their decomposition products are responsible for the mutagenicity of 1,3-dichloropropene in the presence of liver enzymes and that the epoxides bind to deoxyguanosine *in vitro* (Schneider et al., 1998b). Stott et al. (1997a,b), however, found no evidence of DNA adduct formation *in vivo* after subchronic exposures to tumorigenic doses of 1,3-dichloropropene. It is possible that GSH effectively scavenged 1,3-dichloropropene in the subchronic studies and that lifetime exposures to high doses of 1,3-dichloropropene eventually leads to significant GSH depletion and lack of protection from the genotoxic metabolites. 1,3-Dichloropropene may be nongenotoxic at low-dose exposures that do not interfere significantly with normal function of GSH, but bioassay data demonstrating the protective effect of GSH against tumor formation is lacking.

The toxicokinetics of 1,3-dichloropropene have been reasonably characterized. 1,3-Dichloropropene is rapidly absorbed and quickly conjugated with GSH, forming mercapturic acids (Climie et al., 1979; Dietz et al., 1985; Waechter and Kastl, 1988; Waechter et al., 1992), which are rapidly excreted in the urine. The extent of epoxidation, (a minor metabolic pathway identified at ~LD_{50} doses in mice) is reduced by conjugation of 1,3-dichloropropene with GSH. 1,3-Dichloropropene does not bioaccumulate in target tissue to any significant degree (Hutson et al., 1971; Dietz et al., 1984). Repeated high dose exposures to 1,3-dichloropropene are required to significantly deplete GSH in target organs with the exception of nasal tissue. Nonlinear kinetics consistent with saturation of GSH-mediated conjugation systems have been reported at exposure levels of 1363-4086 mg/m^3 in rats (Fisher and Kilgore, 1988a,b). Pharmacokinetic studies have demonstrated that reductions in GSH due to repeated administration of 1,3-dichloropropene occur over a range of doses (22.7-7786 mg/m^3 by inhalation and 12.5-100 mg/kg orally). Significant depletion occurs in most tissues only at high doses, and GSH levels rebound upon cessation of exposure (Stott et al., 1997a).

Thus, it appears likely that toxicity is associated with depletion of GSH. Based on *in vitro* studies and biological monitoring of workers exposed to 1,3-dichloropropene vapors, human toxicokinetics and metabolism via GSH conjugation appear to be similar to that in rodents.

Although the chronic dietary and inhalation bioassays suggest that tumors may not occur at low doses, a nonlinear mechanism of tumor formation is not supported by mechanistic data. In fact, the mutagenic properties of 1,3-dichloropropene suggest a genotoxic mechanism of action. The mutagenic properties and the absence of data to support a nonlinear mechanism of tumor formation require the quantitative assessment to default to a linear model.

7.4.4 Weight of Evidence Evaluation for Carcinogenicity

The evidence associating carcinogenicity in humans to 1,3-dichloropropene exposures is from case studies in which individuals were accidentally exposed to acute high doses and subsequently developed blood cancers (non-Hodgkin's lymphoma and leukemia). These case studies do not provide a firm basis for inferring a causal association between human exposure to 1,3-dichloropropene and blood cancers because the possibility of confounding factors has not been considered or ruled out. Additionally, animal bioassays do not suggest that the hematopoietic system is a target organ of 1,3-dichloropropene carcinogenicity.

Two-year animal bioassays indicate that 1,3-dichloropropene is carcinogenic at relatively high doses. Feeding studies in rodents found a late-onset increase in the incidence of benign hepatocellular adenomas (with one hepatocarcinoma) and forestomach hyperplasia in rats, at 25 mg/kg/day (Stott et al., 1995). No treatment-related malignant tumors were observed in female rats or in male or female mice fed up to 50 mg/kg/day. A gavage study by NTP (1985) found significant incidences of bronchoalveolar, forestomach, and urinary bladder tumors in mice at 50 mg/kg and forestomach and liver tumors in rats at 25 mg/kg. Although many of the observed tumors were benign, evidence for the carcinogenic effects of 1,3-dichloropropene may be found in the increased incidences of urinary bladder tumors in mice, and squamous cell papillomas and carcinomas of the forestomach and liver adenoma in rats. Supporting evidence for carcinogenicity of 1,3-dichloropropene included the increased incidences of alveolar/bronchiolar adenomas of the lung and combined squamous cell papillomas and/or carcinomas of the forestomach (not statistically significant) at the highest dose, 100 mg/kg/day, in female mice. Chronic toxicity of 1,3-dichloropropene was evidenced by hyperplasia of the forestomach in both sexes of rats and mice, and epithelial hyperplasia of the urinary bladder in male and female mice. Based on the serial-sacrifice (ancillary) study (NTP, 1985), development of both hyperplasia and carcinogenicity of the forestomach in rats was dependent on exposure duration (U.S. EPA, 2000e).

In chronic inhalation bioassays, a statistically-significant increase in the incidence of benign lung adenomas was observed in male mice, as well as hypertrophy and hyperplasia of the nasal respiratory epithelium and/or degeneration of the olfactory epithelium in rats and mice (without development of nasal tumors), after 24 months at the highest exposure of 272 mg/m^3 1,3-dichloropropene (Lomax et al., 1989).

The mutagenicity and genotoxicity of 1,3-dichloropropene have been extensively studied in both *in vitro* and *in vivo* assays. Early bacterial studies demonstrated that 1,3-dichloropropene was mutagenic in a variety of test systems in the absence of metabolic activation. Although later studies showed that these findings were due to mutagenic impurities in the 1,3-dichloropropene formulation, even purified 1,3-dichloropropene produced mutations in the presence of S9. Bacterial reversions were prevented, however, by the addition of physiological concentrations of GSH. In the absence (verified or assumed) of mutagenic impurities, 1,3-dichloropropene has produced mixed results in mammalian *in vitro* and *in vivo* genotoxicity studies. Although the positive studies indicate that 1,3-dichloropropene can be mutagenic, the relevance of these studies to mammalian tumor formation is uncertain owing to the high concentrations or doses used. Even the lowest doses used in *in vivo* genotoxicity tests (62.5 mg/kg in rats by Ghia et al., 1993) were more than twice those used in the chronic bioassays (Stott et al., 1995). Although several high-concentration and high-dose genotoxicity studies have shown that 1,3-dichloropropene is mutagenic, the relevance of these studies to tumor formation in chronic rodent bioassays is uncertain because of the lack of information about the relative sensitivity of the test systems. However, the weight of the evidence in the short-term studies suggests that 1,3-dichloropropene is mutagenic (U.S. EPA, 2000e).

Under U.S. EPA's (19990 cancer risk assessment guidelines, the weight of evidence, despite the lack of adequate human data, indicates that 1,3-dichloropropene is clearly a rodent

carcinogen and is "likely to be carcinogenic to humans." This characterization is based on tumors observed in chronic animal bioassays for both oral and inhalation routes of exposure. The animal studies show: similar observations in independent studies; severity of lesions, latency, and lesion progression; and consistency in observations.

Under U.S. EPA's (1987) cancer risk assessment guidelines, l,3-D is classifiable as a "B2," probable human carcinogen, with little or no evidence for carcinogenicity in humans and sufficient evidence in animals. This classification is based on 1) the production of tumors in F344 rats (forestomach, liver) and B6C3F1 mice (forestomach, urinary bladder, and lung) at high bolus doses; 2) observations of benign liver tumors in F344 rats at lower dietary doses; and 3) the formation of mutagenic epoxide metabolites at high doses (at about the LD_{50} level). Inhalation studies showed an increase in the incidence of lung adenomas, however, these were benign tumors.

7.4.5 Sensitive Populations

No human studies are available that provide any insight into the relative sensitivity of children and adults in the general population to the toxic effects of 1,3-dichloropropene. Formulators of 1,3-dichloropropene in manufacturing facilities and applicators of 1,3-dichloropropene in agricultural settings could become sensitive populations due to the potential for their repeated potential exposures to the chemical over periods of time. Some studies suggest that there is a small but distinct subgroup of individuals working with pesticides who develop an allergic reaction upon dermal contact with DD-95® and other pesticides containing mainly 1,3-dichloropropene (Bousema et al., 1991).

Although no animal studies have examined the effect of 1,3-dichloropropene exposure on juvenile animals per se, studies in rats and rabbits provide no evidence of developmental toxicity (Hanley et al., 1988; Linnett et al., 1988; Breslin et al., 1989) even at doses that caused maternal toxicity. Accordingly, it is unlikely that 1,3-dichloropropene causes developmental toxicity in humans, but its effects on children are unknown. Likewise, no human data suggest that gender differences in toxicity or tumorigenicity might occur as a result of exposure to 1,3-dichloropropene. In chronic exposure animal studies, female mice were more sensitive to the urinary bladder toxicity induced by inhalation exposure to 1,3-dichloropropene; male mice exhibited bronchoalveolar adenomas, while the female mice did not (Lomax et al., 1989). Inhalation exposure also produced mild kidney histopathology in female mice and mild kidney and liver histopathology in male mice (Lomax et al., 1989). In a feeding study, male mice also exhibited a decrease in body weight while females did not (Redmond et al., 1995). In a rat feeding study, only males exhibited liver adenomas (Stott et al., 1995), but both sexes manifested neoplastic liver nodules in a gavage study (NTP, 1985). Despite the foregoing, the relevance of gender differences in rodents to those in humans is unknown.

Table 7-2 Genetic and Related Effects of 1,3-Dichloropropene

Test System	EndPoint	Results		Dose	Reference
		With Activation	Without Activation	µg/mL (*in vitro*) mg/kg/day *(in vivo)*	
Prokaryotic organisms:					
***trans*-1,3-Dichloropropene**					
Salmonella typhimurium TA100	Reverse mutation	+	+	10	DeLorenzo et al. (1977)
Salmonella typhimurium TA100	Reverse mutation	+	+	10	Creedy et al. (1984)
Salmonella typhimurium TA100	Reverse mutation	+	+	NG	Neudecker & Henschler (1986)
Salmonella typhimurium TA1535	Reverse mutation	+	+	10	DeLorenzo et al. (1977)
Salmonella typhimurium TA1535	Reverse mutation	+	+	122	Neudecker et al. (1977)
Salmonella typhimurium TA1978	Reverse mutation	+	+	25	DeLorenzo et al. (1977)
***cis*-1,3-Dichloropropene**					
Salmonella typhimurium TA100	Reverse mutation	+	+	10	DeLorenzo et al. (1977)
Salmonella typhimurium TA100	Reverse mutation	+	+	5	Creedy et al. (1984)
Salmonella typhimurium TA100	Reverse mutation	+	+	NG	Neudecker & Henschler (1986)
Salmonella typhimurium TA100	Reverse mutation	+	+	20	Watson et al. (1987)
Salmonella typhimurium TA1535	Reverse mutation	+	+	10	DeLorenzo et al. (1977)
Salmonella typhimurium TA1535	Reverse mutation	+	+	122	Neudecker et al. (1977)
Salmonella typhimurium TA1978	Reverse mutation	+	+	25	DeLorenzo et al. (1977)
Mixture of *trans*- and *cis*-1,3-Dichloropropene					
E. Coli (PQ37)	DNA damage	NT	+	365	von der Hude et al. (1988)

Test System	EndPoint	Results		Dose	Reference
		With Activation	Without Activation	µg/mL (*in vitro*) mg/kg/day *(in vivo)*	
Salmonella typhimurium TA98	Forward mutation (rifampicin resistance)	NT	+	200	Vithayathil et al. (1983)
Salmonella typhimurium TA100	Reverse mutation	+	+	55	Stolzenberg & Hine (1980)
Salmonella typhimurium TA100	Reverse mutation	+	+	17	Haworth et al. (1983)
Salmonella typhimurium TA100 (1,3-dichloropropene purified by chromatography)	Reverse mutation	NT	-	500	Talcott & King (1984)
Salmonella typhimurium TA100	Reverse mutation	NT	+	NG	Talcott & King (1984)
Salmonella typhimurium TA98	Reverse mutation	+	NT	200	Vithayathil et al. (1983)
Eukaryotic organisms:					
Drosophila melanogaster	Sex-linked recessive lethal mutations		+	5750 ppm feed	Valencia et al. (1985)
Drosophila melanogaster	Heritable translocations		-	5750 ppm feed	Valencia et al. (1985)
Chinese hamster lung V79 cells	DNA fragmentation	NT	+	200	Martelli et al. (1993)
Rat primary hepatocytes	DNA fragmentation	NT	+	20	Martelli et al. (1993)
Rat primary hepatocytes	Unscheduled DNA synthesis	NT	+	35	Martelli et al. (1993)
Chinese hamster lung V79 cells	Sister chromatid exchange	-	+	11	von der Hude et al. (1987)
Chinese hamster ovary CHO cells	Sister chromatid exchange	+	+	30	Loveday et al. (1989)

Test System	EndPoint	Results		Dose	Reference
		With Activation	Without Activation	µg/mL (*in vitro*) mg/kg/day *(in vivo)*	
Chinese hamster ovary CHO cells	Chromosomal aberrations	-	-	100	Loveday et al. (1989)
Human hepatocytes	DNA fragmentation	NT	+	35	Martelli et al. (1993)
Human hepatocytes	Unscheduled DNA synthesis	NT	+	35	Martelli et al. (1993)
Human hepatocytes	Sister chromatid exchange	+	+	11	Kevokordes et al. (1996)
Rat liver, kidney and gastric mucosa	DNA fragmentation		+	62.5 ip x 1	Ghia et al. (1993)
Rat hepatocytes	Unscheduled DNA synthesis		-	125 po x 1	Ghia et al. (1993)
Rat bone marrow, spleen and liver cells	Micronucleus test		-	125 po x 1	Ghia et al. (1993)
NMRI mice bone marrow cells	Micronucleus test		+	187 po x 1	Kevokordes et al. (1996)
(C57BL/6 x C3H)F1 mice	Sperm morphology		-	75 ip x 1	Osterloh et al. (1983)

Source: IARC (1986)

Notes: +, positive; -, negative; NT, not tested; NG, not given: LED, lowest effective dose; HID, highest effective dose; PO, oral; ip, intraperitoneal

8.0 DOSE-RESPONSE ASSESSMENT

This section provides discussions of both non-cancer and cancer dose-response assessments and derives toxicity values based on appropriate studies. The dose-response assessments presented in this chapter were abstracted from the *Toxicological Review of 1,3-Dichloropropene* (U.S. EPA, 2000e).

8.1 Dose-Response for Non-Cancer Effects

The derivations of the reference dose (RfD) and reference concentration (RfC) for telone are described below. The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC is an estimate of the daily inhalation exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime.

8.1.1 Reference Dose Determination

Choice of Principal Study and Critical Effect

The rat dietary study of Stott et al. (1995) was selected as the principal study for deriving the RfD. In rats, a statistically-significant increase in the incidence of forestomach histopathology was observed at 12.5 and 25 mg/kg/day for both sexes. Mild basal cell hyperplasia of the mucosal lining was observed, characterized by a prominence of the basal layers of the mucosa due to increased cytoplasmic basophilia and an increased number of cell layers in the basal portion of the mucosa. Forestomach hyperplasia is associated with chronic irritation and is consistent with the observation of primary dermal irritation in other studies (e.g., Nater and Gooskens, 1976) and other portal of entry effects observed in studies of 1,3-dichloropropene exposure (Linnett et al., 1988; Stott et al., 1988; Breslin et al., 1989; Lomax et al., 1989; Haut et al., 1996).

The dose level selected from Stott et al. (1995), an LOAEL of 12.5 mg/kg/day, is consistent with the results of the Stebbins et al. (2000) study, in which rats exhibited basal cell hyperplasia of the non-glandular mucosa of the stomach at the LOAEL of 12.5 mg/kg/day and at the highest dose level of 25 mg/kg/day.

Dose-response Characterization

Table 8-1 documents the incidences for forestomach histopathology in male rats. The lack of chronic irritation (i.e., forestomach hyperplasia) or body weight decrease at 2.5 mg/kg/day defines the study NOAEL. The LOAEL is 12.5 mg/kg/day. No adjustment for exposure duration is necessary because 1,3-dichloropropene was administered daily in the diet for 2 years.

Table 8-1 Incidence of Forestomach Histopathology in Male F344 Rats

Administered dose (mg/kg/day)	Forestomach histopathology (animal incidence)
0	3/100
2.5	4/100
12.5	40/100
25	67/100

Source: Stott et al. (1995)

Methods of Analysis—Benchmark Dose Analysis

Benchmark dose (BMD) analysis was used to derive the RfD (Appendix B). BMD requires a quantitative measure, and the selected study provides a quantitative measure of toxicity in the incidence of treated animals with forestomach histopathology. The BMD_{10} (maximum likelihood estimate at 10% risk) and the $BMDL_{10}$ (95% lower confidence limit on the BMD_{10}) were estimated using the model with the best visual fit, and a statistically-significant goodness-of-fit.

The results for the gamma model were chosen because the visual fit at low doses was the best. The gamma model yielded a BMD_{10} of 5.07 mg/kg/day and a $BMDL_{10}$ of 3.38 mg/kg/day.

Application of Uncertainty Factors (UF) and Modifying Factors (MF)

Uncertainty factors (UFs) are applied to the BMD_{10} and the $BMDL_{10}$ to account for uncertainties in extrapolation from animal data to human exposure conditions, for the variability in human sensitivities, for data deficiencies, and for other factors. Default uncertainty factors are applied for two of the uncertainties listed: for interspecies extrapolation the default uncertainty factor of 10 is applied, since there are no data on the relative sensitivity of rats and humans to stomach irritation; and the default uncertainty factor of 10 is applied to protect sensitive human subpopulations, since there are no data documenting the nature and extent of variability in human susceptibilities to 1,3-dichloropropene. Because the database for 1,3-dichloropropene is substantial and includes studies of genotoxicity, mode of action, pharmacokinetics, reproductive and developmental toxicity, systemic toxicity, and cancer, no additional UFs or MFs are needed.

The BMD_{10} and $BMDL_{10}$ are divided by a total UF of 100 to yield the RfD. Thus, the RfD derived from the $BMDL_{10}$ is 0.03 mg/kg/day (RfD = 3.38 mg/kg/day ÷ 100 = 0.0338 mg/kg/day).

8.1.2 Reference Concentration (RfC) Determination

Choice of Principal Study and Critical Effect

Lomax et al. (1989) was the only chronic inhalation bioassay for 1,3-dichloropropene identified, and thus was chosen as the principal study. In addition, EPA determined that this study was well-designed and well-conducted (EPA, 2000e). The two potential critical effects in

this study are histopathology of the respiratory epithelium in the nasal tract in rats and mice and hyperplasia and inflammation in the urinary bladder in mice.

Nasal histopathology was chosen as the most relevant critical effect because it was also found in subchronic studies of rats or mice (Stott et al., 1988; Breslin et al., 1989) and because it was reported in humans exposed to 1,3-dichloropropene (Markovitz and Crosby, 1984).

Dose-response Characterization

Table 8-2 documents the incidences for nasal histopathology in female mice. The NOAEL is defined by the lack of nasal histopathology at 3.7 mg/m^3. The LOAEL is 14.9 mg/m^3 1,3-dichloropropene.

Table 8-2 Incidence of Nasal Histopathology in Female $B_6C_3F_1$ Mice

Administered dose (mg/m^3)	Adjusted administered dose (mg/m^3) [a]	Nasal hypertrophy/ hyperplasia
0	0	4/50
22.7	3.7	4/50
90.8	14.9	28/50
272	44.7	49/50

Source: Lomax et al. (1989)

[a] Correction for purity of formulation concentration (92%) and correction for intermittent exposure to continuous exposure: 22.7 mg/m^3 × 0.92 × 6/24 hrs × 5/7 days = 3.7 mg/m^3.

Methods of Analysis—Benchmark Concentration Analysis

The gamma model was selected by EPA, since it showed, first, as statistically-significant goodness-of-fit (at p>0.05), and then the best visual fit. This model resulted in a BMC_{10} of 5.91 mg/m^3 and a $BMCL_{10}$ of 3.66 mg/m^3.

1,3-Dichloropropene is a Category 2 gas (U.S. EPA, 1994b), since it is not highly reactive or water soluble and it produces both respiratory (nasal histopathology) and remote effects (urinary bladder histopathology). For Category 2 gases, adjustment of animal exposure to human equivalent concentrations (HECs) is based on algorithms for Category 1 or Category 3 gases depending upon whether the major effect is respiratory or systemic. Algorithms for extrathoracic effects for Category 1 gases are used to adjust animal exposure concentrations of 1,3-dichloropropene to HECs (U.S. EPA, 1994b), because the critical target was the nasal mucosa. The HEC for a Category 1 gas is derived by multiplying the animal BMC_{10} and $BMCL_{10}$ by an interspecies dosimetric adjustment for gas:respiratory effects in the extrathoracic region of the lung, according to the following calculation (U.S. EPA, 1994b):

$$RGDR(ET) = (MV_a/S_a)/(MV_h/S_h)$$

where:

RGDR(ET) = regional gas dose ratio for the extrathoracic area of the lung
MV_a = animal minute volume (mouse = 0.041 L/min)
MV_h = human minute volume (13.8 L/min)
S_a = surface area of the extrathoracic region of the animal lung (mouse = 3 cm^2)
S_h = surface area of the extrathoracic region of the human lung (200 cm^2).

Using default values, the RGDR(ET) = (0.041/3)/(13.8/200) = 0.014/0.069 = 0.198. The animal BMC_{10} and $BMCL_{10}$ are then multiplied by 0.198 to yield the HECs for these values.

$BMC_{10\ HEC}$ = $BMC_{10\ A} \times 0.198 = 5.91 \times 0.198 = 1.17$ mg/m^3
$BMCL_{10\ HEC}$ = $BMCL_{10\ A} \times 0.198 = 3.66 \times 0.198 = 0.725$ mg/m^3

Application of Uncertainty Factors (UF) and Modifying Factors (MF)

For long-term rodent bioassays, the default uncertainty factors for interspecies extrapolation and within-species variability are each 10. Half of that factor, $10^{1/2}$, or 3, reflects the pharmacokinetic component of uncertainty and half represents the pharmacodynamic component of uncertainty. Because 1,3-dichloropropene is rapidly conjugated via GSH-mediated systems to mercapturic acids, excreted in the urine, is not bioaccumulated, and the toxicokinetics in rats and humans are similar, an UF of 3, instead of the default UF of 10, was used for interspecies extrapolation. There are no data documenting the nature and extent of variability in human susceptibility; therefore, the default UF of 10 was used for within-species variation. The database is substantial and includes studies of pharmacokinetics, reproductive and developmental toxicity, systemic toxicity, mechanism of action and mutagenicity/genotoxicity. Therefore, no additional UFs or MFs were applied. Thus, the BMC_{10} and $BMCL_{10}$ are divided by a total uncertainty factor of 30 to yield the RfC for non-cancer effects; using the BMC_{10}, the RfC is 0.04 mg/m^3, and using the $BMCL_{10}$, the RfC is 0.02 mg/m^3 (U.S. EPA, 200f).

8.2 Dose-Response for Cancer Effects

The only human data available are case studies from occupational or accidental exposures, which are inadequate for the assessment of the potential human carcinogenicity of 1,3-dichloropropene. Thus, only the data derived from animal studies were used to assess carcinogenic potential of 1,3-dichloropropene.

In chronic animal bioassays, 1,3-dichloropropene produced tumors in F344 rats (forestomach, liver) and B6C3F1 mice (forestomach, urinary bladder, and lung) at high gavage doses, liver tumors in F344 rats at lower dietary doses, and benign lung tumors in male mice exposed via inhalation. Although 1,3-dichloropropene elicited a positive response for mutagenicity in bacterial assays with the addition of S9, the most compelling evidence for mutagenicity is the isolation of mutagenic epoxide metabolites from mouse liver at high (~LD_{50}) doses. Thus, under EPA's Risk Assessment Guidelines (U.S. EPA, 1987), 1,3-dichloropropene

is a B2, probable human carcinogen, because of the lack of data in humans and sufficient evidence of carcinogenicity in animals (U.S. EPA, 2000g).

The Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996c), characterize 1,3-dichloropropene as a "likely" human carcinogen, based on tumors observed in chronic animal bioassays for both inhalation and oral routes of exposure. Although the chronic dietary and inhalation bioassays suggest that tumors may not occur at low doses, a nonlinear mechanism of tumor formation is not supported by the available mechanistic data. In fact, the mutagenic properties of 1,3-dichloropropene suggest a genotoxic mechanism of action. The mutagenic properties and the absence of data to support a nonlinear mechanism of tumor formation require that the quantitative assessment default to a linear model (U.S. EPA, 2000e).

8.2.1 Choice of Study/Data With Rationale and Justification

Animal carcinogenicity data are sufficient to provide a quantitative assessment of the potential human carcinogenicity of 1,3-dichloropropene. Four lifetime animal studies are available (U.S. EPA, 2000g) that examine the carcinogenicity of 1,3-dichloropropene. Three are oral studies in rats and/or mice (NTP, 1985; Stott et al., 1995; Redmond et al., 1995), and one is an inhalation study in rats and mice (Lomax et al., 1989). The weight of evidence for both the oral and inhalation carcinogenicity of 1,3-dichloropropene indicates that this compound is carcinogenic in animals.

The tumor data chosen for the quantitative oral carcinogenicity assessment are shown in Table 8-3. Since rat liver tumors were observed in both the gavage (NTP, 1985) and feeding studies (Stott et al., 1995), these tumors were chosen for quantitative assessment (U.S. EPA, 2000g). Forestomach tumors, as observed in rats and mice (NTP, 1985), were not chosen due to the confounding effects of epichlorohydrin in the formulation and because the tumors did not appear in the feeding studies (Stott et al., 1995; Redmond et al., 1995). Bronchoalveolar adenoma/carcinoma, as observed in male mice, were considered unacceptable for quantitative assessment, since the control group survival was inadequate due to early deaths attributed to myocarditis. Urinary bladder tumor data were also chosen for quantitative assessment, even though these results were not seen in feeding studies, because the transitional cell carcinoma of the bladder is a rare tumor and because the dosing for mice in the feeding study may have been inadequate as it was not verified by in-cage stability measurements (U.S. EPA, 2000g). In the absence of a single best study, both the NTP (1985) and Stott et al. (1995) studies were evaluated separately and used for the quantitative oral cancer assessment, then the most conservative value was recommended by EPA, as published in the IRIS database (U.S. EPA, 2000g), and as discussed in the IRIS Toxicological Review (U.S. EPA, 2000e).

Table 8-3 Incidence of Tumors in Chronic Oral Bioassays

Administered dose (mg/kg/event)[a]	Human equivalent dose (mg/kg/day)[b]	Hepatocellular adenoma/ carcinoma: male rats (NTP, 1985)	Urinary bladder carcinoma: female mice (NTP, 1985)	Hepatocellular adenoma/ carcinomas: male rats (Stott et al., 1995)
0	0	1/49	0/50	2/49
2.5	0.65	--	--	1/50
12.5	3.22	--	--	6/50
25	2.75	6/48	--	--
25	6.31	--	--	10/49
50	2.88	--	8/50	--
50	5.4	8/50	--	--
100	5.81	--	21/47	--

[a] Daily doses for dietary studies (Stott et al., 1995); dose per gavage for NTP (1985) study.
[b] Administered doses averaged over 7 days/week (if necessary) and adjusted to human equivalent doses by multiplying by (animal body weight/human body weight)$^{1/4}$ and the % of 1,3-dichloropropene in the formulation (92% for NTP [1985] and 96% for Stott et al. [1995]).

The critical study for assessment of cancer inhalation potency is the study by Lomax et al. (1989) in which rats and mice were exposed to up to 272 mg/m^3 1,3-dichloropropene vapors for 6 hours/day, 5 days/week for 2 years. The only neoplastic response observed in any species or sex was an increased incidence of bronchoalveolar adenomas with late onset in male mice in the highest dose group.

8.2.2 Dose Conversion and Dose-Response Analysis

Gavage doses administered three times a week (NTP, 1985) were converted to an average daily dose by multiplying by 3 times/week and dividing by 7 days/week. In accordance with the proposed cancer risk assessment guidelines (U.S. EPA, 1996c), daily doses from all studies were adjusted to human equivalent doses by dividing by (human body weight/animal body weight)$^{1/4}$ using 70 kg as the human body weight and the final body weights of test animals for the animal weights. Doses also were adjusted for the purity of the formulation (U.S. EPA, 2000e).

For the inhalation study by Lomax et al. (1989), the administered dose was adjusted for purity (92%) and for continuous exposure:

272 mg/m^3 x 0.92 x 6/24 hours x 5/7 days = 45 mg/m^3 (human equivalent concentration)

Since the critical target was the lung, algorithms for thoracic effects for Category 1 gases were used to adjust animal exposure concentrations of 1,3-dichloropropene to HECs (U.S. EPA, 1994b). The HEC for a Category 1 gas is derived by multiplying the duration- and purity-adjusted exposure concentrations by an interpecies dosimetric adjustment for gas:respiratory

effects in the tracheobronchial and pulmonary (i.e., thoracic) regions of the lung, according to the following calculation (U.S. EPA, 1994b):

$$RGDR(TH) = (MV_a/S_a)/(MV_h/S_h)$$

where:

RGDR(ET)	= regional gas dose ratio for the thoracic (tracheobronchial and pulmonary) area of the lung
MV_a	= animal minute volume (mouse = 0.041 L/min)
MV_h	= human minute volume (13.8 L/min)
S_a	= surface area of the thoracic region of the animal lung (mouse = 503.5 cm^2)
S_h	= surface area of the thoracic region of the human lung (543,200 cm^2).

Using default values, the RGDR(TH) = (0.041/503.5)/(13.8/543,200) = 3.21. This value is multiplied by the purity- and duration-adjusted animal concentration to derive the Human Equivalent Concentration (HEC):

3.7 mg/m^3 x 3.21 = 11.9 mg/m^3

8.2.3 Extrapolation Model and Rationale

Although the chronic dietary and inhalation bioassays suggest that tumors may not occur at low doses, a nonlinear mechanism of tumor formation is not supported by the available mechanistic data. The mutagenic properties of 1,3-dichloropropene suggest a genotoxic mechanism of action. The mutagenic properties and the absence of data to support a nonlinear mechanism of tumor formation require the quantitative assessment to default to a linear model. To support a nonlinear assessment, the EPA's cancer risk assessment guidelines (1987), require the identification of a nonlinear mode of tumor formation. The available mechanistic data do not support a hypothesis that GSH is protective against tumor formation, which would result in a nonlinear dose-response. Thus, in the absence of support of a nonlinear mechanism of tumor formation, the cancer dose-response assessment uses a linear approach (U.S. EPA, 2000g). The linear approach assumes that a straight line best represents the shape of the dose response from the point of departure to the origin.

Oral cancer potency factors were calculated from each set of tumor data in Table 8-3 using recommendations from the existing cancer risk assessment guidelines (U.S. EPA, 1987) and the proposed cancer risk assessment guidelines (U.S. EPA, 1996c). For analysis by the existing guidelines, the GLOBAL86 linearized multistage model for extra risk was applied to the data to determine the slope at 1 mg/kg/day (Table 8-4).

The multistage model for extra risk from EPA's Benchmark Dose Software, Version 1.1b, was used for analysis in accordance with the proposed guidelines (U.S. EPA, 2000e; U.S. EPA, 2000g). Human equivalent doses and tumor incidences in Table 8-3 were used to calculate

the point of departure, the 95% lower confidence limit of the ED_{10} (LED_{10}) (U.S. EPA, 1996c). The cancer slope factor (i.e., risk at 1 mg/kg/day) was estimated by drawing a straight line from the point of departure to the origin, thus, the cancer slope = $0.1/LED_{10}$ (Table 8-5) (U.S. EPA, 2000e).

For both analyses, the unit risk for drinking water was calculated by multiplying the cancer slope factor by 1/70 kg, 2 L/day, and 0.001 (for conversion of mg to μg). Risk-specific concentrations corresponding to 10^{-4}, 10^{-5}, and 10^{-6} risk were calculated by dividing risk level by unit risk.

Duration-adjusted HECs and tumor incidences from the Lomax et al. (1989) study were used to calculate unit inhalation risk (U.S. EPA, 2000g).

8.2.4 Cancer Potency and Unit Risk

Table 8-4 shows the cancer slope factors (ranging from 5×10^{-2} to 1×10^{-1} $(mg/kg/day)^{-1}$) calculated using the linearized multistage model, as recommended in the existing cancer risk assessment guidelines (U.S. EPA, 1996c).

Table 8-4 Linearized Multistage Oral Cancer Potency Calculations

Parameter	Hepatocellular adenoma/ carcinoma: male rats (NTP, 1985)	Urinary bladder carcinoma: female mice (NTP, 1985)	Hepatocellular adenoma/ carcinoma: male rats (Stott et al., 1995)
Oral slope factor $(mg/kg/day)^{-1}$	5×10^{-2}	1×10^{-1}	5×10^{-2}
Drinking water unit risk (risk per μg/L)	2×10^{-6}	3×10^{-6}	1×10^{-6}
10^{-4} risk (μg/L)	70	40	80
10^{-5} risk (μg/L)	7	4	8
10^{-6} risk (μg/L)	0.7	0.4	0.8

Table 8-5 shows the cancer slope factors (ranging from $4\text{-}5 \times 10^{-2}$ to 1×10^{-1} $(mg/kg/day^{-1})$ calculated using the multistage model, as recommended in the proposed cancer risk assessment guidelines (U.S. EPA, 1996c).

Table 8-5 Multistage Oral Cancer Potency Calculations

Parameter	Hepatocellular adenoma/ carcinoma: male rats (NTP, 1985)	Urinary bladder carcinoma: female mice (NTP, 1985)	Hepatocellular adenoma/ carcinoma: male rats (Stott et al., 1995)
LED_{10}	2 mg/kg/day	1 mg/kg/day	2 mg/kg/day
Oral slope factor $(mg/kg/day)^{-1}$	5×10^{-2}	1×10^{-1}	4×10^{-2}
Drinking water unit risk (risk per μg/L)	1×10^{-6}	3×10^{-6}	1×10^{-6}
10^{-4} risk (μg/L)	70	40	80
10^{-5} risk (μg/L)	7	4	8
10^{-6} risk (μg/L)	0.7	0.4	0.8

The slope factor model of 1×10^{-1} $(mg/kg/day)^{-1}$ calculated using the linearized multistage and the mouse bladder tumor data (NTP, 1985) is recommended (U.S. EPA, 2000e,g), because the proposed cancer guidelines have not been finalized, because there is less uncertainty in the delivered dose in this study compared to the other studies, and because this is the most conservative calculated slope factor. This slope factor results in risk-specific concentrations in drinking water of 40, 4, and 0.4 μg/L corresponding to 10^{-4}, 10^{-5}, and 10^{-6} risk.

The cancer inhalation unit risk factors (i.e., risk at 1 $\mu g/m^3$) were calculated using the duration-adjusted HECs and tumor incidences from the Lomax et al. (1989) study (U.S. EPA, 2000e,g), and using recommendations from both the proposed cancer risk assessment guidelines (U.S. EPA, 1996c) and the existing cancer risk assessment guidelines (U.S. EPA, 1987). The multistage model for extra risk from EPA's Benchmark Dose Software, Version 1.1b, was used for analysis in accordance with the proposed guidelines. HECs and tumor incidences were used to calculate the point of departure, the 95% lower confidence limit of the EC_{10} (LEC_{10}) (U.S. EPA, 1987). The cancer slope factor, or unit risk (i.e., risk at 1 $\mu g/m^3$), was estimated by multiplying the LEC_{10} by 1000 to convert mg to μg, and then drawing a straight line from the point of departure to the origin. Thus, the unit risk = $0.1/(LEC_{10} \times 1000)$. Concentrations corresponding to doses yielding 10^{-4}, 10^{-5}, and 10^{-6} risk levels were calculated by dividing risk level by unit risk, and are 20, 2, and 0.2 $\mu g/m^3$, respectively. The calculated air unit risk for both the multistage and linearized multistage model is 4E-6 $(\mu g/m^3)^{-1}$. EPA (2000g) lists the extrapolation method for this inhalation unit risk as "linearized multistage model, extra risk."

The Health Reference Level (HRL) serves as the benchmark for examining the occurrence data for 1,3-dichloropropene in the Regulatory Determination process. It is the concentration in drinking water equivalent to a one-in-a million risk (10^{-6}) of cancer above background. For 1,3-dichloropropene, the 10^{-6} risk is calculated as follows:

$$10^{-6}\ \text{risk} = \frac{\text{risk x body weight}}{\text{SF x drinking water intake}} = \frac{0.000001 \times 70\ \text{kg}}{0.1\ (\text{mg/kg/day})^{-1} \times 2\text{L/day}} = 3.5 \times 10^{-4}\ \text{mg/L}$$

The HRL is rounded to one significant figure and becomes 0.4 µg/L.

The central tendency estimate is nearly the same as that for the lower bound.

$$10^{-6}\ \text{risk} = \frac{\text{risk x body weight}}{\text{SF x drinking water intake}} = \frac{0.000001 \times 70\ \text{kg}}{0.1\ (\text{mg/kg/day})^{-1} \times 2\text{L/day}} = 3.5 \times 10^{-4}\ \text{mg/L}$$

9.0 REGULATORY DETERMINATION AND CHARACTERIZATION OF RISK FROM DRINKING WATER

9.1 Regulatory Determination for Chemicals on the CCL

The Safe Drinking Water Act (SDWA), as amended in 1996, required the U.S. Environmental Protection Agency (EPA) to establish a list of contaminants to aid the Agency in regulatory priority setting for the drinking water program. EPA published a draft of the first Contaminant Candidate List (CCL) on October 6, 1997 (62 FR 52193, U.S. EPA, 1997b). After review of and response to comments, the final CCL was published on March 2, 1998 (63FR 10273, U.S. EPA, 1998e).

On July 18, 2003, EPA announced final Regulatory Determinations for one microbe and 8 chemicals (68 FR 42897, U.S. EPA, 2003b) after proposing those determinations on June 3, 2002 (67 FR 38222, U.S. EPA, 2002c). The remaining 40 chemicals and ten microbial agents from the first CCL became CCL 2 and were published in the Federal Register on April 2, 2004 (69 FR 17406, U.S. EPA 2004) and finalized on February 24, 2005 (70FR:9071, U.S. EPA, 2005).

EPA proposed Regulatory Determinations for 11 chemicals from CCL2 on May 1, 2007 (72FR 24016) (U.S. EPA, 2007). Determinations for all 11 chemicals were negative based on a lack of national occurrence at levels of health concern. The Agency is given the freedom to determine that there is no need for a regulation if a chemical on the CCL fails to meet one of three criteria established by the SDWA and described in section 9.1.1. After review of public comments and submitted data, the negative determinations for the 11 contaminants have been retained. Each contaminant will be considered in the development of future CCLs if there are changes in health effects and/or occurrence.

9.1.1 Criteria for Regulatory Determination

These are the three criteria used to determine whether or not to regulate a chemical on the CCL:

- The contaminant may have an adverse effect on the health of persons.
- The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern.
- In the sole judgment of the administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The findings for all three criteria are used in making a determination to regulate a contaminant. As required by SDWA, a decision to regulate commits the EPA to publication of a

Maximum Contaminant Level Goal (MCLG) and promulgation of a National Primary Drinking Water Regulation (NPDWR) for that contaminant. The Agency may determine that there is no need for a regulation when a contaminant fails to meet one of the criteria. A decision not to regulate is considered a final Agency action and is subject to judicial review. The Agency can choose to publish a Health Advisory (a nonregulatory action) or other guidance for any contaminant on the CCL, independent of the regulatory determination.

9.1.2 National Drinking Water Advisory Council Recommendations

In March 2000, the U.S. EPA convened a Working Group under the National Drinking Water Advisory Council (NDWAC) to help develop an approach for making regulatory determinations. The Working Group developed a protocol for analyzing and presenting the available scientific data and recommended methods to identify and document the rationale supporting a regulatory determination decision. The NDWAC Working Group report was presented to and accepted by the entire NDWAC in July 2000.

Because of the intrinsic difference between microbial and chemical contaminants, the Working Group developed separate but similar protocols for microorganisms and chemicals. The approach for chemicals was based on an assessment of the impact of acute, chronic, and lifetime exposures, as well as a risk assessment that includes evaluation of occurrence, fate, and dose-response. The NDWAC Protocol for chemicals is a semi-quantitative tool for addressing each of the three CCL criteria. The NDWAC requested that the Agency use good judgement in balancing the many factors that need to be considered in making a regulatory determination.

The U.S. EPA modified the semi-quantitative NDWAC suggestions for evaluating chemicals against the regulatory determination criteria and applied them in decision-making. The quantitative and qualitative factors for 1,3-dichloropropene that were considered for each of the three criteria are presented in the sections that follow.

9.2 Health Effects

The first criterion asks if the contaminant may have an adverse effect on the health of persons. Because all chemicals have adverse effects at some level of exposure, the challenge is to define the dose at which adverse health effects are likely to occur, and to estimate a dose at which adverse health effects are either not likely to occur (threshold toxicant), or have a low probability for occurrence (non-threshold toxicant). The key elements that must be considered in evaluating the first criterion are the mode of action, the critical effect(s), the dose-response for critical effect(s), the RfD for threshold effects, and the slope factor for non-threshold effects.

A full description of the health effects associated with exposure to 1,3-dichloropropene is presented in Chapter 7 of this document and summarized below in Section 9.2.2. Section 9.2.3 presents dose-response information.

9.2.1 Health Criterion Conclusion

The available toxicological data indicate that 1,3-dichloropropene has the potential to cause adverse health effects in humans and animals. Occupational exposure to 1,3-dichloropropene can lead to dermatitis and to acute neurotoxic symptoms. In chronic and subchronic animal studies, histopathologic changes were noted in target organs along the portals of entry (e.g., forestomach for oral administration; nasal mucosa and lung for inhalation) and/or in organs involved in the metabolism (liver) and excretion of conjugated metabolites (e.g., urinary bladder and kidney). 1,3-Dichloropropene is classified by the U.S. EPA as a *likely human carcinogen*, based on a lack of data in humans and sufficient evidence of carcinogenicity in animals. The evidence associating carcinogenicity in humans to 1,3-dichloropropene exposures is from case studies of accidental acute exposure to high doses resulting in blood cancers, however, confounding factors in these studies were not analyzed. 1,3-Dichloropropene is carcinogenic in rats and mice, based on the observations of benign hepatocellular adenomas, hepatocarcinomas, forestomach hyperplasia, bronchoalveolar tumors, urinary bladder tumors, benign lung adenomas, along with hypertrophy and hyperplasia of the nasal respiratory epithelium and/or degeneration of the olfactory epithelium in rats and mice. Although positive mutagenicity studies indicate that 1,3-dichloropropene can be mutagenic, the relevance of these studies to mammalian tumor formation is uncertain because of the high concentrations or doses used. Based on these considerations, the evaluation of the first criterion for 1,3-dichloropropene is positive; 1,3-dichloropropene may have an adverse effect on human health.

9.2.2 Hazard Characterization and Mode of Action Implications

Adverse effects in humans exposed to 1,3-dichloropropene have been observed in occupational epidemiology studies, occupational case studies, community epidemiological studies, and in case reports of accidental ingestion. In occupational epidemiology studies, adverse human health effects caused by exposure to 1,3-dichloropropene have primarily consisted of dermatitis and possible subclinical nephrotoxic effects, as the authors conclude that changes in serum chemistry and urine analysis parameters may have been adaptive responses to detoxification and elimination of 1,3-dichloropropene (serum chemistry and urine analysis parameters of the exposed workers were not subsequently evaluated to assess whether the observed alterations returned to normal values). Exposure to high concentrations can produce acute neurotoxic symptoms, and accidental ingestion of large quantities of 1,3-dichloropropene has been fatal. The quantity and concentrations at which these severe effects occurred are not reported. In a general population study in California near agricultural areas where 1,3-dichloropropene is commonly used, an increased incidence of pancreatic cancer was observed, but concurrent exposures to other agricultural chemicals could have been a confounder (Clary and Ritz, 2003). Actual exposure concentrations were unknown; the surrogate for exposure in this study was pesticide usage.

Acute oral and inhalation toxicity studies in animals indicate that adverse effects occur at different levels with different formulations of 1,3-dichloropropene. Respiratory effects including atelectasis (partial lung collapse), emphysema, and/or edema were observed. In acute dermal

exposure studies, effects included lung congestion, lung hemorrhage, erythema (redness of the skin), edema, and necrosis.

Effects on the forestomach are considered the critical effect of 1,3-dichloropropene exposure in oral subchronic and chronic animal studies. Chronic oral studies of 1,3-dichloropropene also report effects on bone marrow, spleen, stomach, and liver in rats and mice. Subchronic inhalation studies found either no treatment-related effects, or lesions in the nasal turbinates (Stott et al., 1984), hepatocyte enlargement, decreased white blood cell counts, and decreased glutamic pyruvic transaminase activity (Parker et al., 1982), or hyperplasia of the transitional epithelium of the urinary bladder in females (Stott et al., 1988). In chronic inhalation studies, similar to the subchronic studies, nasal tissue effects were observed, as was hyperplasia of the epithelial lining of the nonglandular portion of the stomach (Dow, 1987) and bladder hyperplasia (Lomax et al., 1989).

The rat dietary study by Stott et al. (1995) is the key study selected for derivation of an RfD, based on a statistically-significant increase in the incidence of forestomach histopathology observed at 12.5 and 25 mg/kg/day for both sexes. The histopathology consisted of mild basal cell hyperplasia of the mucosal lining. The LOAEL, 12.5 mg/kg/day, was selected as the basis of the RfD and is consistent with the results of a study in rats (Stebbins et al., 2000), in which rats exhibited basal cell hyperplasia of the nonglandular mucosa of the stomach at the 12.5 and 25 mg/kg/day dose levels.

Several two-year animal bioassays (NTP, 1985; Lomax et al., 1989; Stott et al., 1995; Stebbins et al., 2000) clearly established that 1,3-dichloropropene is carcinogenic. Effects included an increase in the incidence of benign hepatocellular adenomas (with one hepatocarcinoma) in male rats, but no treatment-related tumors in female rats or in male or female mice. A gavage study found significant incidences of bronchoalveolar, forestomach, and urinary bladder tumors in mice, and forestomach and liver tumors in rats (NTP, 1985). However, with the exception of the urinary bladder tumors in mice, most tumors were benign. The EPA has classified 1,3-dichloropropene as a *likely human carcinogen*, because of the lack of data in humans and sufficient evidence of carcinogenicity in animals.

Neither reproductive nor developmental toxicity were observed, even at concentrations that produced parental toxicity. Neurotoxic effects, as judged by clinical signs including hunched posture, pilo-erection, lethargy, ptosis, ataxia, decreased respiratory rate, loss of the righting reflex, have been observed in acute oral and dermal animal studies; however, longer-term animal inhalation studies have not resulted in neurological changes. Human exposures to high concentrations of 1,3-dichloropropene produced severe toxicity manifested by a dose-related range of acute neurotoxic symptoms (Flessel et al., 1978; Hayes, 1982; Markovitz and Crosby, 1984).

9.2.3 Dose-Response Characterization and Implications in Risk Assessment

The principal study utilized for RfD derivation was a 2-year chronic study in rats that reported a statistically-significant increase in the incidence of forestomach histopathology with

an NOAEL of 2.5 mg/kg-day and an LOAEL of 12.5 mg/kg-day (Stott et al., 1995). Decreased body weight gains and decreased food consumption also were observed at an LOAEL of 12.5 mg/kg-day. There was an increased incidence of basal cell hyperplasia of the nonglandular mucosa of the stomach of both sexes at the 12- and 24-month sacrifices at an LOAEL of 12.5 mg/kg/day. Males also had an increase in liver masses and nodules at 12.5 and 25 mg/kg/day. No other clinical signs of toxicity were observed. Benchmark dose (BMD) analysis, with EPA's Benchmark Dose software, version 1.3.2, was used to derive the RfD. The model with the best visual fit and a statistically-significant goodness-of-fit was used to estimate the BMD_{10} (maximum likelihood estimate at 10% risk) and the $BMDL_{10}$ (95% lower confidence limit on the BMD_{10}). The RfD of 0.03 mg/kg-day was derived by dividing the $BMDL_{10}$ by an uncertainty factor of 10 for interspecies differences and an uncertainty factor of 10 to protect sensitive human subpopulations.

The RfC was derived from a 2-year chronic study using both rats and mice (Lomax et al., 1989), in which the critical effects included histopathology of the respiratory epithelium in the nasal tract in rats and mice and hyperplasia and inflammation in the urinary bladder in mice; both effects had an NOAEL of 22.7 mg/m^3 and an LOAEL of 90.8 mg/m^3. Benchmark concentrations (BMC) analysis was used to derive the RfC. The model with the best visual fit was used to estimate the BMC_{10} and $BMCL_{10}$. The uncertainty factor applied was 30, based on a factor of 3 representing the pharmacodynamic component of interpecies uncertainty and a factor of 10 for within-species variation. For long-term rodent bioassays, the uncertainty factors for interspecies extrapolation and within-species variability each may range between 1 and 10. Half of that factor, $10^{1/2}$ or 3, reflects the pharmacokinetic component of uncertainty and the other half (i.e., $10^{1/2}$) represents the pharmacodynamic component of uncertainty. The toxicokinetics of 1,3-dichloropropene are reasonably well understood. Therefore, only half of the full uncertainty factor (i.e., an UF of 3) was used for interspecies extrapolation. This yielded an RfC of 0.02 mg/m^3.

The cancer slope factor is based on two chronic studies in which rat liver tumors were observed via gavage (NTP, 1985) and feeding (Stott et al.,1995), and on the observation of urinary bladder carcinoma in female mice (NTP, 1985). Slope factors were calculated using two models. The slope factor of 1×10^{-1} $(mg/kg/day)^{-1}$, calculated using the linearized multistage model and the mouse bladder tumor data (NTP, 1985), is recommended (U.S. EPA 2000a; U.S. EPA 2000b) because (1) the U.S. EPA's proposed cancer guidelines have not been finalized; (2) there is less uncertainty in the delivered dose in this study compared to the other studies; and (3) this is the most conservative calculated slope factor. The concentration equivalent to a one-in-a-million risk level (0.4 µg/L) was used as the HRL in the analysis of the 1,3-dichloropropene occurrence data.

9.3 Occurrence in Public Water Systems

The second criterion asks if the contaminant is known to occur or if there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern. In order to address this question, the following information was considered:

- Monitoring data from public water systems
- Ambient water concentrations and releases to the environment
- Environmental fate

Data on the occurrence of 1,3-dichloropropene in public drinking water systems were the most important determinants in evaluating the second criterion. EPA looked at the total number of systems that reported detections of 1,3-dichloropropene, as well as those that reported concentrations of 1,3-dichloropropene above an estimated drinking water HRL. For noncarcinogens, the estimated HRL risk level was calculated from the RfD assuming that 20% of the total exposure would come from drinking water. For carcinogens, the HRL was the 10^{-6} risk level. The HRLs are benchmark values that were used in evaluating the occurrence data while the risk assessments for the contaminants were being developed. The HRL for 1,3-dichloropropene is 0.4 µg/L.

The available monitoring data, including indications of whether or not the contamination is a national or a regional problem, are included in Chapter 4 of this document and are summarized below. Additional information on production, use, and environmental fate may be found in Chapters 2 and 3.

9.3.1 Occurrence Criterion Conclusion

The available data on 1,3-dichloropropene use indicate a modestly declining trend since 1988. Available ambient data from national surveys or compiled from historical VOC monitoring data did not detect any 1,3-dichloropropene, even at low minimum reporting levels (MRLs) (e.g., 0.2 µg/L, 0.024 µg/L, or 0.026 µg/L). 1,3-Dichloropropene was detected in a limited number of drinking water systems. All detections in drinking water systems in Round 1 were higher than the HRL of 0.4 µg/L, since the most common MRL, 0.5 µg/L, was higher than the HRL. Round 2 data show greater occurrence of 1,3-dichloropropene across the board, however, detections were at lower levels than those found in Round 1 that did not exceed the health-related benchmarks, possibly due to more sensitive analytical detection methods. In Round 1, the estimated population exposed at ½ the HRL was about 1.8 million people in all states compared to the approximately 900 hundred thousand in Round 2. The Round 1 estimate for exposure above the HRL also was approximately 1.8 million people, compared to about 700 thousand people in Round 2. The decline in the populations exposed to ½ the HRL and the HRL is supported by the ambient data for 1,3-dichloropropene that show no detections at reporting levels from 0.024 to 0.2 µg/L between 1991 and 2001. Based on these results, 1,3-

dichloropropene is not known to occur, nor is it likely to occur in public water systems with a frequency and at levels of public health concern.

9.3.2 Monitoring Data

Drinking water occurrence data for 1,3-dichloropropene are available from the UCM program Round 1 (1988 to 1992) and Round 2 (1992 to 1997) monitoring. It should be noted that the analytical methods used may have resulted in underestimates of actual 1,3-dichloropropene occurrence.

In Round 1 cross-section states, 1,3-dichloropropene was detected at approximately 0.16% of PWSs, affecting 0.86% of the population served, equivalent to approximately 1.8 million people nationally. When all Round 1 results are included in the analysis, 1,3-dichloropropene occurrence appears to be slightly greater. Detections affect 0.20% of PWSs and 0.95% of the population served; exceedances of the HRL (and ½HRL) affect 0.19% of PWSs and 0.94% of the population served. The median concentration of detections for cross-section states was 1 µg/L, while the 99th percentile concentration was 2 µg/L.

In Round 2 cross-section states, 1,3-dichloropropene was detected at 0.35% of PWSs, affecting 0.55% of the population served, equivalent to approximately 1.2 million people nationally. The ½HRL benchmark was exceeded in 0.30% of PWSs, affecting 0.42% of the population served, equivalent to approximately 0.9 million people nationally. The HRL benchmark was exceeded in 0.23% of PWSs, affecting 0.33% of the population served, equivalent to approximately 0.7 million people nationally. When all Round 2 results are included in the analysis, 1,3-dichloropropene occurrence appears to be slightly lower. Detections affect 0.31% of PWSs and 0.47% of the population served; ½HRL exceedances affect 0.27% of PWSs and 0.36% of the population served; and HRL exceedances affect 0.20% of PWSs and 0.27% of the population served. The range of MRLs was 0.08 to 1 µg/L. For cross-section states, the median concentration of detections was 0.5 µg/L, while the 99th percentile was 39 µg/L.

There were no clear geographic or temporal patterns of 1,3-dichloropropene occurrence in PWSs. States with PWSs with detections are distributed from the East to the West Coast, and from the Canadian to the Mexican borders. Even the states with the highest proportion of PWSs with detections are generally distributed across the United States. Eight states (Alaska, Kentucky, Maryland, Minnesota, North Carolina, New Mexico, Ohio, and Washington) contributed 1,3-dichloropropene data to both the Round 1 and Round 2 cross-sections. While these states are not necessarily nationally representative, they enable a preliminary assessment of temporal trends in 1,3-dichloropropene occurrence. Both detections and HRL exceedances began in 1991 and peaked in 1994, and the state with the highest rate of detections, among the eight, was Minnesota.

UCMR 1 monitoring, conducted from 2001 to 2003, assessed 3719 samples from 796 small systems nationwide for the presence of *cis*- or *trans*-1,3-dichloropropene. There were no detections of either isomer with a reporting limit for each isomer of 0.50 µg/L.

9.3.3 Use and Fate Data

1,3-Dichloropropene , marketed under the trade name "Telone," is used as a soil fumigant to control nematodes and other soil pests. It is applied before planting, and generally injected into the soil to minimize volatilization (U.S. EPA, 1998c). 1,3-Dichloropropene was first introduced as a pesticide in 1956 (Hayes, 1982, as cited in HSDB, 2004). It is currently registered for commercial cultivation of all types of food and feed crops, including vegetable, fruit and nut crops, forage crops (grasses, legumes and other non-grass forage crops), tobacco, fiber crops, and nursery crops (ornamental, non-bearing fruit/nut trees and forestry crops). It is not registered for household use (U.S. EPA, 1998c).

National use estimates are available. Using data from a variety of published sources and its own proprietary data, mostly from a 1991 data call-in (DCI), U.S. EPA (1998c) estimated that approximately 23 million pounds of active ingredient (a.i.) were used annually to treat approximately 372 thousand acres during the years 1990-1995. The United States Geological Survey (USGS) used data collected by the National Center for Food and Agricultural Policy (NCFAP) and the Census of Agriculture (CA) to estimate that 40,023,187 lbs a.i./yr of 1,3-dichloropropene were used in agriculture in the early 1990s (Thelin and Gianessi, 2000). The National Center for Food and Agricultural Policy (NCFAP) lists uses of 1,3-dichloropropene on 19 crops totaling approximately 40,083,610 lbs a.i./yr in 1992, and uses on 18 crops totaling approximately 34,717,237 lbs a.i./yr in 1997 (NCFAP, 2003).

1,3-Dichloropropene is listed as a toxic release inventory (TRI) chemical (U.S. EPA, 2003a). TRI data for 1,3-dichloropropene are reported for the years 1988 to 2001 (U.S. EPA, 2002b). Air emissions constitute most of the on-site releases (and total releases), and generally decrease throughout the period of record. A sharp decline is evident between 1995 and 1996, and a modest increase in 2000 and 2001. Surface water discharges are of secondary importance, and no obvious trend is evident. Reported underground injection, releases to land, and off-site releases are generally insignificant. TRI releases of 1,3-dichloropropene were reported from 17 states (AR, CA, DE, FL, GA, HI, IL, KY, LA, MI, MS, NJ, NC, OH, SC, TX, and WA), although not all states reported releases every year.

In soil, the K_{oc} values of 1,3-dichloropropene suggest medium to low soil mobility in the vapor phase. The persistence of 1,3-dichloropropene in soil has been reported to be up to a half-life of 69 days, depending on the type of soil tested. 1,3-Dichloropropene dissipates from soil primarily through volatilization, leaching, abiotic hydrolysis, and aerobic soil metabolism. Runoff of this chemical from soil to water was determined to be, on average, very low.

Volatilization and air emissions of 1,3-dichloropropene during and after application are affected by the rate of degradation of 1,3-dichloropropene in the soil and the application method. Degradation of 1,3-dichloropropene is dependent on soil temperature, moisture content in certain soil types, and addition of soil amendments. Depending on the reaction of 1,3-dichloropropene in air with hydroxyl radicals and ozone molecules, the maximum estimated half-life in air was about 76 days.

The Henry's Law constants of 1,3-dichloropropene indicate that, if discharged to surface water, this chemical is likely to volatilize quickly, with a maximum estimated half-life in water of 50 hours.

9.4 Risk Reduction

The third criterion asks if, in the sole judgement of the Administrator, regulation presents a meaningful opportunity for health risk reduction for persons served by public water systems. In evaluating this criterion, EPA looked at the total exposed population, as well as the population exposed above the estimated HRL. Estimates of the populations exposed and the levels to which they were exposed were derived from the monitoring results. These estimates are included in Chapter 4 of this document and summarized in Section 9.4.2 below.

In order to evaluate risk from exposure through drinking water, EPA considered the net environmental exposure in comparison to the exposure through drinking water. For example, if exposure to a contaminant occurs primarily through ambient air, regulation of emissions to air provides a more meaningful opportunity for EPA to reduce risk than regulation of the contaminant in drinking water. In making the regulatory determination, the available information on exposure through drinking water (Chapter 4) and information on exposure through other media (Chapter 5) were used to estimate the fraction that drinking water contributes to the total exposure. The EPA also evaluated effects on potentially sensitive populations, including fetuses, infants and children. The sensitive population considerations are included in Section 9.4.4.

9.4.1 Risk Criterion Conclusion

Based on the data from the Round 2 cross-section analysis of 20 states, approximately 1.2 million people would be exposed nationally to levels of 1,3-dichloropropene greater than the MRL. When all the Round 2 data are considered, approximately 1 million people nationally are exposed to 1,3-dichloropropene concentrations above the MRL. Aside from potential occupational exposure, no other source of exposure would lead to significant doses of 1,3-dichloropropene. These observations indicate that regulation of 1,3-dichloropropene in drinking water would have little impact on human risk reduction.

9.4.2 Exposed Population Estimates

As described in Section 9.3, a cross-section survey of 20 states in Round 2 reported that 1,3-dichloropropene was detected at 0.35% of PWSs, affecting 0.55% of the population served, equivalent to approximately 1.2 million people nationally. The ½HRL benchmark was exceeded in 0.30% of PWSs, affecting 0.42% of the population served, equivalent to approximately 0.9 million people nationally. The HRL benchmark was exceeded in 0.23% of PWSs, affecting 0.33% of the population served, equivalent to approximately 0.7 million people nationally. When all Round 2 results are included in the analysis, 1,3-dichloropropene occurrence appears to be slightly lower. Detections affect 0.31% of PWSs and 0.47% of the population served; ½HRL exceedances affect 0.27% of PWSs and 0.36% of the population served; and HRL exceedances

affect 0.20% of PWSs and 0.27% of the population served. A national extrapolation of these data indicates that approximately 1 million people would be exposed to 1,3-dichloropropene through the drinking water.

Additionally, the data appear to show a decline in the populations exposed to ½ the HRL and the HRL in Round 1 (1988-1992), as compared to Round 2 (1993-1997). The Round 1 estimate for exposure above the HRL was approximately 1.8 million people, compared to about 700,000 people in Round 2. Similarly, the estimated population exposed at greater than ½ the HRL in Round 1 also was 1.8 million people, as compared to the approximately 900,000 suggested by Round 2 data. The decline in the populations exposed to ½ the HRL and the HRL is supported by the ambient data for 1,3-dichloropropene that show no detections at reporting levels from 0.024 to 0.2 µg/L between 1991 and 2001.

9.4.3 Relative Source Contribution

Relative source contribution analysis compares the magnitude of exposure to 1,3-dichloropropene expected via drinking water and the magnitude of exposure from other media, such as food, air and soil (as described in Section 5). The intake of 1,3-dichloropropene from drinking water can be calculated from the median concentrations described above for both the cross-section study and the study of all the Round 2 states. Using the median 1,3-dichloropropene level from the 20 state cross-section study of 0.5 µg/L, an average daily intake of 2 L/day for an adult, and an average weight of 70 kg for an adult, the corresponding dose would be 1.4×10^{-5} mg/kg-day for adults. For children, assuming an intake of 1 L/day and an average weight of 10 kg, the dose would be 5.0×10^{-5} mg/kg-day.

1,3-Dichloropropene was not detected in any food samples at a detection limit of 1 ppb in one study which examined the concentration of 1,3-dichloropropene in food items (Daft, 1989). Monitoring data or bioconcentration studies to determine concentrations of 1,3-dichloropropene in fish were not located in the literature. A median urban atmospheric concentration of *cis*-1,3-dichloropropene of 0.0239 ppmV (0.11 mg/m^3) is available from the National Ambient Volatile Organic Compounds Database, a compilation of published and unpublished air monitoring data from 1970-1987 for 148 ambient air samples collected from representative urban areas throughout the U. S. (Shah and Heyerdahl, 1989). This urban median value is close to the RfC of 0.02 mg/m^3.

Due to its rapid dissipation in soil, the general population is not likely to be exposed to 1,3-dichloropropene via soil, and intakes are typically expected to be zero. Persons working in treated fields shortly after fumigant treatment may have slightly higher exposures than the general population. An estimate of maximum exposures to 1,3-dichloropropene from soil, occurring around the time of application, can be made based upon the maximum soil concentration reported by Chung et al. (1999) of 16 µg/g. The total daily intake of 1,3-dichloropropene from soil for a 70 kg adult, with a daily intake of 50 mg/day (U.S. EPA, 1997) would be approximately 1.1×10^{-5} mg/kg-day. For a 10-kg child exposed to the same soil concentrations, and an intake rate of 100 mg/day (U.S. EPA, 1997), the total daily intake would

be approximately 1.6 x 10^{-4} mg/kg-day. Both the adult and child estimated daily intake rates are below the RfD of 3 x 10^{-2} mg/kg-day.

As previously mentioned, most exposure to 1,3-dichloropropene appears to occur through air (see Table 5-1). For adults, the estimated daily intake from air (3.15x 10^{-2} mg/kg-day) is 2250 times higher than the estimated daily intake from water (1.4 × 10^{-5} mg/kg-day), while for children, the estimated daily intake from air (1.65 × 10^{-1} mg/kg-day) is 3300 times that from water (5.0 × 10^{-5} mg/kg-day).

9.4.4 Sensitive Populations

Some studies suggest that there is a small but distinct subgroup of individuals working with pesticides who develop an allergic reaction upon dermal contact with DD-95® and other pesticides containing mainly 1,3-dichloropropene (Bousema et al., 1991). Exposed individuals could include formulators, applicators, and agricultural workers.

9.5 Regulatory Determination Decision

As stated in Section 9.1.1, a positive finding for all three criteria is required in order to make a determination to regulate a contaminant. In the case of 1,3-dichloropropene, only the finding for the criterion on health effects is positive. Although there is evidence from animal studies that 1,3-dichloropropene may cause adverse health effects at high doses, available studies indicate that adverse health effects in humans due to 1,3-dichloropropene are limited to production or agricultural workers. Based on monitoring conducted between 1988 to 1997, 1,3-dichloropropene was detected in a limited number of drinking water systems. In Round 1 cross-section states, 1,3-dichloropropene was detected at approximately 0.16% of PWSs, affecting 0.86% of the population served, while in Round 2 cross-section states, 1,3-dichloropropene was detected at 0.35% of PWSs, but only affecting 0.55% of the population served. Accordingly, it appears that 1,3-dichloropropene does not occur in public water systems with a frequency and at levels of public health concern at the present time. Based on the low occurrence of 1,3-dichloropropene in potable water and in the environment, regulation of 1,3-dichloropropene does not present a meaningful opportunity for health risk reduction for persons served by public water systems.

10.0 REFERENCES

Albrecht, W.N. and K. Chenchin. 1985. Dissipation of 1,2-dibromo-3-chloropropane (DBCP), *cis*-1,3-dichloropropene (1,3-DCP), and dichloropropenes from soil to atmosphere. Bull. Environ. Contam. Toxicol. 34:824-831 (as cited in ATSDR, 1992).

Albrecht, W.N., M.R. Hagadone, and K. Chenchin. 1986. Charcoal air sampling tube storage stability and desorption efficiencies of 1,3-dibromo-3-chloropropane and 1,3-dichloropropene. Bull. Environ. Contam. Toxicol. 36:629-634 (as cited in ATSDR, 1994).

Albrecht, W. 1987. Occupational exposure to 1,3-dichloropropene (Telone II®) in Hawaiian pineapple culture. Arch. Environ. Health 42:236-291 (as cited in ATSDR, 1994).

Atkinson, R., K.R. Darnall, A.C. Lloyd, et al. 1979. Kinetics and mechanisms of the reactions of the hydroxyl radical with organic compounds in the gas phase. Adv. Photochem. 11:375-488 (as cited in ATSDR, 1992).

ATSDR (Agency for Toxic Substances and Disease Registry). 1992. Toxicological profile for 1,3-dichloropropene. Available from: <http://www.atsdr.cdc.gov/toxprofiles/tp40.html or from NTIS>.

Bartels, M.J., K.A. Brzak, A.L. Mendrala , et al. 2000. Mechanistic aspects of the metabolism of 1,3-dichloropropene in rats and mice. Chem. Res. Toxicol. 13(11):1096-102.

Basile, M., N. Senesi, and F. Lamberti. 1986. A study of some factors affecting volatilization losses of 1,3-dichloropropene (1,3-D) from soil. Agric. Ecosys. Environ. 17:269-279 (as cited in Gan et al., 1999).

Bean, R.M., B.L. Thomas, and D.A. Neitzel. 1985. Analysis of sediment matter for halogenated products from chlorination of power plant cooling water. In: Proceedings of the 5th Water Chlorination Conference 1357-1370 (as cited in ATSDR, 1992).

Belser, N.O. and C.E. Castro. 1971. Biodehalogenation: Metabolism of the nematocides *cis*- and *trans*-3-chloroallyl alcohol by a bacterium isolated from soil. J. Agric. Food Chem. 19:23-26 (as cited in ATSDR, 1992).

Bousema, M.T., G.R. Wiemer, and T.H. Van Joost. 1991. A classic case of sensitization to DD-95. Cont. Derm. 24(2):132-133 (as cited in U.S. EPA, 2000e).

Brantley, A.S. and T.G. Townsend. 1999. Leaching of pollutants from reclaimed asphalt pavement. Environ. Engineer. Sci. 16(2):105-116.

Breslin, W., H. Kirk, C. Streeter, et al. 1989. 1,3-Dichloropropene: two-generation inhalation reproduction study in Fischer 344 rat. Fundam. Appl. Toxicol. 12:129-143 (as cited in ATSDR, 1992).

Brouwer, E.J., C.T.A. Evelo, A.J.W. Verplanke, et al. 1991. Biological effect monitoring of occupational exposure to 1,3-dichloropropene: effects on liver and renal function and on glutathione conjugation. Br. J. Ind. Med. 48(3):167-172 (as cited in U.S. EPA, 2000e).

Caldwell, J.C., T.J. Woodruff, R. Morello-Frosch, et al. 1998. Application of health information to hazardous air pollutants modeled in EPA's Cumulative Exposure Project. Toxicol. Industrial Health 14(3):429-454. Available from: <http://www.epa.gov/CumulativeExposure/resource/resource.htm>.

California State Water Resources Board, Toxic Substances Control Program. 1983. 1,2-Dichloropropane, 1,3-dichloropropene. Special Projects Report 83-8sp, August 1983.

California Department of Food and Agriculture. 1990. Use of pesticide suspended by CDFA. New Release 90-45. CDFA, Sacramento, CA (as cited in Gan et al., 1998).

Carreon, R. and J. Wall. 1983. Telone II: Skin sensitization potential in the guinea pig. Dow Chemical Company, Midland, Michigan (as cited in ATSDR, 1992).

Castro, C.E. and N.O. Belser. 1968. Biodehalogenation. Reductive dehalogenation of the biocides ethylene dibromide, 1,2-dibromo-3-chloropropane, and 2,3-dibromobutane in soil. Environ. Sci. Technol. 2:779-783 (as cited in ATSDR, 1992).

Castro, C.E. and N.O. Belser. 1966. Hydrolysis of *cis*- and *trans*-1,3-dichloropropene in wet soil. J. Agric. Food Chem. 14:69-70 (as cited in ATSDR, 1992).

ChemIDPlus. 2004. Available from: <http://chem2.sis.nlm.nih.gov/chemidplus/>.

Chen, C., R.E. Green, D.M. Thomas, et al. 1995. Modeling 1,3-dichloropropene fumigant volatilization with vapor-phase advection in the soil profile. Environ. Sci. Technol. 29:1816-1821 (as cited in Gan et al., 1998).

Chung K.-Y., D. W. Dickson and L.-T. Ou. 1999. Differential enhanced degradation of *cis*- and *trans*-1,3-D in soil with a history of repeated field applications of 1,3-D. J. Environ. Sci. Health, Part B: Pestic., Food Contam., Agric. Wastes 34(5):749-768.

Clary, T. and B. Ritz. 2003. Pancreatic cancer mortality and organochlorine pesticide exposure in California, 1989-1996. J. Ind. Med. 43(3):306-13.

Climie, I., D.H. Hutson, B.J. Morrison, et al. 1979. Glutathione conjugation in the detoxification of (Z)-1,3-dichloropropene a component of the nematocide DD® in the rat. Xenobiotica 9:149-156 (as cited in ATSDR, 1992).

Coate, W. 1979a. Addendum to final report on the 90-day inhalation toxicity study in rats and mice -Telone II. Hazelton Laboratories: Vienna, Virginia, for Dow Chemical Company, Midland, Michigan (as cited in ATSDR, 1992).

Coate, W. 1979b. Subacute inhalation toxicity study in rats and mice of Telone II® (1,3-dichloropropene). Hazleton Laboratories: Vienna, Virginia, for Dow Chemical Company, Midland, Michigan.

Coate, W.B., D.L. Keenan, R.J. Hardy, et al. 1978. Final report: Telone II (production grade): Project No. 174-126 [unpublished study]. Prepared by Hazelton Laboratories America, Inc. Submitted by Dow Chemical U.S.A. (as cited in U.S. EPA, 1998b).

Cohen, D.B. 1986. Groundwater contamination by toxic substances. A California assessment. Amer. Chem. Soc. Symp. Series 315:499-529 (as cited in ATSDR, 1992).

Corazza, M., G. Zinna, and A. Virgili. 2003. Allergic contact dermatitis due to 1,3-dichloropropene soil fumigant. Contact Dermat. 48(6):341.

Cracknell S., G. Jackson, and C. Hardy. 1987. Telone II (1,3-dichloropropene) - acute inhalation study in rats-- 4-hour exposure. Huntingdon Research Center: Cambridgeshire, England, for Dow Chemical Europe, Horgen, Switzerland (as cited in ATSDR, 1992).

Creedy, C., T. Brooks, B. Dean, et al. 1984. The protective action of glutathione on the microbial mutagenicity of the Z- and E- isomers of 1,3-dichloropropene. Chem. Biol. Interact. 50:39-48 (as cited in ATSDR, 1992; U.S. EPA, 2000).

Daft, J.L. 1989. Determination of fumigants and related chemicals in fatty and non-fatty foods. J. Agric. Food Chem. 37:560-564 (as cited in ATSDR, 1994).

De Lorenzo, F., S. D. Innocenti, A. Ruocco, et al. 1977. Mutagenicity of pesticides containing 1,3-dichloropropene. Cancer Res. 37:1915-1917 (as cited in ATSDR, 1992).

Delzer, G.C. and T. Ivahnenko. 2003. Occurrence and temporal variability of methyl tert-butyl ether (MTBE) and other volatile organic compounds in select sources of drinking water: Results of the focused survey. U.S. Geological Survey Water-Resources Investigations Report WRIR 02-4084, 65 p. Available from: <http://sd.water.usgs.gov/nawqa/pubs/wrir/wrir02_4084.html>. Link to document from: <http://sd.water.usgs.gov/nawqa/vocns/nat_survey.html>.

Deitz, F., D. Dittenber, and P. Kastl. 1982. 1,3-Dichloropropene: pharmacokinetics, effect on tissue non-protein sulfhydryls, and macromolecular binding in Fischer-344 rats and B6C3F1 mice following oral administration. Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Company, Midland MI (as cited in ATSDR, 1992).

Deitz, F.K., E.A. Hermann, and J.C. Ramsey. 1984. The pharmacokinetics of ^{14}C-1,3-dichloropropene in rats and mice following oral administration. Toxicologist 4:147 (Abstr. No. 585) (as cited in U.S. EPA, 2000e).

Deitz F.K., E.A. Hennann, P. Kastl, et al. 1985. 1,3-Dichloropropene: pharmacokinetics, effect on tissue non-protein sulfhydryls, and macromolecular binding in Fischer 344 rats and B6C3F1 mice following oral administration. The Dow Chemical Company, Midland, MI. No. 86-870023122 (as cited in U.S. EPA, 2000e).

Delzer, G.C. and T. Ivahnenko. 2003. Occurrence and temporal variability of methyl tert-butyl ether (MTBE) and other volatile organic compounds in select sources of drinking water: Results of the focused survey: U.S. Geological Survey Water-Resources Investigations Report WRIR 02-4084, 65 p. Available from: <http://sd.water.usgs.gov/nawqa/pubs/wrir/wrir02_4084.html>. Link to document from: <http://sd.water.usgs.gov/nawqa/vocns/nat_survey.html>.

Dilling, W.L. 1977. Interphase transfer processes. II. Evaporation rates of chloromethanes, ethanes, ethylenes, propanes, and propylenes from dilute aqueous solutions. Comparisons with theoretical predictions. Environ. Sci. Technol. 11:405-409 (as cited in ATSDR, 1992).

Dow. 1987. Dow Chemical Company - Submission of toxicity data to support the reregistration of Telone II soil fumigant containing 1,3-dichloropropene as active ingredient. Transmittal of one study (as cited in U.S. EPA, 1998).

Dowty, B.J., D.R. Carlisle and J.L. Laseter. 1975a. New Orleans drinking water sources tested by gas chromatography-mass spectrometry. Occurrence and origin of aromatics and halogenated aliphatic hydrocarbons. Environ. Sci. Technol. 9:762-765 (as cited in ATSDR, 1992).

Dowty, B.J., D.R. Carlisle, J.L. Laseter, et al. 1975b. Halogenated hydrocarbons in New Orleans drinking water and blood plasma. Science 187:75-77 (as cited in ATSDR, 1992).

Dungan, R.S., J. Gan, and S. Yates. 2001. Effect of temperature, organic amendment rate and moisture content on the degradation of 1,3-dichloropropene in soil. Pest. Manage. Sci. 57:1107-1113.

Eder, E., K. Dornbusch, and G. Fischer. 1987. The role of biotransformation in the genotoxicity of allylic compounds. Arch. Toxicol. 60:182-186 (as cited in ATSDR, 1992).

Eisenreich, S.J., B.B. Looney, and J.D. Thornton. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ. Sci. Technol. 15:30-38 (as cited in ATSDR, 1992).

Fisher, G. and W. Kilgore. 1988a. Tissue level of glutathione following acute inhalation of 1,3-dichloropropene. J. Toxciol. Environ. Health 23(2):171-82 (as cited in U.S. EPA, 2000e).

Fisher, G. and W. Kilgore. 1988b. Mercapturic acid excretion by rats following inhalation exposure to 1,3-dichloropropene. Fundam. Appl. Toxicol. 11:300-307 (as cited in U.S. EPA, 2000e).

Fisher, G. and W. Kilgore. 1989. Pharmacokinetics of S-[3-chloroprop-2-enyl] glutathione in rats following acute inhalation exposure to 1,3-dichloropropene. Xenobiotica 19:269-278 (as cited in ATSDR, 1992).

Flessel, P., J. Goldsmith, E. Kahn, et al. 1978. Acute and possible long-term effects of 1,3-dichloropropene. California. Morbid. and Mortal. Weekly Report 27:5-55 (as cited in ATSDR, 1992).

Gan, J., S.R. Yates, D. Wang, et al. 1998. Effect of application methods on 1,3-dichloropropene volatilization from soil under controlled conditions. J. Environ. Qual. 27(2):432-438.

Gan, J., S.K. Papiernik, S.R. Yates, et al. 1999. Temperature and moisture effects on fumigant degradation in soil. J. Environ. Qual. 28:1436-1441.

Ghia, M., L. Robbiano, A. Allavena, et al. 1993. Genotoxic activity of 1,3-dichloropropene in a battery of *in vivo* short-term tests. Toxicol. Appl. Pharmacol. 120:120-125 (as cited in U.S. EPA, 2000e).

Grady, S.J. 2003. National survey of methyl tert-butyl ether and other volatile organic compounds in drinking-water sources: Results of the random survey: U.S. Geological Survey Water-Resources Investigations Report WRIR 02-4079, 85 p. Available from: <http://sd.water.usgs.gov/nawqa/pubs/wrir/wrir02_4079.html>. Link to document from: <http://sd.water.usgs.gov/nawqa/vocns/nat_survey.html>.

Hamilton, P.A., T.L. Miller, and D.N. Myers. 2004. Water Quality in the Nation's streams and aquifers: overview of selected findings, 1991-2001. USGS Circular 1265. Available on-line at: http://water.usgs.gov/pubs/circ/2004/1265/pdf/circular1265.pdf. Link to document from: http://water.usgs.gov/pubs/circ/2004/1265/ (accessed December 2, 2004).

Hanley, Jr. T.R., J.A. John-Greene, J.T. Young, et al. 1988. Evaluation of the effects of inhalation exposure to 1,3-dichloropropene on fetal development in rats and rabbits. Fund. Appl. Toxicol. 8:562-570 (as cited in U.S. EP A, 2000e).

Hauser, T.R. and S.M. Bromberg. 1982. EPA's monitoring program at Love Canal 1980. Environ. Monit. Assess. 2:249-272 (as cited in ATSDR, 1992).

Haut, K., K. Stebbins, K. Johnson, et al. 1996. Subchronic toxicity of ingested 1,3-dichloropropene in rats and mice. Fundam. Appl. Toxicol. 32:224-232 (as cited in U.S. EPA, 2000e).

Haworth S., T. Lawlor, K. Mortelmans, et al. 1983. *Salmonella* mutagenicity test results for 250 chemicals. Environ. Mutagen. Suppl .1:3-142 (as cited in ATSDR, 1992).

Hayes, W.J. 1982. Pesticides Studied in Man. Baltimore: Williams and Wilkins. pp. 139-171 (as cited in U.S. EPA, 2000e).

Heim, L.G., N.J. Snyder, and I. van Wesenbeeck. 2002. Runoff of 1,3-dichloropropene from field plots exposed to simulated and natural rainfall. J. Soil Water Conserv. 57:16-23.

Hernandez, A.F., J.C. Martin-Rubi, J.L. Ballesteros, et al. 1994. Clinical and pathological findings in a fatal 1,3-dichloropropene intoxication. Hum. Exp. Toxicol. 13(5):303-306 (as cited in U.S. EPA, 2000e)

HSDB (Hazardous Substances Data Base). 2004. Available from: <http://toxnet.nlm.nih.gov/>.

Hutson, D., J. Moss, and B. Pickering. 1971. Excretion and retention of components of the soil fumigant DD® and their metabolites in the rat. Food. Cosmet. Toxicol. 9:677 (as cited in ATSDR, 1992; U.S. EPA, 2000e).

IARC (International Agency for Research on Cancer). 1986. IARC Monographs of the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 41: 1,3-Dichloropropene. World Health Organization, Lyon, France (as cited in ATSDR, 1994).

Ivahnenko, T., S.J. Grady, and G.C. Delzer. 2001. Design of a national survey of methyl tert-butyl ether and other volatile organic compounds in drinking-water sources. U.S. Geological Survey Open-File Report OFR 01-271, 42 p. Available from: <http://sd.water.usgs.gov/nawqa/pubs/ofr/ofr01_271.html>. Link to document from: <http://sd.water.usgs.gov/nawqa/vocns/nat_survey.html>.

Jeffrey, M. 1987a. Telone II soil fumigant: primary eye irritation study in New Zealand white rabbits. Dow Chemical Company, Midland, Michigan (as cited in ATSDR, 1992).

Jeffrey, M. 1987b. Telone II soil fumigant: primary dermal initiation study in New Zealand white rabbits. Dow Chemical Company, Midland, Michigan (as cited in ATSDR, 1992).

Jeffrey, M., J. Battjes, and L. Lamax. 1987. Telone II soil fumigant: acute oral toxicity study in Fischer 344 rats [unpublished study]. Laboratory Project ID: HET M-OO3993-017A. Prepared by Dow Chemical Co. p. 29. (as cited in U.S. EPA, 1998b).

Jones, J.R. 1988a. 1,3-Dichloropropene *cis*-isomer: acute oral toxicity test in the rat. Project Number 44/246. Performed by Safepharm Laboratories Limited, Derby, U.K., for Dow Chemical Company Limited, Oxfordshire, U.K. (as cited in ATSDR,1992).

Jones, J.R. 1988b. 1,3-Dichloropropene *cis*-isomer: acute dermal toxicity test in the rat. Project Number 44/247 [unpublished study to be peer reviewed]. Performed by Safepharm Laboratories Limited, Derby, U.K., for Dow Chemical Company Limited, Oxforshire, U.K. (as cited in ATSDR, 1992).

Jones, J.R. and T. Collier. 1986a. Telone II: OECD 401 acute oral toxicity test in the rat. Safepharm Laboratories Limited: Derby, U.K., for Dow Chemical Europe, Horgen, Switzerland (as cited in ATSDR, 1992).

Jones, J.R. and T. Collier. 1986b. Telone II: OECD 401 acute dermal toxicity test in the rat. Safepharm Laboratories Limited: Derby, U.K., for Dow Chemical Europe, Horgen, Switzerland (as cited in ATSDR, 1992).

Kenaga, E.E. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol. Environ. Safety 4:26-38 (as cited in ATSDR, 1992).

Kevekordes, S., T. Gebel, K. Pay, et al. 1996. Genotoxicity of selected pesticides in the mouse bone-marrow micronucleus test and in the sister-chromatid exchange test with human lymphocytes *in vitro*. Toxicol. Lett. 89:35-42 (as cited in U.S. EPA, 2000e).

Kim, J., S.K. Papiernik, W.J. Farmer, et al. 2003. Effect of formulation on the behavior of 1,3-dichloropropene in soil. J. Environ. Qual. 32:2223-2229.

Kloes, P., L. Calhoun, J. Young, et al. 1983. Telone II; inhalation teratology probe study in Fischer 344 rats and New Zealand white rabbits. Dow Chemical Company, Midland, Michigan (as cited in ATSDR, 1992).

Konishi, Y., A. Kawabata, A. Denda, et al. 1980. Forestomach tumors induced by orally administered epichlorohydrin in male Wistar rats. Gann 71 :922-923 (as cited in U.S. EPA, 2000e).

Krijgsheld, K.R. and A. van der Gen.1986. Assessment of the impact of the emission of certain organochlorine compounds on the aquatic environment. Part II: Allychloride, 1,3- and 2,3-dichloropropene. Chemosphere 15:861-880 (as cited in ATSDR, 1992).

Lao, R.C., R.S. Thomas, P. Bastian, et al. 1982. Analysis of organic priority and non-priority pollutants in environmental samples by GC/MS/computer systems. In: Albaiges, J. (ed.). Analytical techniques in environmental chemistry II. New York, NY: Pergamon Press Ltd. pp. 107-118 (as cited in ATSDR, 1992).

Leahy, P.P. and T.H. Thompson. 1994. The National Water-Quality Assessment Program. U.S. Geological Survey Open-File Report 94-70. p. 4. Available from: <http://water.usgs.gov/nawqa/NAWQA.OFR94-70.html>.

Lee, S., R. McLaughlin, M. Harnly, et al. 2002. Community exposures to airborne agricultural pesticides in California: Ranking of inhalation risks. Environ. Health Perspect. 110(12):1175-1184.

Leiber, M.A. and H.C. Berk. 1984. Development and validation of an air-monitoring method for 1,3-dichloropropene, *trans*-1,2,3-trichloropropene, *cis*-1,2,3-trichloropropene, 1,1,2,3-tetrachloropropene, 2,3,3-trichloroprop-2-en-l-01 and 1,1,2,2,3-pentachloropropane. Anal. Chem. 56:2134-2137 (as cited in ATSDR, 1994).

Leistra, M. 1970. Distribution of 1,3-dichloropropene over the phases in soil. J. Agr. Food Chem. 18:1124-1126 (as cited in Yang, 1986).

Leistra, M. and M.J. Frissel. 1975. Computations on the material balance of pesticides in soil. In F. Coulston and F. Korte (eds.), Pesticides: Environmental Quality and Safety. Supplement Vol. 3. Thieme Publ.: Stuttgart, Germany. pp.817-828 (as cited in Gan et al., 1998).

Lichy, C. and K. Olsen. 1975. Acute toxicological properties of experimental nematicide formulation M-3993 containing 1,3-dichloropropene. Dow Chemical Company, Midland, Michigan (as cited in ATSDR, 1992).

Linnett, S.L., D.G. Clark, D. Blair, et al. 1988. Effects of subchronic inhalation of D-D (1,3-dichloropropene/1,2-dichloropropene) on reproduction in male and female rats. Fundam. Appl. Toxicol. 10:214-223 (as cited in U.S. EPA, 2000e).

Lomax, L., L. Calhoun, W. Scott, et al. 1987. Telone II soil fumigant: 2-year inhalation chronic toxicity-oncogenicity study in rats: Laboratory Project Study ID: M-003993-009R [unpublished study]. Prepared by Dow Chemical Co. p. 739. (as cited in U.S. EP A, 1998b, 2000e).

Lomax L., W. Stott, K. Johnson, et al. 1989. The chronic toxicity and oncogenicity of inhaled technical grade 1,3-dichloropropene in rats and mice. Fundam. Appl. Toxicol. 12:418-431 (as cited in ATSDR, 1992).

Loveday, K.S., M.H. Lugo, and M.A. Resnick. 1989. Chromosome aberrations and sister chromatid exchange tests in Chinese hamster ovary cells *in vitro*. III. Results with 20 chemicals. Environ. Mol. Mutagen. 13:60-94 (as cited in ATSDR, 1992).

Mabey, W.R., K.H. Smith, R.T. Podoll, et al. 1981. Aquatic fate process data for organic priority pollutants. U.S. Environmental Protection Agency, Washington, DC. EPA 440/4-81-014 (as cited in ATSDR, 1992).

Maddy, K.T., F. Schnieder, and S. Frederickson. 1982. Monitoring of Telone II during and following experimental application by shank injection to established trees and grape vines in California in 1980 and 1981. HS-967. Sacramento, CA: California Department of Food and Agriculture, Division of Pest Management, Environmental Protection and Worker Safety (cited in Albrecht 1987; ATSDR, 1992).

Markovitz, A. and W.H. Crosby. 1984. Chemical carcinogenesis. A soil fumigant, 1,3-dichloropropene, as possible cause of hematologic malignancies. Arch. Intern. Med. 144:1409-1411 (as cited in ATSDR, 1994; U.S. EPA, 2000e).

Martelli, A., A. Allavena, M. Ghia, et al. 1993. Cytotoxic and genotoxic activity of 1,3-dichloropropene in cultured mammalian cells. Toxicol. Appl. Pharmacol. 120:114-119 (as cited in U.S. EPA, 2000e).

McKenry, M.V. and I.J. Thomason. 1974. 1,3-Dichloropropene and 1,2-dibromoethane compounds: I. Movement and fate as affected by various conditions in several soils. Hilgardia 42:393-421 (as cited in Gan et al., 1998).

Meulenbelt, J. and I. de Vries. 1997. Acute work-related poisoning by pesticides in The Netherlands; a one year follow-up study. Przegl. Lek. 54(10):665-70.

Mizell, M. 1988. Telone C-17 soil fungicide and nematicide: primary dermal irritation study in New Zealand white rabbits. Dow Chemical Company, Midland, Michigan (as cited in ATSDR, 1992.)

Mizell, M., B.L. Yano, and J. Battjes. 1988a. Telone C-17 soil fungicide and nematicide: Acute oral toxicity in Fischer 344 rats. Dow Chemical Company, Midland, Michigan (as cited in ATSDR, 1992).

Mizell, M., K. Johnson and J. Battjes. 1988b. Telone C-17 soil fungicide and nematicide: acute dermal toxicity study in New Zealand white rabbits. Dow Chemical Company, Midland, Michigan (as cited in ATSDR, 1992).

Munnecke, D.E. and S.D. Vangundy. 1979. Movement of fumigants in soil, dosage, responses, and differential effects. Ann. Rev. Phytopathol. 17:405-429 (as cited in ATSDR, 1992).

Nater, J.P. and V.H.J. Gooskens. 1976. Occupational dermatosis due to a soil fumigant. Contact Dermat. 2(4):227-229 (as cited in U.S. EPA, 2000e).

NCFAP (National Center for Food and Agricultural Policy). 2003. National Pesticide Use Database. Available from: <http://www.ncfap.org/database/default.htm>.

Neudecker, T., A. Stefani, and D. Henschler. 1977. *In vitro* mutagenicity of the soil nematicide 1,3-dichloropropene. Experientia 33:1084-1085 (as cited in ATSDR, 1992).

Neudecker, T. and D. Henschler. 1986. Mutagenicity of chloroolefins in the *Salmonella*/ mammalian microsome test. III. Metabolic activation of the allylic chloropropenes allyl chloride, 1,3-dichloropropene, 2,3-dichloro-1-propene, 1,2,3-trichloropropene, 1,1,2,3-tetrachloro-2-propene and hexachloropropene by S9 mix via two different metabolic pathways. Mutat. Res. 170:1-9 (as cited in ATSDR, 1992; U.S. EPA, 2000).

NIOSH (National Industrial Occupational Safety and Health). 1989. Department of National Industrial Occupational Safety and Health, National Occupational Exposure Survey (NOES). Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health (as cited in ATSDR, 1994).

NRC (National Research Council). 1983. Risk Assessment in the Federal Government: Managing the Process. Washington, DC: National Academy Press.

NRC (National Research Council). 2002. Opportunities to improve the U.S. Geological Survey National Water Quality Assessment Program. National Academy Press. p. 238. Available from: <http://www.nap.edu/catalog/10267.html>.

NTP (National Toxicology Program). 1985. Toxicology and carcinogenesis studies of Telone II in F344/N rats and B6C3F1 mice. National Toxicology Program, U.S. Dept of Health and Human Services. NTP TR 269. NIH Publ. No. 85-2525 (as cited in U.S. EPA, 1998a; U.S. EPA, 1998b; U.S. EPA, 2000e).

Osterloh J., G. Letz, S. Pond, et al. 1983. An assessment of the potential testicular toxicity of 10 pesticides using the mouse-sperm morphology assay. Mutat. Res. 116:407-415 (as cited in ATSDR, 1992).

Osterloh, J.D., B.-S. Cohen B-S, W. Popendorf, et al. 1984. Urinary excretion of the N-acetyl cysteine conjugate of *cis*-1,3-dichloropropene by exposed individuals. Arch. Environ. Health 39:271-275 (as cited in ATSDR, 1994).

Osterloh, J.D., R. Wang, F. Schneider, et al. 1989a. Biological monitoring of dichloropropene: Air concentrations, urinary metabolite, and renal enzyme excretion. Arch. Environ. Health 44:207-213 (as cited in ATSDR, 1994).

Osterloh, J.D., R. Wang, L. O'Connell, et al. 1989b. Pilot study for biological monitoring of 1,3-dichloropropene. Amer. Chem. Soc. Symp. Series 382:218-230 (as cited in ATSDR, 1994).

Otson, R. 1987. Purgeable organics in Great Lakes raw and treated water. Int. J. Environ. Anal. Chem. 31:41-53 (as cited in ATSDR, 1992).

Parker, C.M., W.B. Coaste and R.W. Voelker. 1982. Subchronic inhalation toxicity of 1,3-dichloropropene/l,2-dichloropropene (DD) in mice and rats. J. Toxicol. Environ. Health 9:899-910 (as cited in ATSDR, 1992; U.S. EPA, 2000).

Rawlings, G.D. and M. Samfield. 1979. Toxicity of secondary effluents from textile plants. U.S. Environmental Protection Agency, Washington, DC. EPA 600/7-78-168. (As cited in ATSDR, 1992).

Redmond, J., K. Stebbins, and W. Stott. 1995. Telone II soil fumigant: two-year dietary chronic toxicity/oncogenicity study in B6C3F1 mice – final report: Lab Project Number: —003993-032 [unpublished study]. Prepared by Dow Chemical Co. p. 1244. (as cited in U.S. EPA, 1998).

Roberts, T. and G. Stoydin. 1976. The degradation of (Z)-and (E)-1,3-dichloropropene and 1,2-dichloropropane in soil. Pest. Sci. 7:325-335 (as cited in Yang, 1986).

Rogers, S.E., D.L. Peterson, and W.C. Lauer. 1987. Organic contaminants removal for potable reuse. J. Water Pollut. Control Fed. 59:722-732 (as cited in ATSDR, 1992).

Sable, G.V. and T.P Clark. 1984. Volatile organic compounds as indicators of municipal solid waste leach contamination. Waste Manag. Res. 2:119-130 (as cited in ATSDR, 1992).

SAIC (Systems Applications International, Inc). 1999. Modeling cumulative outdoor concentrations of hazardous air pollutants. Revised Final Report. Volume 1. SYSAPP-99-96/33r2. Available from: <http://www.epa.gov/CumulativeExposure/resource/resource.htm>.

Sanzgiri, U.Y., H.J. Kim, S. Muralidhara, et al. 1995. Effect of route and pattern of exposure on the pharmacokinetics and acute hepatotoxicity of carbon tetrachloride. Toxicol. Appl. Pharmacol. 34:148-154 (as cited in U.S. EPA, 2000e).

Sasaki, Y.F.X., H. Imanishi, K. Matsumoto, et al. 1988. 1,3-Dichloropropene: *in vitro* cytogenetics test. lET 88-0038 [unpublished study to be peer reviewed]. Prepared by Dow Chemical Japan Limited and Shell Kagaku KK., by the Institute of Environmental Toxicology, Tokyo, Japan. (as cited in ATSDR, 1992).

Schenker, M. and S. McCurdy. 1986. Pesticides, viruses and sunlight in the etiology of cancer among agricultural workers. In Becker C.E. and M.J. Coye, (eds.). Cancer Prevention: Strategies in the Workplace. Washington, DC: Hemisphere Publishing Corporation. pp. 29-37 (as cited in ATSDR, 1994).

Schiffmann, D., E. Eder, T. Neudecker, et al. 1983. Induction of unscheduled DNA synthesis in HeLa cells by allylic compounds. Cancer Lett. 20:263-269 (as cited in ATSDR, 1992).

Schneider, R.C., B.S. Sipes, C.H. Oda, R.E. Green and D.P. Schmitt. 1995. Management of 1,3-dichloropropene in pineapple for efficacy and reduced volatile losses. Crop Protect. 14:8:611-618.

Schneider, M., G.B. Quistad, and J.E. Casida. 1998a. N2, 7-Bis (1-hydroxy-2-oxopropyl)-2'-deoxyguanosine: identical noncyclic adducts with 1,3-dichloropropene epoxides and methylglyoxal. Chem. Res. Toxicol. 11:1536-1542 (as cited in U.S. EPA, 2000e).

Schneider, M., G.B. Quistad, and J.E. Casida. 1998b. 1,3-Dichloropropene epoxides: intermediates in bioactivation of the promutagen 1,3-dichloropropene. Chem. Res. Toxicol. 11:1137 -1144 (as cited in U.S. EPA, 2000e).

Shah, J.J. and E.K. Heyerdahl. 1989. National ambient volatile organic compound database update. Nero and associates. EPA 600/3-88/010(a) (as cited in ATSDR, 1994).

Squillace, P.J., M.J. Moran, W.W. Lapham, et al. 1999. Volatile organic compounds in untreated ambient groundwater of the United States, 1985-1995. Environ. Sci. and Technol.. 33(23):4176-4187. Available from: <http://sd.water.usgs.gov/nawqa/pubs/journal/EST.voc.squillace.pdf>. Link to document (and appendices) from: <http://sd.water.usgs.gov/nawqa/pubs/>.

Stebbins, K.E., J.F. Quast, K.T. Haut, et al. 1999. Subchronic and chronic toxicity of ingested 1,3- dichloropropene in dogs. Reg. Toxicol. and Pharmacol. 30:233-243.

Stebbins, K.E., K.A. Johnson, T.K. Jeffries, et al. 2000. Chronic toxicity and oncogenicity studies of ingested 1,3-dichloropropene in rats and mice. Reg. Toxicol. and Pharmacol. 32:1-13.

Stolzenberg, S.J. and C.H. Hine. 1980. Mutagenicity of 2- and 3-carbon halogenated compounds in the *Salmonella*/mammalian-microsome test. Environ. Mutagen. 2:59-66 (as cited in ATSDR, 1992).

Stott, W.T. and P.E. Kastl. 1986. Inhalation pharmocokinetics of technical grade 1,3-dichloropropene in rats. Toxicol. Appl. Pharmacol. 85(3):332-41 (as cited in ATSDR, 1992).

Stott, W., J. Young, L. Calhoun, et al. 1984. Telone II soil fumigant: a 13-week inhalation study in rats and mice [unpublished study]. Prepared by Dow Chemical U.S.A.. p. 65. (as cited in U.S. EPA, 1998b).

Stott, W., J. Young, L. Calhoun, et al. 1988. Subchronic toxicity of inhaled technical grade 1,3-dichloropropene in rats and mice. Fundam. Appl. Toxicol. 11:207-220 (as cited in ATSDR, 1992; U.S. EPA, 2000).

Stott, W.T., K.A. Johnson, T.K. Jeffries, et al. 1995. Telone II soil fumigant: two-year chronic toxicity/oncogenicity study in Fischer 344 rats. Lab Project Number: M-OO3993-031 [unpublished study]. Prepared by Dow Chemical Company, Midland, Michigan. p. 1515. (as cited in USEP A, 1998b and U.S. EPA, 2000e).

Stott, W.T., B.B. Gollapudi, C.M. Clements, et al. 1997a. 1,3-Dichloropropene: mechanisms of action. The Dow Chemical Company (as cited in U.S. EPA, 2000e).

Stott, W.T., T.J. Miller, and A.K. Wardynski. 1997b. 1,3-Dichloropropene: *in vitro* DNA binding. The Dow Chemical Company (as cited in U.S. EPA, 2000e).

Stott, W.T., J.R. Gilbert, R.J. McGuirk, et al. 1998. Bioavailability and pharmacokinetics of microencapsulated 1,3-dichloropropene in rats. Toxicol. Sci. 41 :21-28 (as cited in ATSDR, 1992; U.S. EPA, 2000e).

Streeter, C., J. Battjes, and L. Lomax. 1987. Telone II soil fumigant: an acute vapor inhalation study in Fischer 344 rats. Dow Chemical Company, Midland, Michigan (as cited in ATSDR, 1992).

Streeter, C. and L. Lomax. 1988. Telone C-17 soil fungicide and nematocide: a one-hour acute vapor inhalation study in Fischer 344 rats. Dow Chemical Company, Midland, Michigan (as cited in ATSDR, 1992).

Swann, R.L., D.A. Laskowski, P.J. McCall, et al. 1983. A rapid method for the estimation of the environmental parameters octano/water partition coefficient, soil sorption constant, water to air ratio and water solubility. Res. Rev. 85:17-28 (as cited in ATSDR, 1992).

Tabak, H.H., S.A. Quave, C.I. Mashni, et al. 1981a. Biodegradability studies with organic priority pollutant compounds. J. Water Pollut. Control Fed. 53:1503-1518 (as cited in ATSDR, 1992).

Tabak, H.H., S.A. Quave, C.I. Mashni, et al. 1981b. Biodegradability studies for predicting the environmental fate of organic priority pollutants. In: Test Protocols for Environmental Fate and Movement of Toxicants. Symposium: 94th Annual Meeting of the Association of Official Analytical Chemists, Washington, DC. pp. 267-328 (as cited in ATSDR, 1992).

Talcott, R.E. and J. King. 1984. Mutagenic impurities in 1 ,3-dichloropropene preparations. J. Natl. Cancer Inst. 72(5):1113-1116 (as cited in ATSDR, 1992; U.S. EPA, 2000).

Thelin, G.P. and L.P. Gianessi. 2000. Method for estimating pesticide use for county areas of the conterminous United States. U.S. Geological Survey Open-File Report 00-250. pp. 62. Available from: <http://ca.water.usgs.gov/pnsp/rep/ofr00250/ofr00250.pdf>.

Thomas, R.G. 1982. Volatilization from water. In: Lyman, W.J., W.F. Reehl, and D.H. Rosenblatt (eds.). Chapter 15. New York, NY: McGraw Hill Book Co. (as cited in ATSDR, 1992).

Torkelson, T.R. and F. Oyen. 1977. The toxicity of 1,3-dichloropropene as determined by repeated exposure of laboratory animals. Am. Ind. Hyg. Assoc. J. 38:217-223 (as cited in ATSDR, 1992).

Tuazon, E.C., R. Atkinson, A.M. Winer, et al. 1984. A study of the atmospheric reactions of 1-3-dichloropropene and other selected organochlorine compounds. Arch. Environ. Contam. Toxicol. 13:691-700 (as cited in ATSDR, 1992).

U.S. EPA (United States Environmental Protection Agency). 1981. Treatability manual. U.S. Environmental Protection Agency, Office of Research and Development. p. I.12.14-1 to I.12.14-5.

U.S. EPA (United States Environmental Protection Agency). 1986a. Guidelines for the health risk assessment of chemical mixtures. Fed. Reg.51(185):34014-34025 and <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 1986b. Guidelines for mutagenicity risk assessment. Fed. Reg. 51(185):34006-34012.

U.S. EPA (United States Environmental Protection Agency). 1986c. Test methods for evaluating solid wastes. Volume IB: Laboratory manual, physical/chemical methods: Method 8010

halogenated volatile organics. 3rd ed. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response. pp. 8010-1 to 8010-13.
U.S. EPA (United States Environmental Protection Agency). 1987. Risk assessment guidelines of 1986 (EPA/600/8-87/045, dated August 1987).

U.S. EPA (United States Environmental Protection Agency). 1988. Recommendations for and documentation of biological values for use in risk assessment. EPA 600/6-87/008. Available from: National Technical Information Service, Springfield, VA; PB88-179874/AS.

U.S. EPA (United States Environmental Protection Agency). 1991. Guidelines for developmental toxicity risk assessment. Fed. Reg. 56(234):63798-63826.

U.S. EPA (United States Environmental Protection Agency). 1994a. Interim policy for particle size and limit concentration issues in inhalation toxicity studies. Fed. Reg. 59(206):53799.

U.S. EPA (United States Environmental Protection Agency). 1994b. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F. Available from: National Technical Information Service, Springfield, VA; PB2000-500023, and <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 1995. Use of the benchmark dose approach in health risk assessment. EPA/630/R-94/007. Available from: National Technical Information Service (NTIS) , Springfield, VA; PB95-213765, and <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 1996a. Guidelines for reproductive toxicity risk assessment. Fed. Reg. 61(212):56274-56322.

U.S. EPA (United States Environmental Protection Agency). 1996b. Toxics Release Inventory: Public Data Release Report. Chapter 3: year-to-year comparison of Toxics Release Inventory Data. Available from: <http://www.epa.gov/tri/tridata/tri96/pdr/chap3.pdf>. Link to chapter from: <http://www.epa.gov/tri/tridata/tri96/pdr/>.

U.S. EPA (United States Environmental Protection Agency). 1996c. Proposed guidelines for carcinogen risk assessment, Notice, 1996. Fed. Reg. 61(79):17960-18011.

U.S. EPA (United States Environmental Protection Agency). 1997a. Exposure Factors Handbook Volume 1. Office of Research and Development. Washington, D.C. EPA/600/P-95/002Fa.

U.S. EPA (United States Environmental Protection Agency). 1997b. Announcement of the Draft Drinking Water Contaminant Candidate List. Fed. Reg. 62(193):52193-52219.

U.S. EPA (United States Environmental Protection Agency). 1998a. Guidelines for neurotoxicity risk assessment. Fed. Reg. 63(93):26926-26954.

U.S. EPA (United States Environmental Protection Agency). 1998b. Science policy council handbook: peer review. Prepared by the Office of Science Policy, Office of Research and Development, Washington, DC. EPA 100-B-98-001. Available from: National Technical Information Service, Springfield, VA; PB98-140726, and <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 1998c. Reregistration Eligibility Decision (RED): 1,3-dichloropropene. Prepared by the Office of Prevention, Pesticides, and Toxic Substances. EPA 738-R-98-016. Available from: <http://www.epa.gov/oppsrrd1/REDs/0328red.pdf>.

U.S. EPA (United States Environmental Protection Agency). 1998d. Health effects test guidelines, OPPTS 870.4200, carcinogenicity, prevention, pesticides and toxic substances. EP A/712/C-98-211.

U.S. EPA (United States Environmental Protection Agency). 1998e. Final Contaminant Candidate List (CCL), March 2, 1998 (63 FR 10273).

U.S. EPA (United States Environmental Protection Agency). 1999. Guidelines for carcinogen risk assessment [review draft]. Risk Assessment Forum, Washington, DC; NCEA-F-0644. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 2000a. Science policy council handbook: peer review. 2nd edition. Prepared by the Office of Science Policy, Office of Research and Development, Washington, DC. EPA 100-B-00-001. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 2000b. Science policy council handbook: risk characterization. Prepared by the Office of Science Policy, Office of Research and Development, Washington, DC. EPA 100-B-00-002. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 2000c. Benchmark dose technical guidance document [external review draft]. EPA/630/R-00/001. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 2000d. Supplemental guidance for conducting for health risk assessment of chemical mixtures. EPA/630/R-00/002. Available on-line at: http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA (United States Environmental Protection Agency). 2000e. Toxicological review of 1,3-dichloropropene. Prepared by the National Center for Environmental Assessment. NCEA S-0660.

U.S. EPA (United States Environmental Protection Agency). 2000f. What is the Toxic Release Inventory. Available from: <http://www.epa.gov/triinter/whatis.htm>.

U.S. EPA (United States Environmental Protection Agency). 2000g. IRIS substance file: 1,3-dichloropropene (Section II, Carcinogenicity Assessment for Lifetime Exposure, last update 5/25/2000). Available from: <http://www.epa.gov/iris/subst/0224.htm>.

U.S. EPA (United States Environmental Protection Agency). 2002a. A review of the reference dose and reference concentration processes. Risk Assessment Forum, Washington, DC; EPA/630/P-02/0002F. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 2002b. TRI Explorer: Trends. Search for 1,3-dichloropropylene. Available from: <http://www.epa.gov/triexplorer/trends.htm>.

U.S. EPA (United States Environmental Protection Agency). 2002c. Announcement of preliminary regulatory determinations for priority contaminants on the Drinking Water Contaminant Candidate List. Fed. Reg. 67:38222-38244.

U.S. EPA (United States Environmental Protection Agency). 2003a. Table II: EPCRA section 313 chemical list for reporting year 2003 (including Toxic Chemical Categories). Available from: <http://www.epa.gov/tri/chemical/RY2003ChemicalList.pdf>.

U.S. EPA (United States Environmental Protection Agency). 2003b. Announcement of regulatory determinations for priority contaminants on the Drinking Water Contaminant Candidate List. Fed. Reg. 68(138): 42897-42906.

U.S. EPA (United States Environmental Protection Agency). 2004. Drinking Water Contaminant Candidate List 2; Notice. Fed. Reg. 69(64):17406-17415.

U.S. EPA (United States Environmental Protection Agency). 2005. Drinking Water Contaminant Candidate List 2; Final Notice. Fed. Reg. 70(36):9071-9077.

USGS (United States Geological Survey). 2001. Summary publications from 51 NAWQA study units sampled in 1991-2001. Available from: <http://water.usgs.gov/pubs/nawqasum>.

U.S. EPA(United States Environmental Protection Agency). 2007. Drinking Water: Regulatory Determinations Regarding Contaminants on the Second Drinking Water Contaminant Candidate List - Preliminary Determinations: Proposed Rule Fed. Reg. 72(83):24016-24058.

USGS (United States Geological Survey). 2004. 1997 Pesticide Use Maps. Available from: <http://ca.water.usgs.gov/pnsp/pesticide_use_maps_1997/>.

Valencia R., J. Mason, R. Woodruff, et al. 1985. Chemical mutagenesis testing in *Drosophila*. III. Results of 48 coded compounds tested for the National Toxicology Program. Environ. Mutagen. 7:325-348 (as cited in ATSDR, 1992).

Van der Hude, W., M. Scheutwinkel, U. Gramlich et al. 1987. Genotoxicity of three-carbon compounds evaluated in the SCE test *in vitro*. Environ. Mutagen. 9:401-410 (as cited in U.S. EPA, 2000e).

Van der Hude W., C. Behm, R. Guertler R, et al. 1988. Evaluation of the SOS chromatest. Mutat. Res. 203:81-94 (as cited in U.S. EPA, 2000e).

Van der Pas, L.J.T. and M. Leistra. 1987. Movement and transformation of 1,3-dichloropropene in the soil of flower-bulb fields. Arch. Environ. Contam. Toxicol. 16:417-422 (as cited in ATSDR, 1992).

Van Dijk, H. 1974. Degradation of 1,3-dichloropropenes in soil. Agro-Ecosystems 1:193-204 (as cited in Yon et al., 1991).

Van Duuren, B., B. Goldschmidt, G. Loewengart, et al. 1979. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J. Natl. Cancer Inst. 63:1433-1439 (as cited in ATSDR, 1992).

Van Joost, T. and G. de Jong. 1988. Sensitization to DD soil fumigant-during manufacture. Contact Dermat. 18(5):307-308 (as cited in ATSDR, 1992).

Van Welie, R.T.H., P. van Duyn, and D.R. Brouwer. 1991. Inhalation exposure to 1,3-dichloropropene in the Dutch flower-bulb culture. Part II. Biological monitoring by measurement of urinary excretion of two mercapturic acid metabolites. Arch. Environ. Contam. Toxicol. 20(1):6-12 (as cited in U.S. EPA, 2000a).

Verplanke, A.J.W., L.J. Bloemen, E.J. Brouwer, et al. 2000. Occupational exposure to *cis*-1,3-dichloropropene: biological effect monitoring of kidney and liver function. Occup. Environ. Med. 57(11): 745-751.

Vithayathil, A.J., C. McClure, and J.W. Myers. 1983. *Salmonella*/microsome multiple indicator mutagenicity test. Mutat. Res. 121:33-37 (as cited in ATSDR, 1992).

Von der Hude, W., C. Behm, R. Guertler, et al. 1988. Evaluation of the SOS chromotest. Mutat. Res. 203:81-94 (as cited in ATSDR, 1992).

Waechter, J. and P. Kastl. 1988. 1,3-Dichloropropene: pharmacokinetics and metabolism in Fischer 344 rats following repeated oral administration. Dow Chemical Company, Midland Michigan (as cited in ATSDR, 1992; U.S. EPA, 2000e).

Waechter, J.M., K.A. Brzak, L.P. McCarty, et al. 1992. 1,3-Dichloropropene (Telone II soil fumigant): inhalation pharmacokinetics and metabolism in human volunteers (internal report). Dow Chemical Company, Midland MI (as cited in U.S. EPA, 2000e).

Wang, G.M. 1984. Decision making. Reg. Toxicol. Pharmacol. 4:316-371 (as cited in ATSDR, 1994).

Watson, P.W., T.M. Brooks, K.R. Huckle, et al. 1987. Microbial mutagenicity studies with (2)-1,3-Dichloropropene. Chern-Biol/Interactions 61:17-30 (as cited in ATSDR, 1992; U.S. EPA, 2000).

Williams, I. 1968. Recovery of *cis*-and *trans*-dichloropropene residues from two types of soil and their detection and determination by electron capture gas chromatography. J. Econ. Entomol. 61:1432-1435 (as cited in Yang, 1986).

Woodruff, T.J, D. Axelrad, J. Caldwell, R. Morello-Frosch and A. Rosenbaum. 1998. Public health implications of 1990 air toxics concentrations across the United States. Environ. Health Perspect. 106(5):245-251.

Yang, R.S. 1986. 1,3-Dichloropropene. Residue Rev. 97:19-35.

Yon, D.A., G.A. Morrison, and A.S. McGibbon. 1991 The dissipation of 1,3-dichloropropene in ditch bottom sediment and associated aerobic ditch water. Pestic. Sci. 32(2):147-160.

APPENDIX A: Abbreviations and Acronyms

ABP	androgen binding protein
ANOVA	analysis of variance
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area under the curve
BMD	benchmark dose, maximum likelihood estimate of dose corresponding to BMR
BMDL	the 95% lower confidence limit on the benchmark dose
BMR	benchmark response
bw	body weight
cAMP	cyclic adenosine monophosphate
CAS	Chemical Abstracts Registry
CCL	Contaminant Candidate List
CFSII	Continuing Survey of Food Intakes
CNS	central nervous system
CSAF	chemical-specific adjustment factors
CV	coefficient of variation
1,3-D	1,3-dichloropropene
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
FEV_1	forced expiratory volume in 1 sec
FR	Federal Register
FSH	follicle stimulating hormone
FVC	forced vital capacity
g	gram
gd	gestation day
GFR	glomerular filtration rate
HRL	health reference level
HSDB	Hazardous Substances Database
ICPMS	inductively coupled plasma-mass spectrometry
IEHR	Institute for Evaluating Health Risks
IOC	inorganic compounds
IOM	Institute of Medicine
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
kg	kilogram
L	liter
LH	luteinizing hormone
LOAEL	lowest observed adverse effect level
m	meter
MCLG	Maximum Contaminant Level Goal
mg	milligram
ml	milliliter
MRL	minimum reporting level
MTD	maximum tolerated dose
NAWQA	National Water Quality Assessment
NDWAC	National Drinking Water Advisory Council

NIOSH	National Institute for Occupational Safety and Health
NIRS	National Inorganics and Radionuclides Survey
NOAEL	no observed adverse effect level
NPDWR	National Primary Drinking Water Regulation
NTP	National Toxicology Program
PA	plasminogen activators
ppm	parts per million
PWS	public water systems
RfC	reference concentration
RfD	reference dose
SBR	standardized birth ratio
SD	standard deviation
SDWA	Safe Drinking Water Act
TD	toxicodynamics
TDI	tolerable daily intake
TK	toxicokinetics
TRI	Toxic Release Inventory
TWA	time-weighted average
UCM	unregulated contaminant monitoring
UF	uncertainty factor
UFA	interspecies variability (animal-to-human) uncertainty factor
UFH	interindividual variability (sensitive humans) uncertainty factor
UL	upper intake level
U.S. FDA	U.S. Food and Drug Administration
USGS	U.S. Geological Service
U.S. EPA	U.S. Environmental Protection Agency
VOC	volatile organic compound
WHO	World Health Organization

APPENDIX B: Benchmark Dose Modeling
From: U.S. EPA, 2000e

Benchmark Dose Analysis for Development of the Reference Dose

The incidence of treated animals with forestomach histopathology is a quantitative measure of toxicity amenable to benchmark dose (BMD) analysis. BMD analysis was chosen because it uses the entire dose-response curve to identify the point of departure, it does not depend upon dose spacing, and it is sensitive to the number of animals used in the study. The data available met the suggested criteria (U.S. EPA, 1995) of at least three dose levels, with two doses eliciting a greater than minimum and less than maximum response.

The seven statistical models for dichotomous data from U.S. EPA's Benchmark Dose Software Version 1.1b were used to identify the model that best fit the dose-response curve (Appendix A of EPA, 200f). The best model was chosen by eliminating all models that did not have a statistically-significant goodness-of-fit (p>0.05). The remaining models were then ranked by best visual fit of the data, especially for the lower doses, as observed in the graphical output of the Benchmark Dose Software. The model with the best visual fit and a statistically-significant goodness-of-fit was used to estimate the BMD_{10} (maximum likelihood estimate at 10% risk) and the $BMDL_{10}$ (95% lower confidence limit on the BMD_{10}).

The results for gamma, multistage, and Weibull models were statistically significant for goodness-of-fit. The gamma model was chosen because the visual fit at low doses was the best of the three models. The gamma model yielded a BMD_{10} of 5.07 mg/kg/day and a $BMDL_{10}$ of 3.38 mg/kg/day (Appendix A).

Benchmark Concentration Analysis for Development of the Reference Concentration

Benchmark concentration (BMC) analysis was chosen because it uses the entire dose-response curve to identify the point of departure, it does not depend upon dose spacing, and it is sensitive to the number of animals used in the study. The data available met the suggested criteria of at least three dose levels with two doses eliciting a greater than minimum and less than maximum response (U.S. EPA, 1995).

The seven statistical models for dichotomous data from U.S. EPA's Benchmark Dose Software Version 1.1b were applied to the incidence data for the adjusted administered doses (see Appendix A). The best model fit was determined by eliminating all models that did not have a statistically-significant goodness-of-fit (p>0.05). The remaining models were then ranked by best visual fit of the data, especially for the lower doses, as observed in the graphical output of the Benchmark Dose Software. The model with statistically-significant goodness-of-fit and best visual fit was used to estimate the BMC at 10% risk and the 95% lower confidence limit of the BMC, the $BMCL_{10}$.

The gamma, logistic, multistage, Weibull, and quantal-quadratic models provided statistically significant fits (see Appendix A). The gamma model was the best fit overall because it provided the best visual fit. This model yielded a BMC_{10} of 5.91 mg/m^3 and a $BMCL_{10}$ of 3.66 mg/m^3 (Appendix A of EPA, 200f).

1,3-Dichloropropene is a Category 2 gas (U.S. EPA, 1994b) because it is not highly reactive or water soluble and it produces both respiratory (nasal histopathology) and remote effects (urinary bladder histopathology). For Category 2 gases, adjustment of animal exposure to human equivalent concentrations (HECs) is based on algorithms for Category 1 or Category 3 gases, depending upon whether the major effect is respiratory or systemic. Because the critical target was the nasal mucosa, algorithms for extrathoracic effects for Category 1 gases are used to adjust animal exposure concentrations of 1,3-dichloropropene to HECs (U.S. EPA, 1994b). The HEC for a Category 1 gas is derived by multiplying the animal BMC_{10} and $BMCL_{10}$ by an interspecies dosimetric adjustment for gas:respiratory effects in the extrathoracic area of the respiratory tract, according to the following calculation (U.S. EPA, 1994b):

$RGDR(ET) = (MV_a/S_a)/(MV_h/S_h)$ where:

RGDR(ET) = regional gas dose ratio for the extrathoracic area of the respiratory tract
MV_a = animal minute volume (mouse = 0.041 L/min)
MV_h = human minute volume (13.8 L/min)
S_a = surface area of the extrathoracic region in the animal (mouse = 3 cm^2)
S_h = surface area of the extrathoracic region in the human (200 cm^2).

Using default values, the RGDR(ET) = (0.041/3)/(13.8/200) = 0.014/0.069 = 0.198. The animal BMC_{10} and $BMCL_{10}$ are then multiplied by 0.198 to yield the HECs for these values:

$BMC_{10\ HEC} = BMC_{10} \times 0.198 = 5.91 \times 0.198 = 1.17$ mg/m^3 $BMCL_{10\ HEC} = BMCL_{10} \times 0.198 = 3.66 \times 0.198 = 0.725$ mg/m^3.