

TOXICOLOGICAL PROFILE FOR
1,3-DICHLOROPROPENE

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

- (A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.
- (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about 1,3-dichloropropene and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). 1,3-Dichloropropene has been found at 3 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for 1,3-dichloropropene. As EPA evaluates more sites, the number of sites at which 1,3-dichloropropene is found may change. The information is important for you because 1,3-dichloropropene may cause harmful effects and because these sites are potential or actual sources of human exposure to 1,3-dichloropropene.

When a chemical is released from a large area such as an industrial plant, or from a container such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed in the environment by breathing; eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous substance such as 1,3-dichloropropene, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS 1,3-DICHLOROPROPENE?

1,3-Dichloropropene is a colorless liquid with a sweet smell. It dissolves in water and evaporates easily. There are two kinds of 1,3-dichloropropene, cis-1,3-dichloropropene and trans-1,3-dichloropropene, which are very closely related. These different forms of the same chemical behave very much alike and are usually combined in different amounts to form mixtures. The mixtures are mainly used in farming to kill tiny pests called nematodes that eat the roots of important crops. Sometimes, these mixtures also have small amounts of other chemicals that are very similar to 1,3-dichloropropene.

When 1,3-dichloropropene is used in farm fields, it is sprayed into the ground. Once in the soil, some of it is likely to be broken down into smaller chemicals by either water or living things. These smaller chemicals may also pose a health hazard. Some of it may be carried deeper into the ground and may reach underground water supplies. However, in high crop-producing states like California where it has been used often, very little 1,3-dichloropropene has actually been found in groundwater. 1,3-Dichloropropene, however, may be

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a problem at hazardous waste sites, where a variety of different chemicals are often buried in the ground together. These other chemicals can stop 1,3-dichloropropene from breaking down. Therefore, it is possible for 1,3-dichloropropene to reach groundwater from a hazardous waste site.

Some of the 1,3-dichloropropene sprayed onto the ground will evaporate into the air. In the air, 1,3-dichloropropene will be broken down into smaller chemicals by sunlight. Some of the 1,3-dichloropropene in air may be washed down into the ground, lakes, or streams by rain. In water, 1,3-dichloropropene is expected to break down into small chemicals. Some of the 1,3-dichloropropene in water will also go back into the air.

You will find more information on the chemical properties of 1,3-dichloropropene in Chapter 3. The uses of 1,3-dichloropropene are described in Chapter 4. More information on how 1,3-dichloropropene will behave in the environment is given in Chapter 5.

1.2 HOW MIGHT I BE EXPOSED TO 1,3-DICHLOROPROPENE?

You can breathe 1,3-dichloropropene from the air. It can also get on your skin. The people most likely to breathe air containing 1,3-dichloropropene or to get it on their skin are workers who use it for farming or make it in factories. Small amounts of 1,3-dichloropropene can form in your drinking water when chlorine is added to the water supply. (Chlorine is added to kill germs in the water.)

Crops that are grown in fields treated with 1,3-dichloropropene are most likely to contain it. However, food grown in 1,3-dichloropropene treated fields has not been shown to contain 1,3-dichloropropene. We do not know if this is because 1,3-dichloropropene is rapidly removed or broken down in the environment, or the treated crops break it down.

Very small amounts of 1,3-dichloropropene from sewage treatment facilities, electrical power stations, and industrial facilities that use water to cool high-temperature furnaces may go into streams, rivers, and lakes. Some may go into the air.

People who live near garbage dumps or places where chemicals are stored or buried, including hazardous waste sites, may breathe 1,3-dichloropropene if it escapes into the air or have 1,3-dichloropropene in their well water. They may drink some 1,3-dichloropropene in the tap water. They may also be exposed through skin contact with soil containing it. 1,3-Dichloropropene has been discovered at only three hazardous waste sites and in only a few underground water supplies. Again, we do not know if this is because 1,3-dichloropropene is not at other sites, or because it has not been looked for at other sites. In general, very little information is available about how much 1,3-dichloropropene is in the environment. We do not know the levels in soil, water, and air.

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You can find more information on how much 1,3-dichloropropene has been found in the environment and how you can be exposed to it in Chapter 5.

1.3 HOW CAN 1,3-DICHLOROPROPENE ENTER AND LEAVE MY BODY?

1,3-Dichloropropene can enter your body if you breathe air that contains it, if you drink water that is contaminated with it, or even if you touch it. Studies with animals have shown that if you breathe air that has 1,3-dichloropropene in it, most of the chemical will get into your bloodstream. Of course, the longer you breathe air with 1,3-dichloropropene in it, the more of it will enter your body. Also, the more water you drink with 1,3-dichloropropene in it, the more will pass into your bloodstream from your stomach or intestines. The longer 1,3-dichloropropene is in contact with your skin, the more of it will get into your body. If you live or work near a hazardous waste site where 1,3-dichloropropene is stored, you might breathe it if it escapes into the air. 1,3-Dichloropropene can get into the groundwater and into wells that supply drinking water, so you could drink water contaminated with it. You can also get 1,3-dichloropropene on your skin if you come into contact with soil contaminated with it. People who live in farming communities where 1,3-dichloropropene is used as a pesticide are also likely to come into contact with this chemical.

Your body can get rid of 1,3-dichloropropene fairly quickly. Studies with animals have shown that most 1,3-dichloropropene leaves the body within 2 days. Most 1,3-dichloropropene leaves your body in urine, and smaller amounts leave in feces and the air you breathe out. For more information on how 1,3-dichloropropene gets into and leaves your body, see Chapter 2.

1.4 HOW CAN 1,3-DICHLOROPROPENE AFFECT MY HEALTH?

The main health effects seen in humans who breathed 1,3-dichloropropene are: nausea; vomiting; irritation of the skin, eyes, nose, and throat; breathing difficulties; coughing; headache; and fatigue. Some people who breathed 1,3-dichloropropene could smell it when the amount reached 1 part 1,3-dichloropropene per million parts of air (ppm), but you may be able to smell it at even lower amounts. We do not know if 1,3-dichloropropene causes cancer in humans; however, three men who breathed 1,3-dichloropropene during the cleanup of a spill or during field spraying developed similar kinds of cancer, but we cannot be sure if 1,3-dichloropropene was the cause. Mice and rats that swallowed 1,3-dichloropropene got cancer. We do not know whether 1,3-dichloropropene can cause birth defects in humans. Although 1,3-dichloropropene did not cause birth defects in animals, pregnant rats that breathed it gave birth to fewer rat pups.

Rats had lung damage and eye irritation and rabbits had difficulty getting on their feet and walking after they breathed high levels of 1,3-dichloropropene for short periods of time. Some rats even died. Rats and mice had damage to the lining of the nose, and mice had damage to the lining

1. PUBLIC HEALTH STATEMENT

of the bladder after breathing lower levels of 1,3-dichloropropene for longer periods of time. Rats that swallowed single high doses of 1,3-dichloropropene had damage to the lining of the stomach, lung congestion, and difficulty walking. These effects were worse in rats that swallowed even higher doses, and included bleeding of the stomach, intestines, liver, and lungs. Some of the rats died. Rats had increased liver and kidney weights, which may indicate harmful effects in these organs, after swallowing lower doses every day for longer periods of time. Rats had damage to the lining of the stomach and some had cancer of the stomach and liver after swallowing low doses for most of their lives. Mice that swallowed low doses of 1,3-dichloropropene for most of their lives had stomach and kidney damage, and some had cancer of the stomach, urinary bladder, and lungs. Rabbits had irritated skin and hair loss, and guinea pigs had irritated skin and became allergic to 1,3-dichloropropene after a small amount was painted onto their backs. Rats that had large amounts of 1,3-dichloropropene painted onto their backs had skin irritation, difficulty breathing and walking, and bleeding from the lungs, stomach, and under the skin, and some even died. Rabbits had muscle bleeding, open sores and hair loss, and some even died after a large amount of 1,3-dichloropropene was painted onto their backs.

You can find a more complete discussion of the health effects of 1,3-dichloropropene in humans and animals in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 1,3-DICHLOROPROPENE?

It is possible to measure 1,3-dichloropropene or its breakdown products in blood and urine. The presence of 1,3-dichloropropene or its breakdown products in blood and urine, however, could also mean you were exposed to some other chemical that breaks down to 1,3-dichloropropene. In humans, the blood levels of breakdown products from 1,3-dichloropropene could be used to predict how much 1,3-dichloropropene has been breathed. However, tests for 1,3-dichloropropene in the blood and urine would only be useful for recent exposures, because 1,3-dichloropropene leaves the body within 1-2 days. You can find more information about these tests in Chapters 2 and 6.

1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

EPA has set 100 pounds as the limit of 1,3-dichloropropene that can be released into the environment at any particular site; releases of more than that must be reported. EPA has also set a limit of 87 micrograms 1,3-dichloropropene per liter of water (87 $\mu\text{g/L}$ or 87 parts per billion [ppb]) for the amount of 1,3-dichloropropene that can be in lakes and streams. The Occupational Safety and Health Administration (OSHA) has set a limit of 1 ppm of 1,3-dichloropropene in the air you breathe at work. For more information on the regulations for 1,3-dichloropropene, see Chapter 7.

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1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 1,3-dichloropropene and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for 1,3-dichloropropene based on toxicological studies and epidemiological investigations.

1,3-Dichloropropene is widely used as a preplanting soil fumigant for the control of nematodes, and it has been available for agricultural use in many formulations. Formulations, instead of pure 1,3-dichloropropene, were used in most of the studies discussed here. The trade names and components of these formulation are listed below:

<u>Formulation</u>	<u>Composition</u>
Telone®	40.2% cis, 38.3% trans (not otherwise specified)
Telone C-17®	40%-41% cis, 38%-39% trans 19%-21% chloropicrin
Telone II®a	48-53% cis, 42-45% trans 1% epichlorohydrin (not otherwise specified)
Telone II®b	48%-53% cis, 42%-45% trans 2% epoxidized soybean oil
DD®	25%-28% cis, 25%-27% trans 25%-29% 1,2-dichloropropane
DD-92®	92% cis/trans (not otherwise specified)
M-3993	48%-53% cis, 42%-45% trans 1% epichlorohydrin (not otherwise specified)

In some studies, the investigation of the toxicity of 1,3-dichloropropene may have been confounded by other components in a formulation (e.g., chloropicrin and epichlorohydrin). This possibility is discussed in the appropriate sections of the text. Separate tables and figures for each formulation of 1,3-dichloropropene are not presented. Instead, the formulation used in each study is identified in the appropriate

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table. Further information on the formulations of 1,3-dichloropropene can be found in Chapter 4.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing noobserved- adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these

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kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to 1,3-dichloropropene.

LC₅₀ values for inhalation exposure to 1,3-dichloropropene have been determined in rats (Streeter and Lomax 1988; Streeter et al. 1987). The LC₅₀ for female rats exposed to Telone II®a for 4 hours was 904 ppm (95% confidence interval= 846-990 ppm) (Streeter et al. 1987). The LC₅₀ for male rats could not be determined in this study but fell in the range 855-1035 ppm 1,3-dichloropropene. Telone C-17® appears to be more toxic than Telone II's; the LC₅₀ for rats after a 1-hour exposure to Telone C-17® was 253 ppm (no range reported) (Streeter and Lomax 1988). Telone C-17® contains a relatively high proportion of chloropicrin, which may account for the enhanced toxicity. 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).

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

Intermediate- or chronic-duration exposures of mice, rats, guinea pigs, rabbits, and dogs to Telone II®a or Telone 11% (1-150 ppm for 4 weeks to 2 years) had no effect on survival rates compared to control groups that were untreated or exposed to filtered room air (Coate 1979a, 1979b; Linnett et al. 1988; Lomax et al. 1989; Stott et al. 1988; Torkelson and Oyen 1977).

The LC₅₀ values, the highest NOAEL values, and all reliable LOAELs for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

The systemic effects observed in humans and animals after inhalation exposure to 1,3-dichloropropene are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect for each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. Humans exposed to 1,3-dichloropropene (not otherwise specified) after a tank truck spill complained of mucous membrane

TABLE 2-1. Levels of Significant Exposure to 1,3-Dichloropropene - Inhalation

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference	Formulation
					Less serious (ppm)	Serious (ppm)		
ACUTE EXPOSURE								
Death								
1	Rat	1 d 1 hr/d				253 (LC ₅₀)	Streeter and Lomax 1988	T C-17
2	Rat	1 d 4 hr/d				904 (LC ₅₀ females)	Streeter et al. 1987	T IIa
3	Rat	1 d 4 hr/d		595		676 (6/10 died)	Cracknell et al. 1987	T IIa
4	Rabbit	13 d Gd 6-18 6 hr/d		150		300 (6/7 died)	Kloes et al. 1983	T IIa
Systemic								
5	Rat	1 d 4 hr/d	Resp Other	582 595	595 (swollen lungs) 676 (adrenal congestion)	676 (lung congestion)	Cracknell et al. 1987	T IIa
6	Rat	1 d 1 hr/d	Resp Derm/oc		206 (atelectasis) 206 (eye irritation)		Streeter and Lomax 1988	T C-17
7	Rat	1 d 4 hr/d	Resp Derm/oc		775 (eye irritation)	1,035 (lung hemorrhage)	Streeter et al. 1987	T IIa
8	Rat	1 d 1 hr/d	Derm/oc			1,146 (eye irritation)	Yakel and Kociba 1977	T IIa
Neurological								
9	Rabbit	13 d 6 hr/d		150	300 (ataxia)		Kloes et al. 1983	T IIa
Developmental								
10	Rat	10 d Gd 6-15 6 hr/d		150		300 (decreased litter size)	Kloes et al. 1983	T IIa

TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference	Formulation
					Less serious (ppm)	Serious (ppm)		
11	Rabbit	13 d Gd 6-18 6 hr/d		150			Kloes et al. 1983	T IIa
INTERMEDIATE EXPOSURE								
Death								
12	Rat	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
13	Rabbit	6 mo 5 d/wk 0.5-4 hr/d		3			Torkelson and Oyen 1977	T IIa
14	Gn pig	6 mo 5 d/wk 0.5-4 hr/d		3			Torkelson and Oyen 1977	T IIa
15	Mouse	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
16	Dog	6 mo 5 d/wk 0.5-4 hr/d		3			Torkelson and Oyen 1977	T IIa
Systemic								
17	Rat	13 wk 5 d/wk 6 hr/d	Resp Cardio Hepatic Renal	10 ^b 90 90 90	30 (nasal epithelial changes)		Coate 1979a	T IIa
18	Rat	10 wk 5 d/wk 6 hr/d	Hemato Hepatic Renal	90 90 90			Linnett et al. 1988	DD ^c

TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference	Formulation
					Less serious (ppm)	Serious (ppm)		
19	Rat	180 d 5-7 d/wk 6 hr/d	Resp Gastro Hepatic Renal	30 90 90 90	90 (nasal lesions)		Breslin et al. 1989	T IIb
20	Rat	13 wk 5 d/wk 6 hr/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc	30 150 150 150 150 150 150	90 (nasal hyperplasia)		Stott et al. 1988	T IIa
21	Rat	6 mo 5 d/wk 7 hr/d	Resp Cardio Hemato Hepatic	3 3 3 3			Torkelson and Oyen 1977	T IIa
22	Rabbit	6 mo 5 d/wk 0.5-4 hr/d	Resp Cardio Hemato Hepatic Renal	3 3 3 3 3			Torkelson and Oyen 1977	T IIa
23	Gn pig	6 mo 5 d/wk 0.5-4 hr/d	Resp Cardio Hemato Hepatic Renal	3 3 3 3 3			Torkelson and Oyen 1977	T IIa

TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference	Formulation
					Less serious (ppm)	Serious (ppm)		
24	Mouse	13 wk 5 d/wk 6 hr/d	Resp	30	90 (nasal hyperplasia)		Stott et al. 1988	T IIa
			Cardio	150				
			Gastro	150				
			Hemato	150				
			Musc/skel	150				
			Hepatic	150				
Renal	30	90 (bladder hyperplasia)						
25	Mouse	6-12 mo 5 d/wk 6 hr/d	Resp	5	20 (hyperplasia)		Lomax et al. 1989	T IIb
			Cardio	60				
			Gastro	60				
			Hemato	60				
			Musc/skel	60				
			Hepatic	60				
			Renal	20	60 (bladder hyperplasia)			
Derm/oc	60							
26	Mouse	13 wk 5 d/wk 6 hr/d	Resp		90 (nasal epithelial changes)		Coate 1979a	T IIa
			Cardio	90				
			Hepatic	90				
			Renal	90				
27	Dog	6 mo 5 d/wk 0.5-4 hr/d	Resp	3		Torkelson and Oyen 1977	T IIa	
			Cardio	3				
			Gastro	3				
			Hemato	3				
			Musc/skel	3				
			Renal	3				
Immunological								
28	Rat	6-12 mo 5 d/wk 6 hr/d		60		Lomax et al. 1989	T IIb	

TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference	Formulation
					Less serious (ppm)	Serious (ppm)		
29	Rat	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
30	Rat	6-12 wk 5 d/wk 6 hr/d		50			Parker et al. 1982	DD ^o
31	Mouse	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
32	Mouse	6-12 mo 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
33	Mouse	6-12 wk 5 d/wk 6 hr/d		50			Parker et al. 1982	DD ^o
Neurological								
34	Rat	6-12 mo 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
35	Rat	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
36	Rat	6-12 wk 5 d/wk 6 hr/d		50			Parker et al. 1982	DD ^o
37	Rabbit	6 mo 5 d/wk 0.5-4 hr/d		3			Torkelson and Oyen 1977	T IIa

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TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference	Formulation
					Less serious (ppm)	Serious (ppm)		
38	Gn pig	6 mo 5 d/wk 0.5-4 hr/d		3			Torkelson and Oyen 1977	T IIa
39	Mouse	6-12 wk 5 d/wk 6 hr/d		50			Parker et al. 1982	DD ^b
40	Mouse	6-12 mo 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
41	Mouse	13 wk 5 d/wk 6 hr/d		90			Coate 1979a	T IIa
42	Mouse	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
43	Dog	6 mo 5 d/wk 0.5-4 hr/d		3			Torkelson and Oyen 1977	T IIa
Developmental								
44	Rat	180 d 5-7 d/wk 6 hr/d		90			Breslin et al. 1989	T IIb
Reproductive								
45	Rat	6-12 mo 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
46	Rat	180 d 5-7 d/wk 6 hr/d		90			Breslin et al. 1989	T IIb

TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference	Formulation
					Less serious (ppm)	Serious (ppm)		
47	Rat	6-12 wk 5 d/wk 6 hr/d		50			Parker et al. 1982	DD ^o
48	Rat	10 wk 5 d/wk 6 hr/d		90			Linnett et al. 1988	DD ^o
49	Rat	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
50	Mouse	6-12 mo 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
51	Mouse	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
52	Mouse	6-12 wk 5 d/wk 6 hr/d		50			Parker et al. 1982	DD ^o
CHRONIC EXPOSURE								
Death								
53	Rat	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
54	Mouse	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb

TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference	Formulation
					Less serious (ppm)	Serious (ppm)		
Systemic								
55	Rat	2 yr 5 d/wk 6 hr/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc	20 60 60 60 60 60 60 60	60 (epithelial degeneration)		Lomax et al. 1989	T I Ib
56	Mouse	2 yr 5 d/wk 6 hr/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc	5 ^c 60 20 60 60 60 60 60	20 (hyperplasia) 60 (hyperplasia)		Lomax et al. 1989	T I Ib
Immunological								
57	Rat	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T I Ib
Neurological								
58	Rat	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T I Ib
59	Mouse	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T I Ib

TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference	Formulation
					Less serious (ppm)	Serious (ppm)		
Reproductive								
60	Rat	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T I Ib
61	Mouse	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T I Ib

^aThe number corresponds to the entries in Figure 2-1.

^bUsed to derive an intermediate inhalation minimal risk level (MRL) of 0.003 ppm; concentration adjusted for intermittent exposure, converted to a human equivalent concentration, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

^cUsed to derive a chronic inhalation MRL of 0.002 ppm; dose adjusted for intermittent exposure, converted to a human equivalent concentration, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

Cardio = cardiovascular; d = day(s); DD^o = (25% cis-1,3-dichloropropene, 27% trans-1,3-dichloropropene, 29% 1,2-dichloropropane); Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gd = gestation day; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LC₅₀ = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; T C-17 = Telone C-17^o (40% cis-1,3-dichloropropene, 39% trans-1,3-dichloropropene, 21% chloropicrin); T I Ia = Telone II^o (53% cis-1,3-dichloropropene, 45% trans-1,3-dichloropropene, 1% epichlorohydrin); T I Ib = Telone II^o (50% cis-1,3-dichloropropene, 43% trans-1,3-dichloropropene, 2% epoxidized soybean oil); wk = week(s); yr = year(s)

FIGURE 2-1. Levels of Significant Exposure to 1,3-Dichloropropene - Inhalation

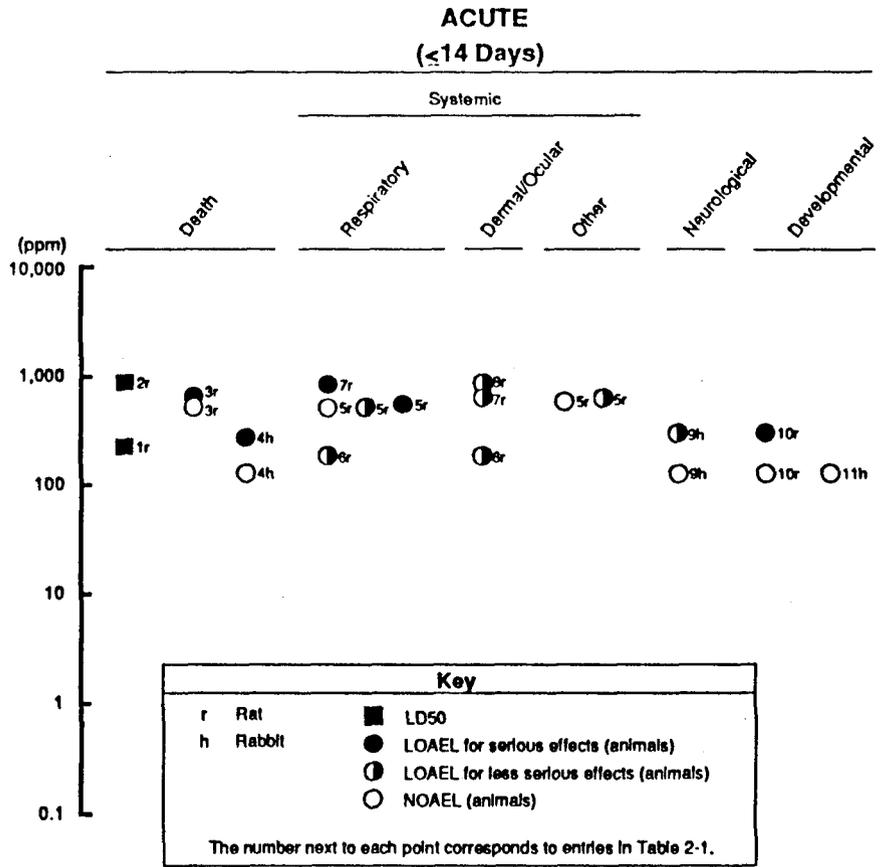


FIGURE 2-1 (Continued)

INTERMEDIATE
(15-364 Days)

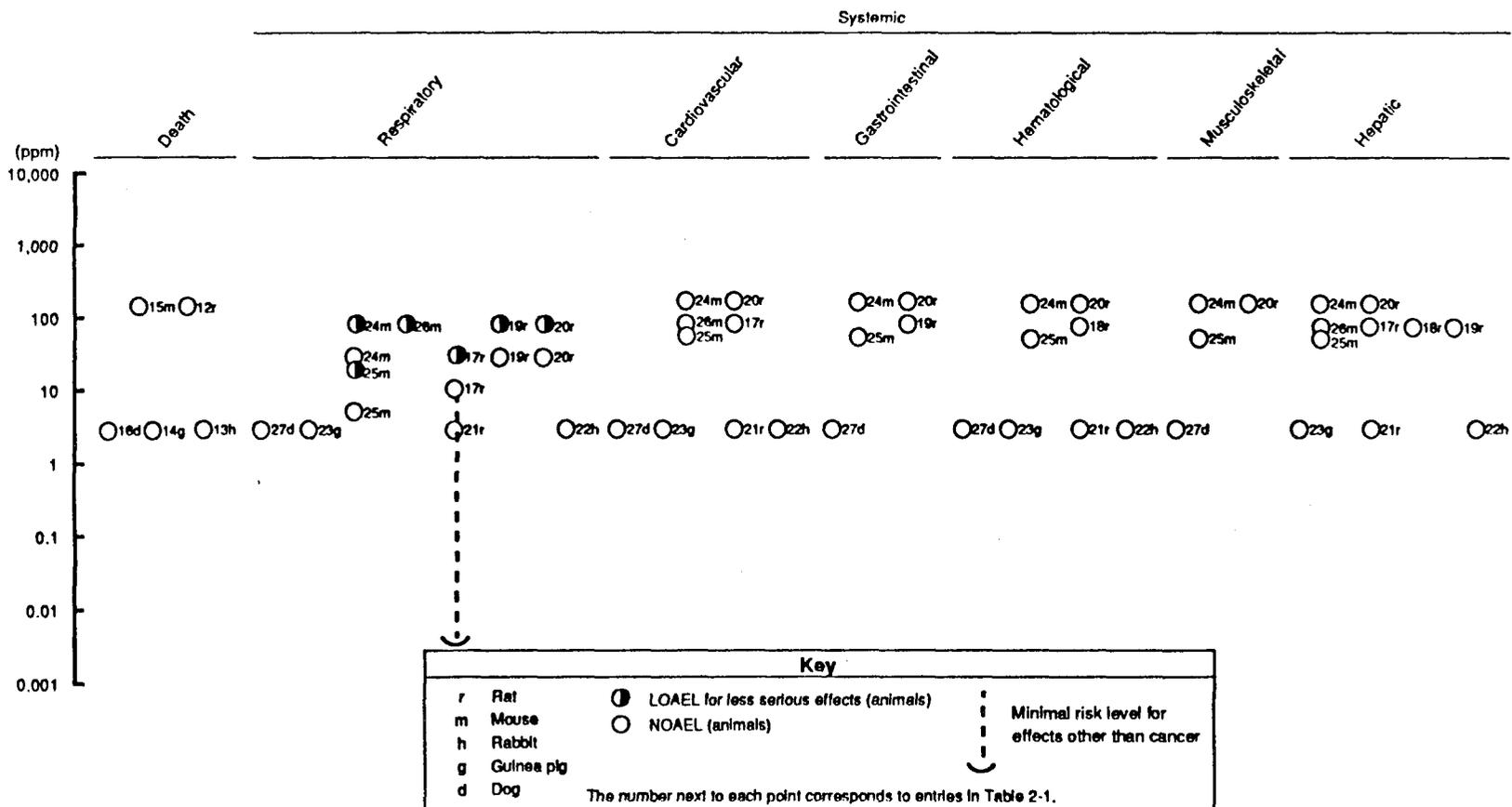


FIGURE 2-1 (Continued)

INTERMEDIATE (Continued)

(15-364 Days)

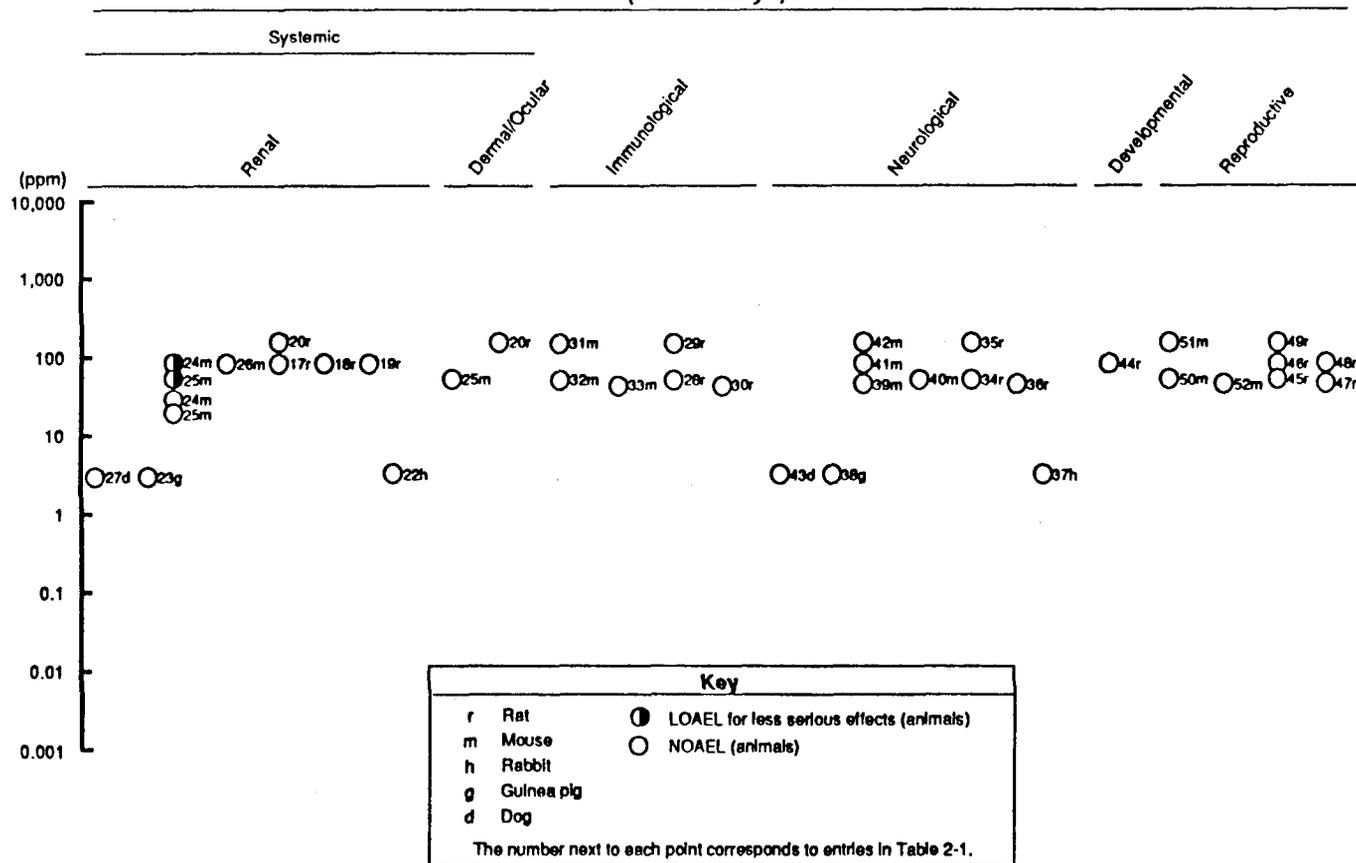
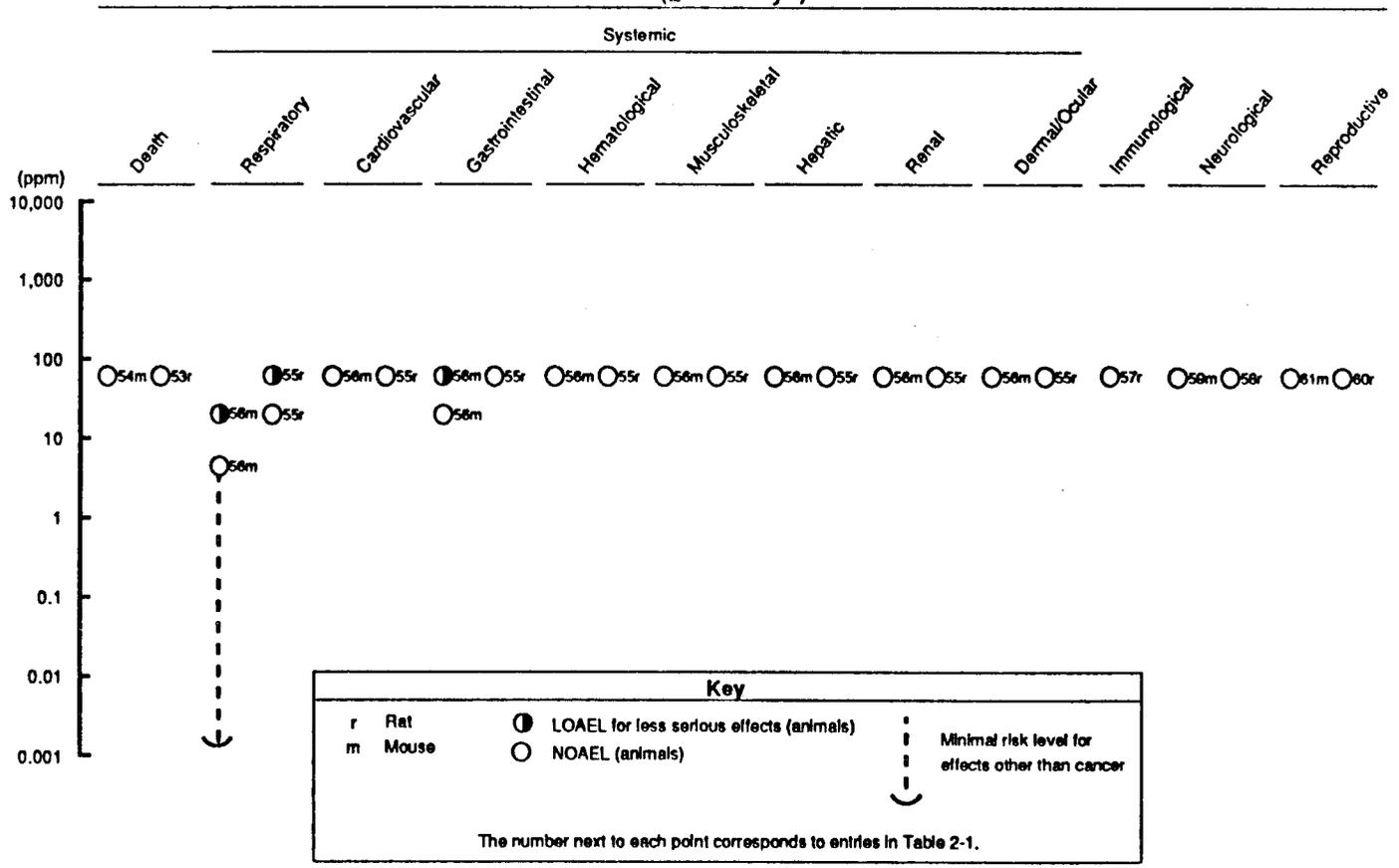


FIGURE 2-1 (Continued)

CHRONIC
(≥ 365 Days)



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irritation, chest pain, cough, and breathing difficulties (Flessel et al. 1978; Markovitz and Crosby 1984).

Acute-duration exposures of rats to various formulations of 1,3-dichloropropene caused respiratory effects. Gross pathological examination revealed atelectasis, 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 in Section 2.2.1.1, Telone C-17® also appears to be more toxic than Telone II®a after acute-duration exposure. The presence of chloropicrin may enhance the toxicity of Telone C-17®. No respiratory effects were noted in rats after a 4-hour exposure to 582 ppm of Telone II®a, although swollen lungs were observed in rats after a 4-hour exposure to 595 ppm. This indicated a steep concentration-response curve (Cracknell et al. 1987). In the same study, rats exposed to 676 ppm had lung congestion, tracheal congestion, and fluid in the thoracic cavity (Cracknell et al. 1987). Multifocal lung hemorrhage was observed in rats exposed for 4 hours to 1,035 ppm of Telone II®a (Streeter et al. 1987).

Intermediate-duration exposure studies indicate that effects on the upper respiratory tract appear to be concentration- and duration-related. Rats and mice had no respiratory lesions attributable to Telone II®a after exposure to 30 ppm or less for 4 weeks (Coate 1979b). Similarly, no respiratory lesions attributable to DD® were observed after gross and microscopic evaluation of rats exposed to 50 ppm or less for 6-12 weeks (Parker et al. 1982). No respiratory effects were observed in rats exposed to 10 ppm Telone II®a for 13 weeks (Coate 1979a). In contrast, rats exposed to 30 ppm Telone II®a or more for 13 weeks developed epithelial changes in the nasal turbinates that included loss of cytoplasm, nuclei disorganization, and occasional necrotic cells (Coate 1979a). Based on the NOAEL for respiratory effects from this study (Coate 1979a), an intermediate inhalation MRL of 0.003 ppm was calculated as described in the footnote to Table 2-1. The epithelial lesions were more severe in rats exposed to 90 ppm or more of Telone II®a for 13 weeks or more and included hyperplasia and focal necrosis (Breslin et al. 1989; Coate et al. 1979a; Stott et al. 1988). No significant respiratory effects were observed in rats exposed to 60 ppm Telone II®b, the highest concentration tested, for 6 or 12 months (Lomax et al. 1989). Mice also developed hyperplastic and/or degenerative lesions of the nasal epithelium after exposure to 90 ppm Telone II®a for 13 weeks (Stott et al. 1988) or to 20 or 60 ppm Telone 11®b for 6-12 months. No respiratory effects were noted on gross and histopathological examinations after an intermediate inhalation exposure of rats, guinea pigs, rabbits, or dogs to 3 ppm Telone II®a for 6 months (Torkelson and Oyen 1977). Higher concentrations were not tested.

Although exposure to 60 ppm of Telone 11®b for 6-12 months did not result in respiratory effects in rats, exposure to the same concentration for 2 years caused olfactory epithelium degeneration (Lomax et al. 1989). A statistically

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significant increase in bronchioalveolar adenomas, benign lung tumors, was also noted in males exposed to 60 ppm but not in females. In mice exposed to 20 or 60 ppm Telone II®b, the epithelial hypertrophy/hyperplasia did not progress in severity or extent from 6 to 24 months. Degeneration of the olfactory epithelium, however, was noted in 48 of 50 male mice and 45 of 50 female mice exposed to 60 ppm, and in 1 of 50 males and 1 of 50 females exposed at 20 ppm (Lomax et al. 1989). Based on the NOAEL for respiratory effects in mice in this study, a chronic inhalation MRL of 0.002 ppm was calculated as described in the footnote in Table 2-1.

These data indicate that acute exposure to 1,3-dichloropropene has effects on the lungs of rats, while intermediate or chronic inhalation exposure to 1,3-dichloropropene produces hyperplastic lesions of the upper respiratory tract in rats and mice and degeneration of the olfactory epithelium in mice.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after inhalation exposure to 1,3-dichloropropene.

No lesions attributable to Telone II®a were found upon histological evaluation of the heart and aorta from rats and mice exposed to 150 ppm or less for up to 13 weeks (Coate 1979a, 1979b; Stott et al. 1988), rats and mice exposed to 60 ppm Telone II®b for 6, 12, or 24 months (Lomax et al. 1989), or rats exposed to 50 ppm DD® for 6-12 weeks (Parker et al. 1982).

Although other indices of cardiovascular toxicity were not examined, 1,3-dichloropropene does not appear to have cardiovascular effects.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to 1,3-dichloropropene.

No gastrointestinal effects were noted after gross and histologic examinations of the stomachs and intestines of rats exposed to 50 ppm or less of DD® for 6-12 weeks (Parker et al. 1982), rats or mice exposed to 150 ppm or less of Telone II®a for 13 weeks (Stott et al. 1988), or rats or mice exposed to 60 ppm of Telone II®b for 6 or 12 months (Lomax et al. 1989). Similarly, no gastrointestinal lesions attributable to 1,3-dichloropropene were observed in rats exposed to 60 ppm of Telone II®b for 2 years (Lomax et al. 1989). In contrast, 8 of 50 male mice exposed to 60 ppm Telone II® for 2 years had hyperplasia and hyperkeratosis of the forestomach. The NOAEL for this effect was 20 ppm in the male mice. Female mice did not develop hyperplasia or hyperkeratosis of the forestomach (Lomax et al. 1989).

Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to 1,3-dichloropropene.

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Hematological parameters have been examined in many studies of intermediate or chronic duration in which several species were exposed by inhalation to formulations of 1,3-dichloropropene. No exposure-related hematological effects were observed in rats, guinea pigs, rabbits, or dogs exposed to 3 ppm Telone II®a for 6 months (Torkelson and Oyen 1977), in rats and mice exposed to 150 ppm Telone II®a for 13 weeks (Stott et al. 1988), to 60 ppm Telone II®b for 6-24 months (Lomax et al. 1989), or in male or female rats exposed to DD® at concentrations up to 90 ppm for up to 10 weeks (Linnett et al. 1988; Parker et al. 1982).

Histological examination of bone marrow also did not reveal any adverse effects in either intermediate or chronic duration exposure studies (Lomax et al. 1989; Stott et al. 1988).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to 1,3-dichloropropene.

Gross and histopathological examination of bone and skeletal muscle did not reveal any differences between exposed and control groups of rats and mice exposed to up to 50 ppm DD® for 6-12 weeks (Parker et al. 1982), 150 ppm Telone II®a for 13 weeks (Stott et al. 1988), or 60 ppm Telone II®b for 6-24 months (Lomax et al. 1989).

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to 1,3-dichloropropene.

Gross and histopathological examination of livers did not reveal any differences between exposed and control groups of rats and mice after inhalation exposure to up to 150 ppm of Telone II®a for 13 weeks or less (Coate et al. 1979b; Stott et al. 1988), up to 50 ppm DD® for 6-12 weeks (Parker et al. 1982), or up to 60 ppm Telone II®b for 24 months or less (Lomax et al. 1989).

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to 1,3-dichloropropene.

Male and female rats exposed to 3 ppm Telone II®a for 6 months developed reversible cloudy swelling of the renal tubular epithelium (Torkelson and Oyen 1977). No adverse renal effects were observed in rats allowed to recover for 3 months following the last exposure. The cloudy swelling observed in these rats was not confirmed in more recent studies, even at longer durations and/or higher concentrations. Exposure to 1 ppm in this study had no renal effects in the rats. Guinea pigs, rabbits, and dogs exposed to 3 ppm suffered no renal effects under the same exposure protocol (Torkelson and Oyen 1977).

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Gross and histological examination of the kidneys from rats and mice exposed to up to 150 ppm Telone II®a for 4-13 weeks (Coate et al. 1979b; Stott et al. 1988), to 50 ppm DD® for 6-12 weeks (Parker et al. 1982), or to 60 ppm Telone II®b for 6-24 months (Lomax et al. 1989) revealed no differences between exposed and control groups. Urinalysis also revealed no differences between exposed and control groups of rats and mice (Lomax et al. 1989; Parker et al. 1982; Stott et al. 1988).

Moderate hyperplasia of the transitional epithelium of the urinary bladder was found in female mice exposed to 90 or 150 ppm Telone I®a for 13 weeks (Stott et al. 1988). Mice exposed to 30 ppm did not show hyperplasia of the urinary bladder. Similarly, mice exposed to up to 60 ppm Telone II®a for 6-24 months did not show hyperplasia of the urinary bladder (Lomax et al. 1989).

Female mice administered Telone II®a in a 2-year gavage study also showed a dose-related increase in urinary bladder hyperplasia (Section 2.2.2.2) (NTP 1985).

Dermal/Ocular Effects. No studies were located regarding dermal or ocular effects in humans after inhalation exposure to 1,3-dichloropropene.

Gross and histological examination of the eyes and skin of rats and mice exposed to up to 150 ppm Telone II®a for 13 weeks (Stott et al. 1988) to 60 ppm for 6-24 months (Lomax et al. 1989) revealed no differences between exposed and control groups.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans after inhalation exposure to 1,3-dichloropropene.

Gross and histological examination of 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. 1982), to 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) revealed no lesions attributable to 1,3-dichloropropene exposure. However, more sensitive tests for immune system function were not used.

The highest NOAEL values for each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

No neurological effects were observed in humans occupationally exposed to 1,3-dichloropropene at levels high enough to require medical attention (Markovitz and Crosby 1984).

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Ataxia of the hindlimbs and loss of the righting reflex was observed in pregnant rabbits exposed to 300 ppm of Telone II®a during gestation days 6-18. No neurological signs of toxicity were observed in rabbits exposed to 50 or 150 ppm nor 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), 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 1979a; Lomax et al. 1989; Stott et al. 1988). More sensitive tests for neurological effects, however, were not included in these studies.

The acute LOAEL value in rabbits and the highest NOAEL values for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to 1,3-dichloropropene.

No developmental effects were found in groups of rats exposed to 50 or 150 ppm Telone II®a during gestation days 6-15 (Kloes et al. 1983). In contrast, rats exposed to 300 ppm Telone II®a during gestation days 6-15 had fewer fetuses per litter, an increase in the incidence of litters totally resorbed, and an increase in the number of litters with resorptions. Rats exposed to 300 ppm Telone II®a had urine and fecal staining, nasal exudate, a red crusty material around the eyes, and significantly decreased food and water consumption and body weight. These observations indicate serious maternal toxicity in rats exposed to 300 ppm, which could account for the decreased litter size, increased resorptions, and increased number of litters with resorptions. Rabbits were evaluated for developmental effects after exposure to up to 300 ppm Telone II®a during gestation days 6-18 (Kloes et al. 1983). No developmental effects attributable to 1,3-dichloropropene exposure were observed in the 50 and 150 ppm groups. In contrast, marked maternal toxicity in the 300 ppm group precluded evaluation of developmental effects; signs of maternal toxicity included ataxia, loss of the righting reflex, significantly decreased body weight, and the death of six of seven rabbits.

No developmental effects were observed in the progeny of groups of male and female rats exposed to 90 ppm or less Telone II®b for two generations (Breslin et al. 1989), or in pregnant rats and rabbits exposed to 120 ppm or less Telone II®a during gestation days 6-15 (Hanley et al. 1987). The parameters monitored included pup survival, pup body weight, pup crown-rump length, and gross pathology. Delayed ossification was noted in 14 rat pups of

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21 litters exposed in utero to 120 ppm, but this may have been due to the decreased food and water consumption and body weight of the dams (Hanley et al. 1987).

The LOAEL in rabbits and the highest NOAEL values for developmental effects are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to 1,3-dichloropropene.

No adverse reproductive effects and no histological changes in reproductive organs were observed in parental groups or progeny of male and female rats exposed to up to 90 ppm Telone II® for two generations (Breslin et al. 1989). Male and female rats evaluated for libido, fertility, estrus cycling (females), and histological changes of reproductive organs showed no adverse effects after exposure to 90 ppm DDe for 10 weeks (Linnett et al. 1988).

Gross and histological examination of reproductive organs and tissues of rats and mice exposed to 150 ppm of Telone II® for 13 weeks (Stott et al. 1988), 60 ppm Telone II® for 6-24 months (Lomax et al. 1989), or 50 ppm of DDe for 6-12 weeks (Parker et al. 1982) revealed no lesions attributable to 1,3-dichloropropene. More sensitive tests for reproductive effects, however, were not included in these studies.

The highest NOAEL values for intermediate-duration reproductive effects in each species are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxicity in humans or animals after inhalation exposure to 1,3-dichloropropene. Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located that convincingly link inhalation exposure to 1,3-dichloropropene with the development of cancer in humans. A clinical report describing three cases of neoplasms that developed after exposure to 1,3-dichloropropene, however, suggests that there may be an association (Markovitz and Crosby 1984). Nine firemen were exposed to 1,3-dichloropropene during cleanup of a tank truck spill. Six years later, two of the men developed histiocytic lymphomas that were refractory to treatment. Both men soon died. In addition, a 52-year-old farmer who had been in good health developed pain in the right ear, nasal mucosa, and pharynx after being exposed

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to 1,3-dichloropropene (not otherwise specified) from his tractor for 30 days. The hose carrying the 1,3-dichloropropene had a small leak that sprayed the chemical near the right side of the man's face. Over the next year, the man developed leukemia that was refractory to treatment. He died of pneumonia 5 weeks after hospital admission.

In the only study regarding the carcinogenic potential of 1,3-dichloropropene in animals after inhalation exposure, a statistically significant increase in the incidence of bronchioalveolar adenomas was observed in male mice exposed to 60 ppm Telone II® for 24 months (Lomax et al. 1989). An increased incidence of this benign lung tumor, however, was not observed in female mice nor in male or female rats exposed to Telone II® under the same protocol.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to 1,3-dichloropropene.

Several studies were located that reported oral LD₅₀ values for 1,3-dichloropropene in various formulations. The oral LD₅₀ for M-3993 was 713 mg/kg (no range calculable) in male rats and 470 mg/kg (95% confidence limits-337-636 mg/kg) in female rats (Lichy and Olson 1975). In a similar study, the oral LD₅₀ for Telone C-17® was 519 mg/kg (95% confidence interval-305-1,009 mg/kg) in male rats and 304 mg/kg (95% confidence interval-147-516 mg/kg) in female rats (Mizell et al. 1988). These data indicate that female rats are more sensitive to 1,3-dichloropropene in its various formulations than male rats. A much lower LD₅₀ value of 150 mg/kg (95% confidence interval-130-170 mg/kg) was reported for Telone II®a in WY-strain Sprague-Dawley rats (Jones and Collier 1986a). Similarly, the LD₅₀ value determined for the cis-isomer of 1,3-dichloropropene for male and female rats combined was 121 mg/kg (95% confidence interval-107-137 mg/kg); for male rats only, 126 mg/kg (95% confidence interval=108-148 mg/kg); and for female rats only, 117 mg/kg (95% confidence interval=96-142 mg/kg) (Jones 1988a). The variability in LD₅₀ values could result from different rat stocks or strains, or, more likely, from differences in the 1,3-dichloropropene formulations used.

No deaths were reported among rats that received gavage doses of Telone® for 13 weeks (Til et al. 1973). No differences were observed in the survival rates of rats that received 0, 25, or 50 mg/kg, or of mice that received 0, 50, or 100 mg/kg Telone II®b by gavage in corn oil for 2 years (NTP 1985).

The LD₅₀ values in rats and the highest NOAEL values for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

TABLE 2-2. Levels of Significant Exposure to 1,3-Dichloropropene - Oral

Key to figure ^a	Species	Route	Exposure frequency/duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference	Formulation
						Less serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE									
Death									
1	Rat	(GO)	1 d 1x/d				150 (LD ₅₀)	Jones and Collier 1986a	T IIa
2	Rat	(GO)	1 d 1x/d		75		121 (LD ₅₀)	Jones 1988a	cis
3	Rat	(G)	1 d 1x/d				713 (LD ₅₀ - males) 470 (LD ₅₀ - females)	Lichy and Olson 1975	M-3993
4	Rat	(GO)	1 d 1x/d				519 (LD ₅₀ - males) 304 (LD ₅₀ - females)	Mizzell et al. 1988a	T C-17
Systemic									
5	Rat	(GO)	1 d 1x/d	Gastro		100 (hyperkeratosis)		Mizell et al. 1988a	T C-17
6	Rat	(GO)	1 d 1x/d	Resp Gastro Hepatic			110 (lung hemorrhage) 110 (intestinal hemorrhage) 110 (liver hemorrhage)	Jones 1988a	cis
7	Rat	(GO)	1 d 1x/d	Resp Gastro Hepatic Renal		75 (lung congestion) 75 (multiple white raised areas in nonglandular regions) 110 170 (mottled, dark liver) 170 (dark kidneys)	250 (lung hemorrhage) 170 (stomach hemorrhage)	Jones and Collier 1986a	T IIa
Neurological									
8	Rat	(GO)	1 d 1x/d			75 (ataxia)		Jones 1988a	cis

TABLE 2-2 (Continued)

Key to figure ^a	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference	Formulation
						Less serious (mg/kg/day)	Serious (mg/kg/day)		
INTERMEDIATE EXPOSURE									
Death									
9	Rat	(GO)	13 wk 6 d/wk 1x/d		30			Til et al. 1973	T
Systemic									
10	Rat	(GO)	9 mo 3 d/wk 1x/d	Gastro Hepatic Renal	50 50 50			NTP 1985	T IIa
11	Rat	(GO)	13 wk 6 d/wk 1x/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal	30 30 30 30 30 30 30			Til et al. 1973	T
CHRONIC EXPOSURE									
Death									
12	Rat	(GO)	2 yr 3 d/wk 1x/d		50			NTP 1985	T IIa
13	Mouse	(GO)	2 yr 3 d/wk 1x/d		50	100		NTP 1985	T IIa

TABLE 2-2 (Continued)

Key to figure ^a	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference	Formulation
						Less serious (mg/kg/day)	Serious (mg/kg/day)		
Systemic									
14	Rat	(GO)	2 yr 3 d/wk 1x/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc	50 50 50 50 50 50 50	25 (basal cell hyperplasia)		NTP 1985	T IIa
Systemic									
15	Mouse	(GO)	2 yr 3 d/wk 1x/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc	100 100 100 100 100 100 100	50 (hyperplasia)	50 (hydronephrosis)	NTP 1985	T IIa
Immunological									
16	Rat	(GO)	2 yr 3 d/wk 1x/d		50			NTP 1985	T IIa
17	Mouse	(GO)	2 yr 3 d/wk 1x/d		100			NTP 1985	T IIa
Neurological									
18	Rat	(GO)	2 yr 3 d/wk 1x/d		50			NTP 1985	T IIa

TABLE 2-2 (Continued)

Key to figure ^a	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference	Formulation
						Less serious (mg/kg/day)	Serious (mg/kg/day)		
19	Mouse	(GO)	2 yr 3 d/wk 1x/d		100			NTP 1985	T IIa
Reproductive									
20	Rat	(GO)	2 yr 3 d/wk 1x/d		50			NTP 1985	T IIa
21	Mouse	(GO)	2 yr 3 d/wk 1x/d		100			NTP 1985	T IIa
Cancer									
22	Rat	(GO)	2 yr 3 d/wk 1x/d			25 (hepatic tumors, forestomach tumors)		NTP 1985	T IIa
23	Mouse	(GO)	2 yr 3 d/wk 1x/d			50 (bladder, forestomach tumors)		NTP 1985	T IIa

^aThe number corresponds to the entries in Figure 2-2.

Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; G = gavage - not specified; Gastro = gastrointestinal; GO = gavage - oil; Hemato = hematological; LD₅₀ = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M-3993 = Telone II^a; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; T = Telone^a (40% cis-1,3-dichloropropene, 38% trans-1,3-dichloropropene); T C-17 = Telone C-17^a (40% cis-1,3-dichloropropene, 39% trans-1,3-dichloropropene, 21% chloropicrin); T IIa = Telone II^a (53% cis-1,3-dichloropropene, 45% trans-1,3-dichloropropene, 1% epichlorohydrin); wk = week(s); yr = year(s)
x = time(s)

FIGURE 2-2. Levels of Significant Exposure to 1,3-Dichloropropene - Oral

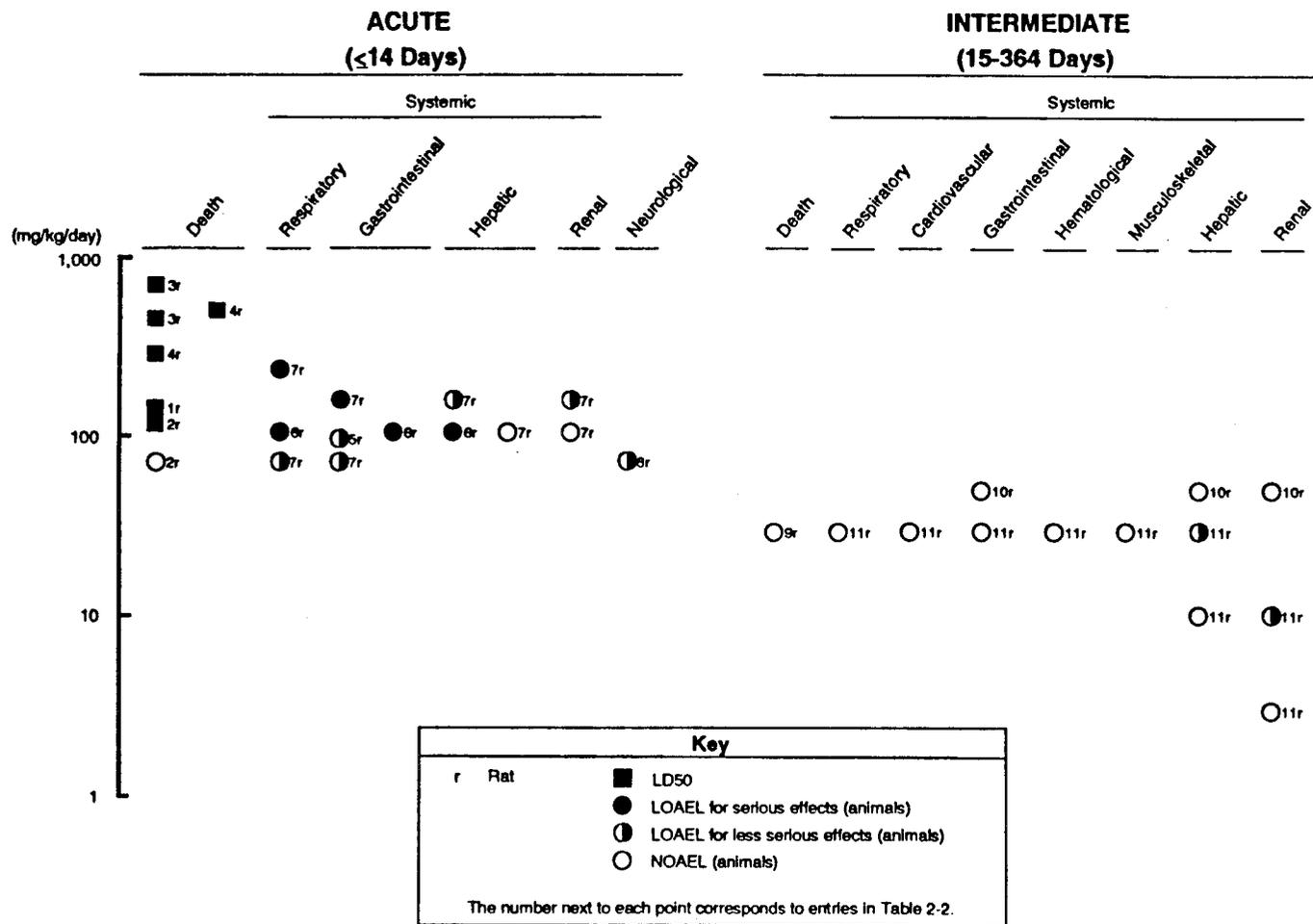
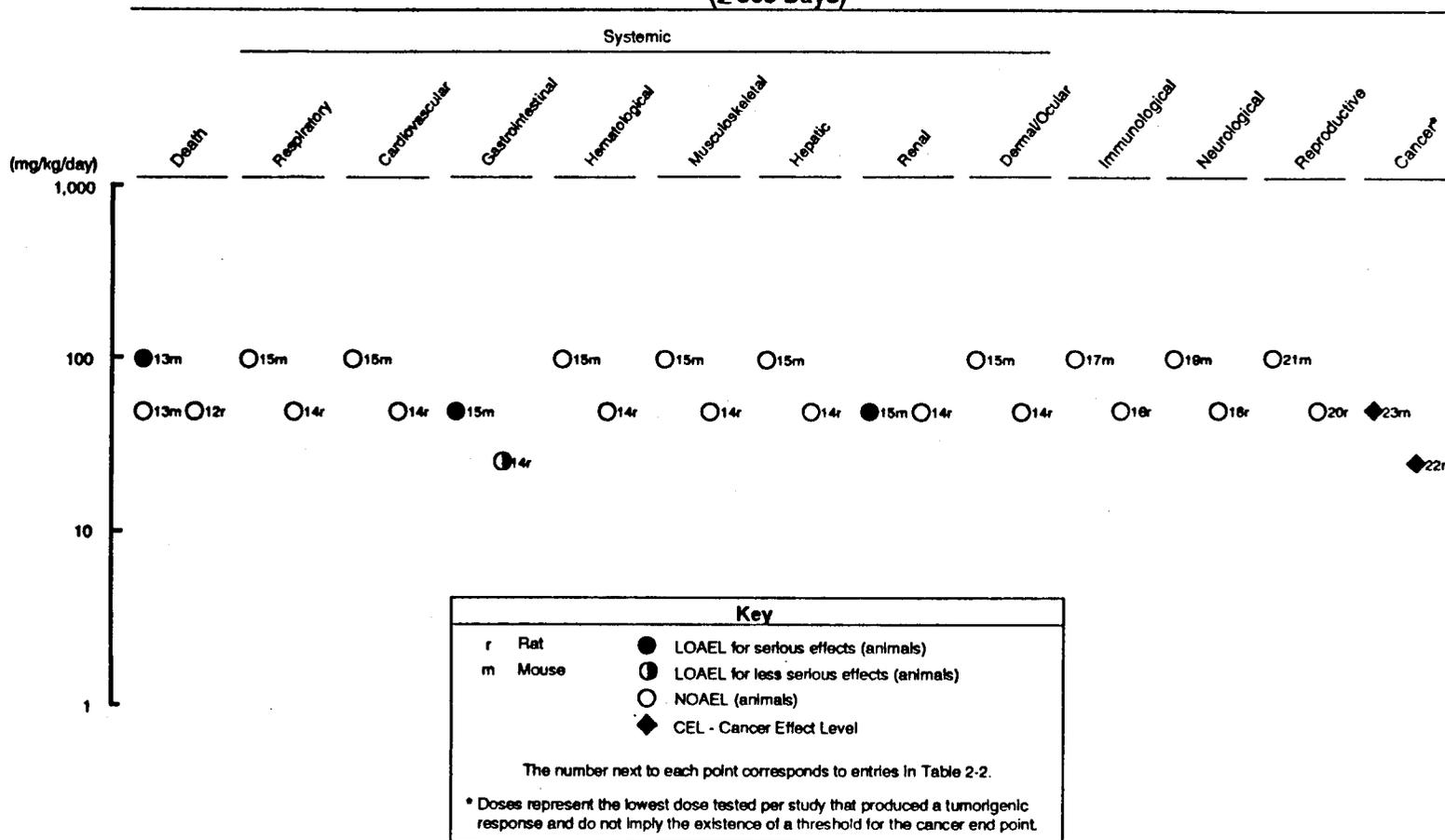


FIGURE 2-2 (Continued)

CHRONIC
(≥ 365 Days)



2. HEALTH EFFECTS

2.2.2.2 Systemic Effects

The systemic effects observed in animals after oral exposure to 1,3-dichloropropene are discussed below. The highest NOAELs and all reliable LOAELs for each systemic effect for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to 1,3-dichloropropene.

In a rat LD₅₀ study, a single oral administration of Telone II®a caused dose-related respiratory effects including lung congestion and lung hemorrhage (Jones and Collier 1986a). Abnormally red and hemorrhagic lungs were observed in rats that received a single oral dose of cis-1,3-dichloropropene in an LD₅₀ study (Jones 1988a).

Gross and microscopic examination of male and female rats that received 30 mg Telone®/kg/day or less for 13 weeks revealed no respiratory effects (Til et al. 1973).

Gross and histological examination revealed no neoplastic or nonneoplastic respiratory lesions in rats and no nonneoplastic respiratory lesions in mice attributable to gavage doses of Telone II®a for 2 years (NTP 1985). In contrast, an increased incidence of bronchioalveolar adenomas was observed in female mice receiving Telone II®a for 2 years (Section 2.2.2.8).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to 1,3-dichloropropene.

Histological evaluation of the hearts of rats that received 30 mg/kg or less of Telone® for 13 weeks revealed no lesions attributable to Telone® (Til et al. 1973).

Gross and histological examination of hearts revealed no cardiovascular lesions in rats that received up to 50 mg/kg or in mice that received up to 100 mg Telone II®a/kg by gavage for 2 years (NTP 1985). Data in male mice were of limited value, because 25 of 50 vehicle controls died of myocarditis after 48-51 weeks.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to 1,3-dichloropropene.

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 (Jones and Collier 1986a). Rats that received a single oral dose of 110 mg cis-1,3-dichloropropene/kg or more developed ulcerations of the glandular stomach and hemorrhage of the small intestine (Jones 1988a).

2. HEALTH EFFECTS

Hyperkeratosis of the non-glandular stomach was found in rats that received a single gavage dose of 100 mg/kg Telone C-17® (Mizell et al. 1988).

Gross and microscopic evaluation of the gastrointestinal tract revealed no lesions attributable to oral administration of 30 mg/kg or less of Telone® to rats for 13 weeks (Til et al. 1973). Similarly, no gastrointestinal lesions were found in rats that received 50 mg/kg or less of Telone II®a for 9 months (NTP 1985).

Chronic oral exposure to 1,3-dichloropropene causes preneoplastic and neoplastic lesions in the gastrointestinal systems of rats and mice. Significant dose-related increases in basal cell or epithelial cell hyperplasia of the forestomach were observed in male and female rats that received 25 mg/kg or more Telone I®a for 2 years (NTP 1985). Additionally, female rats that received 50 mg/kg had hyperkeratosis of the forestomach. Male rats suffered an increase in pancreatic periarteritis at both 25 and 50 mg/kg.

Dose-related increases in epithelial cell hyperplasia of the forestomach were observed in female mice receiving 50 mg/kg or more Telone I®a (NTP 1985). Although data in male mice were limited, the incidence of forestomach epithelial cell hyperplasia was similar to that in the females. Neoplastic lesions of the stomach were also observed in rats and mice that received gavage doses of Telone II®a for 2 years (Section 2.2.2.8).

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to 1,3-dichloropropene.

Evaluation of hematological profiles and clinical chemistry revealed no adverse effects in rats that received 30 mg/kg or less of Telone® (Til et al. 1973).

Extensive clinical chemistry and hematological profiles of male and female rats exposed to up to 50 mg/kg 1,3-dichloropropene for 2 years revealed no signs of adverse effects (NTP 1985). Therefore, 1,3-dichloropropene does not cause adverse hematological effects after oral administration of doses of 50 mg/kg or less for up to 2 years.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,3-dichloropropene.

Gross and histological examination of male rats that received up to 50 mg/kg 1,3-dichloropropene by gavage for 2 years revealed no musculoskeletal effects (NTP 1985). Neither female rats nor male or female mice were examined for musculoskeletal effects.

2. HEALTH EFFECTS

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to 1,3-dichloropropene.

Rats that received a single gavage dose of 110 mg cis-1,3-dichloropropene/kg or more developed dark and patchy livers and hemorrhage of the liver (Jones 1988a). Similarly, a single gavage dose of 170 mg/kg Telone II®a produced mottled and dark livers in rats (Jones and Collier 1986a).

An increased liver:body weight ratio was observed in rats that received 30 mg/kg, but not 10 mg/kg or less, of Telone® for 13 weeks (Til et al. 1973).

Histological examination revealed no hepatic lesions that were attributable to oral administration of 50 mg/kg Telone II®a to rats for 9-24 months (NTP 1985). Similarly, no hepatic lesions attributable to Telone II®a were found in mice after they received gavage doses for 2 years. In contrast, an increased incidence of hepatic neoplastic nodules was observed in male rats that received Telone II®a for 2 years (Section 2.2.2.8).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to 1,3-dichloropropene.

A single gavage dose of 170 mg/kg Telone II®a produced dark kidneys in rats (Jones and Collier 1986a). The toxicological significance of this observation was not discussed. The NOAEL for this effect was 110 mg/kg.

An increase in the kidney:body weight ratio was observed in rats that received 10 mg/kg, but not 3 mg/kg, Telone® for 13 weeks (Til et al. 1973). In contrast, no renal lesions were observed after gross and microscopic examination in rats that received 50 mg/kg or less of Telone I®a for 9-24 months (NTP 1985).

Female mice developed a dose-related increase in kidney hydronephrosis after oral exposure to 50 or 100 mg/kg Telone I®a for 2 years (NTP 1985). A primary target organ of 1,3-dichloropropene in female mice was the urinary bladder, where a dose-related increase in epithelial cell hyperplasia and transitional cell carcinoma (Section 2.2.2.8) was observed. male mice were not adequate, Although data for there was some indication that Telone I®a also caused transitional cell carcinomas in the urinary bladder. Similar neoplastic and nonneoplastic lesions were not found in male and female rats exposed to up to 50 mg/kg 1,3-dichloropropene for 2 years (NTP 1985).

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans after oral exposure to 1,3-dichloropropene.

Gross and histological examination of the eyes and skin in rats and of the skin only in mice that received gavage doses of Telone II®a for 2 years revealed no lesions attributable to Telone II®a (NTP 1985):

2. HEALTH EFFECTS

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to 1,3-dichloropropene.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to cis-1,3-dichloropropene.

Clinical signs of neurotoxicity were observed at 1 and 4 hours after a single oral dose 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, however, were not used.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to 1,3-dichloropropene.

2.2.2.6 Reproductive Effects

Histological evaluation of reproductive organs and tissues from rats and mice that received oral doses of Telone 1I@a 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.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to 1,3-dichloropropene.

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to 1,3-dichloropropene.

Substantial evidence exists for 1,3-dichloropropene-related carcinogenicity in rats and mice after oral exposure. In a 2-year gavage study, rats that received 25 or 50 mg Telone II@a/kg/day developed squamous cell papillomas and carcinomas of the forestomach (NTP 1985). Male rats also developed neoplastic nodules of the liver. Female mice that received 50 or 100 mg/kg/day developed squamous cell papillomas and carcinomas of the forestomach, transitional cell carcinomas of the urinary bladder, and an increased incidence of alveolar/bronchiolar adenomas. The data in male mice

2. HEALTH EFFECTS

were considered inadequate for assessment of carcinogenicity, because 25 of 50 vehicle controls died of myocarditis during weeks 48-51 of the study; however, there was some indication that the same neoplastic lesions found in increased incidences in female mice also occurred in male mice (NTP 1985). How much the epichlorohydrin component (1%) of Telone 1I@a contributes to the development of papillomas and carcinomas of the forestomach is not known. Although oral administration of epichlorohydrin produced papillomas and carcinomas of the forestomach in male mice (NTP 1989), it is doubtful that Telone 1I@a contained enough epichlorohydrin for the tumor response to be due solely to epichlorohydrin.

The cancer effect levels (CELs) in rats and mice are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to 1,3-dichloropropene.

The acute dermal LD₅₀ for cis-1,3-dichloropropene in male and female rats combined was 794 mg/kg (95% confidence interval-669-942 mg/kg); for males only, 758 mg/kg (95% confidence interval-604-950 mg/kg); and for females only, 841 mg/kg (95% confidence interval-633-1118 mg/kg) (Jones 1988b). The acute dermal LD₅₀ for Telone 1I@a in rats was 1,200 mg/kg (95% confidence interval-1,000-1,400 mg/kg) (Jones and Collier 1986b). The acute dermal LD₅₀ in rabbits for M-3993 was 713 mg/kg for males and 407 mg/kg for females, for an average of 504 mg/kg (95% confidence limits= 220-1,150 mg/kg) (Lichy and Olson 1975). In a similar study, the dermal LD₅₀ for Telone 1I@a in rabbits was 333 mg/kg (95% confidence interval-102-610 mg/kg) (Jeffrey et al. 1987). 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-17æ (Mizell et al. 1988b).

The LOAEL in rats and the LD₅₀ and LOAEL values in rabbits are recorded in Table 2-3.

2.2.3.2 Systemic Effects

The systemic effects observed in animals after dermal exposure to 1,3-dichloropropene are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect for each species and duration category are recorded in Table 2-3.

TABLE 2-3. Levels of Significant Exposure to 1,3-Dichloropropene - Dermal

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect)		Reference	Formulation
				Less Serious	Serious		
ACUTE EXPOSURE							
Death							
Rat	1 d 24 hr/d		500 mg/kg		794 mg/kg (LD50)	Jones 1988b	cis
Rat	1 d 24 hr/d		500 mg/kg		1,200 mg/kg (LD ₅₀)	Jones and Collier 1986b	T IIa
Rabbit	1 d 24 hr/d				500 mg/kg (6/10 died)	Mizell et al. 1988b	T C-17
Rabbit	1 d 24 hr/d				713 mg/kg (LD ₅₀ - males) 470 mg/kg (LD ₅₀ - females)	Lichy and Olson 1975	M-3993
Rabbit	1 d 24 hr/d				333 mg/kg (LD ₅₀)	Jeffrey et al. 1987	T IIa
Systemic							
Rat	1 d 24 hr/d	Resp		500 mg/kg (lung congestion)	800 mg/kg (lung hemorrhage)	Jones and Collier 1986b	T IIa
		Gastro	500 mg/kg		800 mg/kg (stomach hemorrhage)		
		Derm/oc		500 mg/kg (subcutaneous hemorrhage)			
Rat	1 d 24 hr/d	Resp		800 mg/kg (abnormally red lungs)		Jones 1988b	cis
		Gastro			800 mg/kg (stomach hemorrhage, stomach ulcers)		
		Hepatic		800 mg/kg (dark liver)			
		Derm/oc		500 mg/kg (edema, eschar formation, skin hardening)			
Rabbit	1 d 4 hr/d	Derm/oc		0.5 mL (necrosis/exfoliation)		Mizell 1988a	T C-17

TABLE 2-3 (Continued)

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect)		Reference	Formulation
				Less Serious	Serious		
Rabbit	1 d 24 hr/d	Derm/oc		200 mg/kg (erythema, necrosis)		Jeffrey et al. 1987	T IIa
Rabbit	1 d 4 hr/d	Derm/oc		0.5 mL (erythema/edema)		Jeffrey 1987c	T IIa
Rabbit	1 d 1x/d	Derm/oc		0.1 mL (eye irritation)		Lichy and Olson 1975	M-3993
Rabbit	1 d 1x/d	Derm/oc		0.1 mL (eye irritation)		Jeffrey 1987b	T IIa
Rabbit	3 d 1x/d	Derm/oc		0.5 mL (erythema/edema)		Lichy and Olson	M-3993
Rabbit	1 d 24 hr/d	Musc/skel		500 mg/kg (skeletal muscle hemorrhage)		Mizell et al. 1988	T C-17
		Derm/oc			500 mg/kg (necrosis)		
Gn pig	14 wk 1 d/wk 6 hr/d	Derm/oc		0.4 mL (erythema) of 1% solution		Mizell 1988b	T C-17
Gn pig	1 wk 4x/wk	Derm/oc		0.1 mL (erythema) of 10% solution		Carreon and Wall 1983	T IIa
Neurological							
Rat	1 d 24 hr/d			500 mg/kg (lethargy, salivation)	800 mg/kg (decreased respiration, ataxia, ptosis)	Jones 1988b	cis
INTERMEDIATE EXPOSURE							
Systemic							
Gn pig	4 wk 1 d/wk 6 hr/d	Derm/oc		0.4 mL (erythema) of 0.1% solution		Jeffrey 1987a	T IIa

TABLE 2-3 (Continued)

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect)		Reference	Formulation
				Less Serious	Serious		
Immunological							
Gn pig	3 wk 3 d/wk 6 hr/d			0.2 mL (contact of a sensitization) 0.5% solution		Jones 1988c	cis

d = day(s); Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gn pig = guinea pig; hr = hour(s); LD₅₀ = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M-3993 = Telone IIa; ml = milliliter(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; T C-17 = Telone C-17 (40% cis-1,3-dichloropropene, 39% trans-1,3-dichloropropene, 21% chloropicrin); T IIa = Telone II^a (53% cis-1,3-dichloropropene, 45% trans-1,3-dichloropropene, 1% epichlorohydrin); wk = week(s)

2. HEALTH EFFECTS

No studies were located regarding cardiovascular, hematological, or renal effects in humans or animals after dermal exposure to 1,3-dichloropropene.

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to 1,3-dichloropropene. 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 I® developed lung congestion, and at 800 mg/kg, lung hemorrhage (Jones and Collier 1986b).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following dermal exposure to 1,3-dichloropropene.

Gross necropsy revealed that rats that received a single dermal application of 800 mg cis-1,3-dichloropropene/kg had hemorrhage and ulceration of the glandular gastric mucosa (Jones 1988b). Similarly, rats that received a single dermal application of 800 mg/kg Telone II® suffered hemorrhage of the stomach and congestion and hemorrhage of the intestines (Jones and Collier 1986b). No gastrointestinal effects were observed in rats that received 500 mg/kg cis-1,3-dichloropropene or 500 mg/kg Telone II®.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following dermal exposure to 1,3-dichloropropene.

Of six rabbits that died following dermal application of 500 mg/kg Telone C-17®, two had developed skeletal muscle hemorrhage underneath the site of application (Mizell et al. 1988b).

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to 1,3-dichloropropene.

Gross necropsy revealed abnormally dark livers in rats that received a single dermal application of 800 mg cis-1,3-dichloropropene/kg or more (Jones 1988b). The toxicological significance of this observation was not discussed. No other studies were located regarding hepatic effects in animals after dermal exposure to 1,3-dichloropropene.

Dermal/Ocular Effects. No studies were located regarding dermal or ocular effects in humans following dermal exposure to 1,3-dichloropropene.

Skin sensitization to 1,3-dichloropropene was noted in a 26-year-old male exposed during the manufacture of the soil fumigant DD-92® (Van Joost and de Jong 1988). Skin contact produced an itchy rash in this subject.

2. HEALTH EFFECTS

Acute dermal application of dilute or full strength Telone II®a or M-3993 rapidly produced erythema and edema in rats, rabbits, and guinea pigs (Carreon and Wall 1983; Jeffrey 1987c; Jones and Collier 1986b; Lichy and Olson 1975; Mizell 1988a). At concentrations of 200 mg/kg or more, necrosis and subcutaneous/skeletal muscle hemorrhage were observed (Jones and Collier 1986b; Mizell 1988a; Mizell et al. 1988b).

Telone I®a and Telone C-17® also produced a delayed-type hypersensitivity in guinea pigs (Carreon and Wall 1983; Jeffrey 1987a; Mizell 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 1987b; Lichy and Olson 1975).

2.2.3.3 Immunological Effects

Skin sensitization to DD-92® was noted as an itchy rash on the hands and feet of a 26-year-old male exposed during the manufacture of a soil fumigant (Van Joost and de Jong 1988). Positive patch tests for 1,3-dichloropropene confirmed the sensitization.

Delayed-type hypersensitivity reactions to Telone II®a and Telone C-17® were observed in guinea pigs (Carreon and Wall 1983; Jeffrey 1987a; Mizell 1988b). Guinea pigs also developed contact sensitization to cis-1,3-dichloropropene (Jones 1988c).

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to 1,3-dichloropropene.

Rats that received single dermal applications of 500 mg cis-1,3-dichloropropene/kg 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 1,300 mg/kg and 2,000 mg/kg (Jones 1988b). Rats that received a single dermal application of 1,300 mg/kg or more of Telone II®a became ataxic and lost the righting reflex, indicating neurological deficits (Jones and Collier 1986b). Several studies 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 (Jeffrey et al. 1987; Jones and Collier 1986b; Mizell et al. 1988).

2. HEALTH EFFECTS

No studies were located regarding the following effects in humans or animals after dermal exposure to 1,3-dichloropropene:

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans after dermal exposure to 1,3-dichloropropene.

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. 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). Therefore, 1,3-dichloropropene does not appear able to initiate or induce skin tumors in mice.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

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

Evidence from animal studies supports this observation in humans. Mixtures of cis and trans isomers of 1,3-dichloropropene were rapidly absorbed by rats after inhalation exposure (Stott and Kastl 1986). The rate of uptake in rats exposed to 30, 90, 300, or 900 ppm was 144±14, 307±13, 880±83, or 1810±76 nmol/minute, respectively. This corresponds to 82%, 65%, 66%, or 62% uptake, respectively. A decrease in the respiratory rate was observed in rats exposed to 90 ppm or more, which could account for the decrease in uptake at these concentrations. Steady-state blood levels were reached within 1 hour at 30 and 90 ppm and within 2-3 hours at 300 ppm, but did not reach steady state within 3 hours at 900 ppm. The increased length of time required to reach steady state at 300 and 900 ppm was likely a function of the observed decrease in respiratory rate. Nonlinear excretion kinetics also contributed to the decreased uptake observed at 300 and 900 ppm; disproportionate increases in the blood levels of cis-1,3-dichloropropene at 900 ppm and of

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trans-1,3-dichloropropene at 300 and 900 ppm could indicate changes in distribution and/or metabolism.

Steady-state blood levels of the glutathione-conjugate of 1,3-dichloropropene were reached within 15 minutes in rats exposed to 78, 155, or 404 ppm Telone II@a, indicating that absorption was rapid (Fisher and Kilgore 1989).

2.3.1.2 Oral Exposure

No studies were located regarding absorption of 1,3-dichloropropene in humans after oral exposure.

1,3-Dichloropropene was well absorbed following gavage administration of ¹⁴C-labeled cis- and/or trans-1,3-dichloropropene in rats (Climie et al. 1979; Hutson et al. 1971). Recovery of [¹⁴C]cis-1,3-dichloropropene in 24-hour urine collections was 82%-84% in rats (Climie et al. 1979). Similarly, 82%-84% of ¹⁴C-labeled cis-1,3-dichloropropene was recovered in urine, and 2%-3% was recovered in feces during a 96-hour urine collection period after gavage administration in rats (Hutson et al. 1971). In contrast, only 55%-60% of the ¹⁴C-labeled trans-1,3-dichloropropene was recovered in the urine and 2% in the feces during the same period. These data indicate that both isomers of 1,3-dichloropropene are extensively absorbed by the oral route of exposure, which could lead to distribution throughout the body.

2.3.1.3 Dermal Exposure

No studies were located regarding the absorption of 1,3-dichloropropene after dermal exposure in humans or animals. The dermal LD₅₀ for 1,3-dichloropropene in rabbits has been determined and indicates that this compound is absorbed by the dermal route of exposure (Lichy and Olson 1975).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the distribution of 1,3-dichloropropene after inhalation exposure in humans or animals.

2.3.2.2 Oral Exposure

No studies were located regarding distribution of 1,3-dichloropropene in humans after oral exposure.

Analysis of the distribution of radioactivity 48 hours after gavage administration of ¹⁴C-cis/trans-1,3-dichloropropene 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

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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.

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of 1,3-dichloropropene after inhalation exposure in humans or animals.

2.3.3 Metabolism

2.3.3.1 Inhalation Exposure

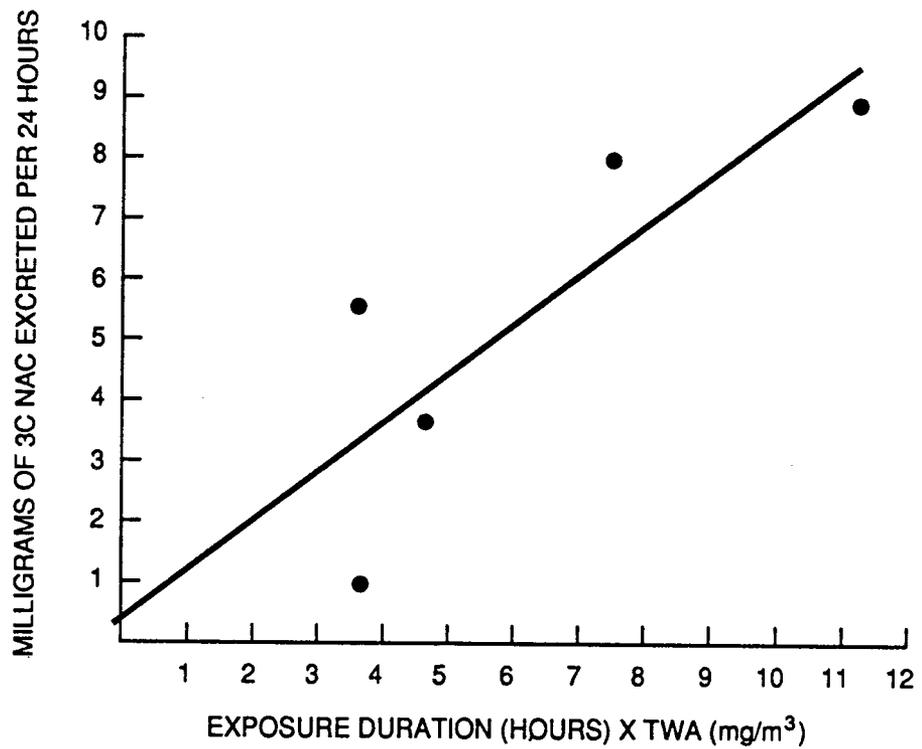
The N-acetyl-cysteine conjugate of cis-1,3-dichloropropene was detected in the urine of four men exposed occupationally to Telone II@a, indicating that glutathione conjugation is a metabolic pathway in humans (Osterloh et al. 1984). Exposure levels were monitored by personal dosimeters. A strong correlation was found between exposure levels of 1,3-dichloropropene and urinary excretion of the N-acetyl-cysteine conjugate ($r=0.83$). These data are presented in Figure 2-3.

1,3-Dichloropropene was rapidly metabolized to the glutathione conjugate in rats after inhalation exposure (Fisher and Kilgore 1989). The blood level of the glutathione conjugate reached a steady state of 116 nmol/mL within 15 minutes after exposure of rats to Telone I@a. The increase in blood levels of the glutathione conjugate correlated with the decrease in nonprotein sulfhydryl (glutathione) content of nasal tissues (Fisher and Kilgore 1988a). Glutathione levels in the kidney and liver were also decreased after inhalation exposure of rats to Telone II@a, but lung levels were not affected (Stott and Kastl 1986). The data indicate that conjugation with glutathione can occur in the nasal tissue, kidney, and liver. The glutathione conjugate of 1,3-dichloropropene is then converted to the mercapturic acid and acetylated for excretion as the N-acetyl-cysteine metabolite (Fisher and Kilgore 1988b).

The two isomers of 1,3-dichloropropene appear to be metabolized at different rates. Plateau blood levels of the cis and trans isomers were 0.085 ± 0.024 and 0.12 ± 0.03 $\mu\text{g/mL}$, respectively, in rats exposed to 30 ppm Telone II@a for 1 hour, and 0.20 ± 0.04 and 0.26 ± 0.03 $\mu\text{g/mL}$, respectively, in rats exposed to 90 ppm Telone II@a for 1 hour. Plateau blood levels reached after 2-3 hours in rats exposed to 300 ppm were 0.89 ± 0.2 and 1.87 ± 0.27 $\mu\text{g/mL}$ 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).

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FIGURE 2-3. Correlation of Exposure to 1,3-Dichloropropane with Urinary Excretion of the N-Acetyl Cysteine Metabolite*



*Derived from Osterloh et al. 1984

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2.3.3.2 Oral Exposure

Orally administered 1,3-dichloropropene is also metabolized by conjugation with glutathione (Climie et al. 1979). Urine collected for 24 hours after oral administration of ¹⁴C-labeled cis-1,3-dichloropropene in rats yielded 82%-84% of the radioactivity as the N-acetyl-cysteine conjugate of 1,3-dichloropropene. Two other urinary metabolites that accounted for 3% and 5% of the administered radioactivity were found but not identified (Climie et al. 1979). Tissue nonprotein sulfhydryl content was assayed in mice following a single gavage administration of 50 mg/kg cis- and trans-1,3-dichloropropene (Dietz et al. 1982). Decreased tissue nonprotein sulfhydryl levels were observed in the forestomach, glandular stomach, liver, and kidney, which indicated that glutathione conjugation occurred at these sites.

No differences were observed in the distribution or the rate and extent of metabolism or excretion of 1,3-dichloropropene after gavage administration between rats that received a single dose and rats that received repeated doses. Furthermore, no differences in distribution, metabolism, or excretion of 1,3-dichloropropene were observed between male and female rats (Waechter and Kastl 1988). The proposed metabolic pathway for 1,3-dichloropropene in rats is presented in Figure 2-4.

2.3.3.3 Dermal Exposure

No studies were located regarding metabolism of 1,3-dichloropropene after dermal exposure in humans or animals.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

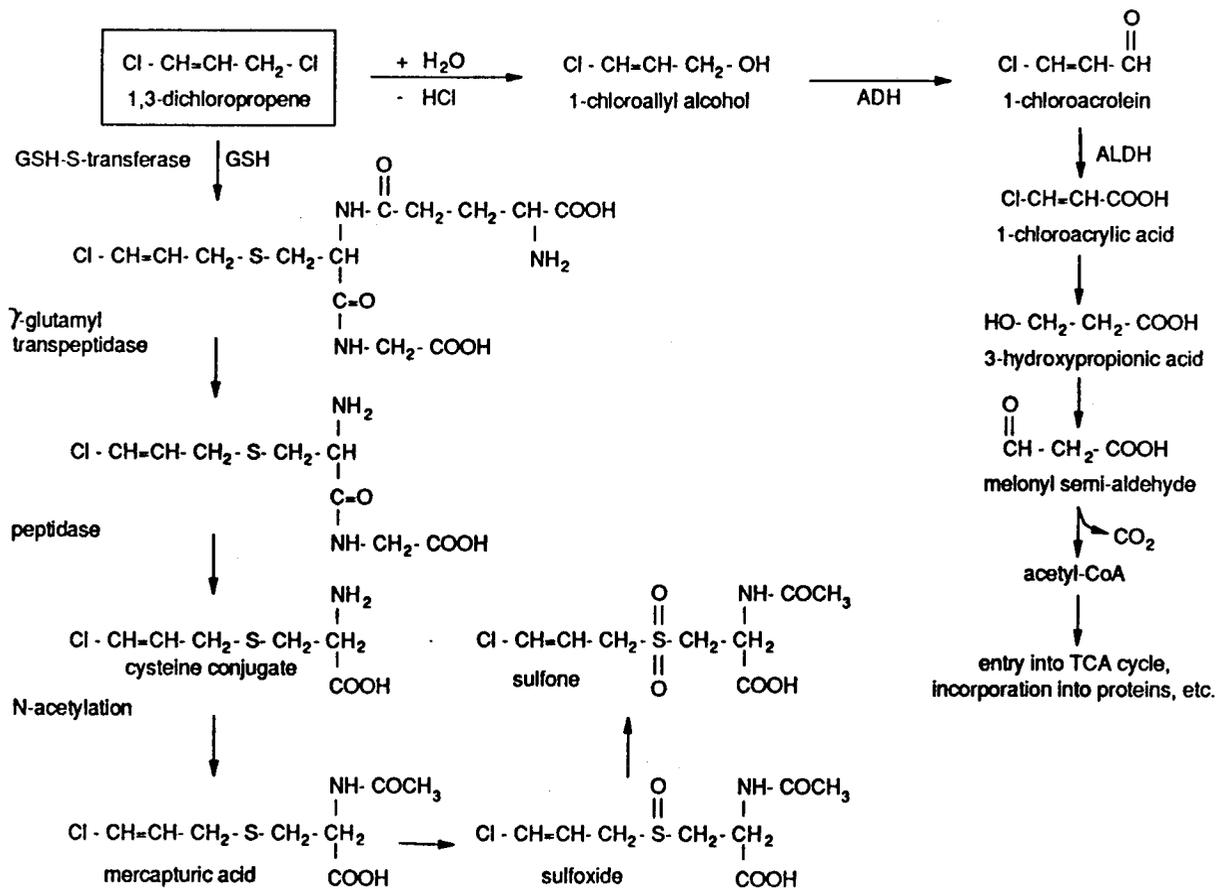
A strong correlation was reported for humans between occupational exposure to Telone II@a and urinary levels of the N-acetyl-cysteine conjugate of cis-1,3-dichloropropene ($r=0.83$) (Osterloh et al. 1984). Rats exposed by inhalation for 1 hour to 0, 40, 107, 284, 398, or 789 ppm Telone II@a excreted 0, 0.11, 0.49, 2.7, 3.7, or 4.0 μmol N-acetyl-cysteine conjugate/ml of urine in the 24 hours following exposure (Fisher and Kilgore 1988b). Uptake levels, however, were not measured, which precludes correlation with excretion.

2.3.4.2 Oral Exposure

No studies were located regarding excretion of 1,3-dichloropropene after oral exposure in humans.

Significant recoveries of ¹⁴C-labeled 1,3-dichloropropene were reported in two studies with rats after oral exposure (Climie et al. 1979; Hutson et al. 1971). In both studies, 82%-84% of the administered cis isomer was

FIGURE 2-4. Proposed Metabolic Pathway for 1,3-Dichloropropene in the Rat



*Derived from Waechter and Kastl 1988

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recovered as the mercapturic acid conjugate of 1,3-dichloropropene in a 24-hour collection of urine. Two other minor metabolites that accounted for 3% and 5% of the radioactivity were observed, but these metabolites were not identified (Climie et al. 1979). Comparison of the excretory pathways for the cis and trans isomers of 1,3-dichloropropene revealed that 82%-84% of the cis isomer was recovered as the mercapturic acid conjugate in the 24-hour urine collection; 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 $^{14}\text{CO}_2$ (22%-25%). A smaller percentage of each isomer was recovered in the feces: 2%-3% of the cis and 2% of the trans isomer. Less than 2% of either compound remained in the carcass after 4 days (Hutson et al. 1971). These data indicate that neither isomer of 1,3-dichloropropene has a tendency to concentrate in the body.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of 1,3-dichloropropene after dermal exposure in humans or animals.

2.4 RELEVANCE TO PUBLIC HEALTH

Humans are most likely to be exposed to 1,3-dichloropropene in an occupational setting or in agricultural areas where this chemical is in use. 1,3-Dichloropropene is widely used in agriculture as a preplanting pesticide. Both inhalation and dermal exposure is possible during the application of 1,3-dichloropropene to fields or during the cleanup of an accidental spill. 1,3-Dichloropropene has been found in the water supplies of agricultural areas where it is used; therefore, oral exposure is possible.

Human health effects observed after accidental exposure at the site of a tank truck spill included headache, mucous membrane irritation, dizziness, chest discomfort, nausea, vomiting, abdominal discomfort, and malaise. Three men occupationally exposed to high concentrations of 1,3-dichloropropene developed hematological malignancies that may have been associated with the chemical. Skin sensitization to 1,3-dichloropropene has also been reported after exposure during the manufacture of a pesticide containing 1,3-dichloropropene.

The effects of 1,3-dichloropropene exposure observed in animals include death, damage to the nasal tissues, lungs, liver, kidneys, and urinary bladder. 1,3-Dichloropropene has also caused lung adenomas, stomach papillomas and carcinomas, neoplastic liver nodules, and urinary bladder carcinomas in animals.

The information on effects of acute inhalation exposure to 1,3-dichloropropene is limited to effects on respiratory and dermal irritation, and neurological and developmental effects. An acute inhalation MEL was not derived because the available NOAEL and LOAEL values for respiratory effects

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(the end point on which intermediate- and chronic-duration MRLs are based) and for neurological and developmental effects are higher than or too close to acute inhalation LC₅₀ values. Sufficient information is available on the health effects of 1,3-dichloropropene to derive MRLs for intermediate- and chronic-duration exposure. Based on a NOAEL of 10 ppm for histological changes in the nasal epithelium of rats (Coate 1979a), an intermediate-duration inhalation MRL of 0.003 ppm was calculated by adjusting the NOAEL for intermittent exposure, converting the adjusted NOAEL to an equivalent concentration in humans, and dividing the equivalent concentration by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). The LOAEL for effects on the nasal epithelium was 30 ppm (Coate 1979a). Nasal lesions also occurred in rats (Breslin et al. 1989) and mice (Coate 1979a) exposed to 90 ppm 1,3-dichloropropene for intermediate durations. No effects in other organs and tissues were observed in rats and mice exposed to 1,3-dichloropropene at 190 ppm (Breslin et al. 1989; Coate 1979a; Linnett et al. 1988) or in dogs exposed to 3 ppm (Torkelson and Oyen 1977) for intermediate durations. Based on a NOAEL of 5 ppm for nasal epithelial hyperplasia of mice (Lomax et al. 1989), a chronic-duration inhalation MRL of 0.002 ppm was calculated by adjusting the NOAEL for intermittent exposure, converting the adjusted NOAEL to an equivalent concentration in humans, and dividing the equivalent concentration by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). The LOAEL for nasal epithelial changes was 20 ppm (Lomax et al. 1989). Rats exposed chronically to 60 ppm 1,3-dichloropropene had nasal epithelial degeneration (Lomax et al. 1989). Other than hyperplasia and hyperkeratosis of the forestomach in mice exposed to 60 ppm, no other effects were noted in rats or mice chronically exposed to 1,3-dichloropropene by inhalation.

An acute oral MRL was not derived because the available NOAEL and LOAEL values for systemic and neurological effects are higher than or too close to LD₅₀ values. An intermediate-duration oral MRL was not derived because the available studies did not identify target organs or systems for this duration category. A chronic-duration oral MRL was not derived because hydronephrosis, a serious effect, was observed at the same dose level (50 mg/kg/day) that was a NOAEL value for all other systemic effects, except forestomach hyperplasia. The LOAEL for forestomach hyperplasia (25 mg/kg/day) was lower than the serious LOAEL for nephrosis, but forestomach hyperplasia is not an appropriate end point for the MRL because it represents a preneoplastic lesion. Both the rats and the mice developed forestomach papilloma and carcinoma at comparable doses in this study (NTP 1985).

Acute-, intermediate-, and chronic-duration dermal MRLs were not derived for 1,3-dichloropropene due to the lack of an appropriate methodology for the development of dermal MRLs.

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Death. No deaths in humans have been reported after inhalation, oral, or dermal exposure to 1,3-dichloropropene. Several animal studies, however, have reported death as an end point after exposure by all routes. Available LC₅₀ values for animals after inhalation exposure range from 253 ppm for Telone C-17® to 904 ppm for Telone II®a (Cracknell et al. 1983; Streeter and Lomax 1988; Streeter et al. 1987). Human exposures to such high concentrations are not likely near hazardous waste sites, but may occur accidentally or through faulty equipment during its application in agriculture. Seven of 10 human subjects could detect 1 ppm Telone II® and described the odor as noticeably fainter than 3 ppm (Torkelson and Oyen 1977). Therefore, evacuation from an area that contained 1,3-dichloropropenecontaminated air would be possible before exposure caused harm.

Workers who were involved in the agricultural application of 1,3-dichloropropene were exposed to concentrations under 1 ppm (Albrecht 1987; Maddy et al. 1980, 1982a; Osterloh et al. 1984). Therefore, exposure to 1,3-dichloropropene at concentrations that could cause death in humans is not likely in an occupational setting. Furthermore, because 1,3-dichloropropene is rapidly cleared from the body after inhalation exposure (Fisher and Kilgore 1989), it would not be expected to accumulate in the body after repeated exposure to low concentrations.

Systemic Effects

Respiratory Effects. Inhalation exposure to 1,3-dichloropropene causes marked respiratory effects in humans and animals. Humans exposed to 1,3-dichloropropene after a tank truck spill complained of mucous membrane irritation, chest pain, and cough (Flessel et al. 1978). Rats exposed to 1,3-dichloropropene had lung congestion, tracheal congestion, and fluid in the thoracic cavity (Cracknell et al. 1987). Atelectasis, emphysema, and/or pulmonary edema, and lung hemorrhage have been observed in rats exposed to 1,3-dichloropropene vapors (Streeter and Lomax 1988; Streeter et al. 1987). The most consistent pathological finding after inhalation exposure in animals was hyperplasia and/or degeneration of the nasal epithelium (Breslin et al. 1989; Lomax et al. 1989; Stott et al. 1988). Severe respiratory effects would not be expected in humans exposed occupationally to 1,3-dichloropropene, because measured exposure levels are lower than those that produced respiratory effects in animals. Occupational accidents, however, may result in harmful exposure levels. Near hazardous waste sites, humans would be aware of 1,3-dichloropropene-contaminated air because of the chemical's odor; measures to prevent respiratory effects could then be taken.

Oral exposure to 1,3-dichloropropene caused an increased incidence of bronchioalveolar adenomas in mice (NTP 1985). Similar neoplasms were not found in rats under the same exposure protocol. Reasons for the species difference are not clear, although it may have resulted from aspiration of 1,3-dichloropropene in the mice after gavage administration. Oral exposure of

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rats has also resulted in lung hemorrhage at doses that were fatal. Oral exposure to 1,3-dichloropropene in an occupational setting is not likely. Nevertheless, 1,3-dichloropropene has been found in human mother's milk (Pellizzari et al. 1982), in drinking water supplies located where 1,3-dichloropropene has been in use (Yang 1986), and in municipal water supplies, indicating that oral exposure can occur from environmental contamination with 1,3-dichloropropene (Dowty et al. 1975a, 1975b). The levels detected from these sources, however, were far lower than those that produced neoplasms in mice.

Rats that received a single dermal application of 1,3-dichloropropene (500 or 800 mg/kg) developed lung congestion (500 mg/kg) and lung hemorrhage (800 mg/kg) (Jones and Collier 1986b). Whether these respiratory effects were a direct effect of 1,3-dichloropropene was not clear. Dermal exposure in humans is a likely route of exposure, particularly during field application or during cleanup of an accidental spill. Although no studies were located regarding respiratory effects in humans after dermal exposure, it is possible that adverse respiratory effects could occur.

Gastrointestinal Effects. Humans exposed to 1,3-dichloropropene after a tank truck spill complained of nausea and vomiting (Flessel et al. 1978), which indicates that gastrointestinal effects are possible. Mice exposed to 60 ppm Telone 11% for 2 years by inhalation developed hyperplasia and hyperkeratosis of the forestomach (Lomax et al. 1989). These gastrointestinal effects were not observed in rats under the same exposure protocol, nor were they observed in mice examined after 6 or 12 months of exposure. Gastrointestinal effects were not observed in other studies of inhalation exposure. Whether gastrointestinal effects would occur in humans after inhalation exposure to 1,3-dichloropropene during field application or at hazardous waste sites cannot be determined on the basis of the available data.

Although no studies were located regarding gastrointestinal effects in humans after oral exposure to 1,3-dichloropropene, animal studies indicate that humans who reside near hazardous waste sites or are occupationally exposed to 1,3-dichloropropene could suffer gastrointestinal effects if oral exposure were to occur. Chronic oral exposure of rats and mice to 1,3-dichloropropene produced neoplastic and preneoplastic lesions of the stomach (NTP 1985). An increased incidence of forestomach squamous cell papillomas and carcinomas was observed in rats and mice after 2 years of gavage administration of 1,3-dichloropropene. These lesions were accompanied by an increased incidence of forestomach basal cell or epithelial cell hyperplasia.

Dermal exposure of rats to 1,3-dichloropropene caused stomach hemorrhage and intestinal congestion and hemorrhage (Jones 1988b; Jones and Collier 1986b). Whether these effects were directly related to 1,3-dichloropropene exposure was not discussed. Thus, the risk of gastrointestinal effects

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following dermal exposure in humans who reside near hazardous waste sites or are occupationally exposed cannot be determined.

Hematological Effects. Limited human data suggest that hematological malignancies may be associated with 1,3-dichloropropene exposure but other hematological effects have not been reported. No hematological effects have been observed in numerous animal studies by inhalation or oral exposure (see Section 2.2), even in studies that included extensive hematological analysis. The available data indicate that nonneoplastic hematological effects are probably not associated with 1,3-dichloropropene exposure.

Musculoskeletal Effects. Musculoskeletal effects after 1,3-dichloropropene exposure have not been reported in humans. A single study described skeletal muscle hemorrhage after dermal application of large amounts of 1,3-dichloropropene in rabbits (Mizell et al. 1988). It is possible that dermal exposure to large amounts of 1,3-dichloropropene could have similar effects in humans.

Hepatic Effects. Hepatic effects in humans after 1,3-dichloropropene exposure have not been reported. Rats and mice did not develop hepatic lesions attributable to 1,3-dichloropropene after 24 months or less of inhalation exposure (Coate 1979b; Lomax et al. 1989; Parker et al. 1982; Stott et al. 1988). The only nonneoplastic hepatic effects reported in animals were mottled dark livers in rats after acute oral or dermal exposure (Jones 1988b; Jones and Collier 1986a) and increased liver weight in rats after exposure for 13 weeks (Til et al. 1973). On the basis of these animal data, it is possible that minimal adverse hepatic effects could occur in humans orally exposed to 1,3-dichloropropene that had leached into drinking water in agricultural areas or near hazardous waste sites. It is less likely that hepatic effects would be associated with inhalation exposure.

Renal Effects. No data are available regarding the renal effects of 1,3-dichloropropene exposure by any route in humans. Gross and histopathological evaluation of rats and mice exposed to 1,3-dichloropropene by inhalation for up to 2 years revealed no kidney lesions attributable to the chemical (Coate 1979b; Lomax et al. 1989; Parker et al. 1982; Stott et al. 1988). Urinary bladder hyperplasia, however, was a consistent finding in mice exposed to 1,3-dichloropropene by inhalation for up to 2 years (Lomax et al. 1989; Stott et al. 1988). Oral administration of 1,3-dichloropropene to mice also caused urinary bladder hyperplasia (NTP 1985). Similar lesions were not observed in rats under the same protocol. These data indicate that urinary tract effects may occur in humans after inhalation or oral exposure to 1,3-dichloropropene.

Dermal/Ocular Effects. Dermal application of 1,3-dichloropropene consistently produces erythema and edema in rats, rabbits, and guinea pigs (Carreon and Wall 1983; Jeffrey 1987c; Jones and Collier 1986b; Lichy and Olson 1975; Mizell 1988a). Higher concentrations can also produce necrosis

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and subcutaneous or skeletal muscle hemorrhage (Jones and Collier 1986; Mizell 1988a; Mizell et al. 1988). Such effects would also be expected to occur by the dermal route in humans.

Serious ocular effects have been observed in rabbits that had 1,3-dichloropropene instilled into the conjunctival sac. These effects include conjunctival irritation, corneal irritation, and corneal opacity (Jeffrey 1987b; Lichy and Olson 1975). Inhalation exposure may also result in eye irritation. Clinical signs noted in rabbits and rats exposed to 1,3-dichloropropene by inhalation included palpebral closure and lacrimation (Jeffrey et al. 1987; Jones and Collier 1986; Mizell et al. 1988). Therefore, humans who reside near hazardous waste sites or are occupationally exposed to 1,3-dichloropropene could suffer eye and/or skin irritation.

Immunological Effects. A delayed-type hypersensitivity to 1,3-dichloropropene has been described in humans (Van Joost and de Jong 1988). Delayed-type hypersensitivity or contact sensitization has also been demonstrated in guinea pigs (Carreon and Wall 1983; Jeffrey 1987a; Jones 1988c; Mizell et al. 1988b). These data also indicate that immunological effects may result from dermal exposure to 1,3-dichloropropene.

Neurological Effects. No neurological effects were observed in humans exposed to 1,3-dichloropropene at levels that were high enough to require medical attention (Markovitz and Crosby 1984). Nausea and vomiting, however, were clinical signs noted in humans exposed to 1,3-dichloropropene after a tank truck spill (Flessel et al. 1978). These symptoms may indicate neurological effects. Ataxia of the hindlimbs and loss of the righting reflex were observed in pregnant rabbits exposed by inhalation to 300 ppm 1,3-dichloropropene during gestation days 6-18 (Kloes et al. 1983). No neurological signs were noted in rabbits exposed to 50 or 150 ppm Telone 1I@a in the same study. Dermal application of 1,300 mg/kg Telone II@a caused ataxia and loss of the righting reflex in rats (Jones and Collier 1986b). For humans who are exposed occupationally or are near hazardous waste sites, these data indicate that neurological effects may accompany 1,3-dichloropropene exposure.

Developmental Effects. No data were located regarding developmental effects in humans following exposure to 1,3-dichloropropene by any route. Animal studies indicate that inhalation exposure to 1,3-dichloropropene is not fetotoxic or teratogenic in rats or rabbits (Breslin et al. 1989; Hanley et al. 1987). No adverse developmental effects were observed in rats exposed to Telone 11% for two generations (Breslin et al. 1989). These data indicate that developmental effects would probably not occur in humans exposed to 1,3-dichloropropene.

Reproductive Effects. No data were located regarding reproductive effects in humans after exposure to 1,3-dichloropropene by any route. No

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reproductive effects were observed in rats exposed by inhalation to 1,3-dichloropropene for two generations. Male and female rats evaluated for libido, fertility, and estrus cycling were not adversely affected by inhalation exposure to 1,3-dichloropropene (Linnett et al. 1988). Gross and histologic examination of reproductive tissues and organs revealed no lesions attributable to 1,3-dichloropropene exposure by inhalation or gavage in rats or mice (Breslin et al. 1989; Hanley et al. 1987; Linnett et al. 1988; NTP 1985; Parker et al. 1982; Stott et al. 1988;). These data indicate that reproductive effects would probably not result from 1,3-dichloropropene exposure in humans. Based on oral exposure studies with rats, however, 1,3-dichloropropene or its metabolites are distributed to reproductive tissues including the ovaries and testes (Waechter and Kastl 1988).

Genotoxic Effects. No studies were located regarding genotoxic effects in humans or animals after inhalation, oral, or dermal exposure to 1,3-dichloropropene. In a *Drosophila melanogaster* feeding study, however, 1,3-dichloropropene produced sex-linked recessive lethal mutations (Valencia et al. 1987). Genotoxicity studies of 1,3-dichloropropene in vitro test systems are described in Table 2-4.

Several groups have reported that 1,3-dichloropropene is mutagenic in vitro with and without metabolic activation in *Salmonella typhimurium* (Creedy et al. 1984; De Lorenzo et al. 1977; Eder et al. 1982a, 1982b; Haworth et al. 1983; Neudecker and Henschler 1986; Neudecker et al. 1977; Stolzenberg and Hine 1980; Vithayathil et al. 1983). 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 the mutagenic activity (Talcott and King 1984). An independent group confirmed these observations and also found that the impurities alone were mutagenic (Watson et al. 1987).

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

These data indicate that exposure of humans to formulations of 1,3-dichloropropene may result in genotoxic effects.

Cancer. Evidence for the carcinogenicity of 1,3-dichloropropene in humans is very limited. Clinical reports describing the development of neoplasms in three men following inhalation (and possibly dermal) exposure suggest, however, that 1,3-dichloropropene might cause cancer in humans. Two of the men were exposed to 1,3-dichloropropene during the cleanup of a tank truck spill. Six years later, both men simultaneously developed and succumbed to histiocytic lymphoma that was refractory to treatment (Markovitz and Crosby

TABLE 2-4. Genotoxicity of 1,3-Dichloropropene In Vitro

Species (test system)	End point	Results		Reference	Isomer/ formulation
		With activation	Without activation		
Prokaryotic organisms:					
<u>Salmonella typhimurium</u> (TA100)	Reverse mutation	+	+	Creedy et al. 1984	cis, trans
<u>S. typhimurium</u> (TA1978)	Reverse mutation	+	-	DeLorenzo et al. 1977	Telone DD ^o
<u>S. typhimurium</u> (TA1535)	Reverse mutation	+	+	DeLorenzo et al. 1977	Telone DD ^o
<u>S. typhimurium</u> (TA100)	Reverse mutation	+	+	DeLorenzo et al. 1977	Telone DD ^o
<u>S. typhimurium</u> (TA1537)	Reverse mutation	-	-	DeLorenzo et al. 1977	Telone DD ^o
<u>S. typhimurium</u> (TA98)	Reverse mutation	-	-	DeLorenzo et al. 1977	Telone DD ^o
<u>S. typhimurium</u> (TA1535)	Reverse mutation	+	+	DeLorenzo et al. 1977	cis, trans
<u>S. typhimurium</u> (TA1978)	Reverse mutation	+	+	DeLorenzo et al. 1977	cis, trans
<u>S. typhimurium</u> (TA100)	Reverse mutation	+	+	DeLorenzo et al. 1977	cis, trans
<u>S. typhimurium</u> (TA100)	Reverse mutation	+	+	Eder et al. 1982a	cis, trans
<u>S. typhimurium</u> (TA100)	Reverse mutation	+	+	Eder et al. 1982b	cis, trans
<u>S. typhimurium</u> (TA100)	Reverse mutation	+	+	Haworth et al. 1983	cis, trans
<u>S. typhimurium</u> (TA1535)	Reverse mutation	+	+	Haworth et al. 1983	cis, trans
<u>S. typhimurium</u> (TA1537)	Reverse mutation	+	+	Haworth et al. 1983	cis, trans
<u>S. typhimurium</u> (TA98)	Reverse mutation	+	+	Haworth et al. 1983	cis, trans
<u>S. typhimurium</u> (TA1535)	Reverse mutation	+	+	Neudecker et al. 1977	cis, trans
<u>S. typhimurium</u> (TA1537)	Reverse mutation	+	+	Neudecker et al. 1977	cis, trans
<u>S. typhimurium</u> (TA1538)	Reverse mutation	+	+	Neudecker et al. 1977	cis, trans
<u>S. typhimurium</u> (TA100)	Reverse mutation	+	+	Neudecker et al. 1980	cis, trans
<u>S. typhimurium</u> (TA100)	Reverse mutation	+	+	Neudecker and Henschler 1986	cis, trans
<u>S. typhimurium</u> (TA100)	Reverse mutation	+	+	Stolzenberg and Hine 1980	cis, trans
<u>S. typhimurium</u> (TA100)	Reverse mutation	No data	-	Talcott and King 1984	Not pure ^a
	Reverse mutation	No data	-	Talcott and King 1984	Purified ^a
	Reverse mutation	No data	+	Talcott and King 1984	Not pure ^b
	Reverse mutation	No data	-	Talcott and King 1984	Purified ^b
	Reverse mutation	No data	+	Talcott and King 1984	Not pure ^c
	Reverse mutation	No data	-	Talcott and King 1984	Purified ^c
	Reverse mutation	No data	+	Talcott and King 1984	Not pure ^d
	Reverse mutation	No data	-	Talcott and King 1984	Purified ^d
	Reverse mutation	No data	+	Talcott and King 1984	cis + trans ^e
<u>S. typhimurium</u> (TA98)	Reverse mutation	No data	+	Vithayathil et al. 1983	cis, trans
<u>S. typhimurium</u> (TA98)	Rifampicin resistance	No data	+	Vithayathil et al. 1983	cis, trans
<u>Escherichia coli</u> (PQ37)	DNA damage	No data	+	Von der Hude et al. 1988	cis, trans
<u>S. typhimurium</u> (TA100)	Reverse mutation	+	+	Watson et al. 1987	Not pure ^f
	Reverse mutation	-	-	Watson et al. 1987	Purified ^f
	Reverse mutation	+	+	Watson et al. 1987	Impurities ^g

TABLE 2-4 (Continued)

Species (test system)	End point	Results		Reference	Isomer/ formulation
		With activation	Without activation		
Eukaryotic organisms:					
HeLa cells	Unscheduled DNA synthesis	No data	+	Eder et al. 1987	cis, trans
HeLa cells	Unscheduled DNA synthesis	No data	+	Schiffman et al. 1983	cis, trans
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Loveday et al. 1989	Telone II ^b
Chinese hamster ovary cells	Chromosomal aberrations	-	-	Loveday et al. 1989	Telone II ^b
Chinese hamster V79 cells	Sister chromatid exchange	-	+	von der Hude et al. 1987	cis, trans
Chinese hamster lung cells	Mitotic aberrations	+	+	Sasaki et al. 1988	cis + trans

^acis and trans 1,3-Dichloropropene supplied by K&K Laboratories

^bcis and trans 1,3-Dichloropropene supplied by Pfaltz and Bauer, Inc.

^cLow-boiling 1,3-Dichloropropene supplied by K&K Laboratories

^dHigh-boiling 1,3-Dichloropropene supplied by K&K Laboratories

^ePfaltz and Bauer 1,3-dichloropropene was purified; impurities were then added back (refluxed) for the mutagenicity assay.

^fcis-1,3-Dichloropropene

^gImpurities from purified cis-1,3-dichloropropene

+ = positive response; - = negative response

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1984). The same report described a farmer who developed acute myelomonocytic leukemia after being exposed to 1,3-dichloropropene while applying the chemical to his fields. This leukemia was also refractory to treatment, and the man died approximately 1 year later.

Evidence for carcinogenicity in animals is available. Rats that received 1,3-dichloropropene (Telone II®) by gavage developed an increased incidence of forestomach squamous cell papillomas and carcinomas, liver neoplastic nodules, thyroid adenomas and carcinomas, and adrenal gland pheochromocytomas (NTP 1985). The increase in stomach neoplasms was accompanied by an increase in forestomach basal cell hyperplasia. Similarly, mice that received 1,3-dichloropropene (Telone II®) by gavage developed an increased incidence of forestomach squamous cell papillomas and carcinomas (NTP 1985). Mice also developed an increased incidence of urinary bladder transitional cell carcinomas and lung adenomas and carcinomas. These neoplastic changes were accompanied by an increase in forestomach epithelial cell hyperplasia and urinary bladder hyperplasia. How much the epichlorohydrin component (1%) of Telone II® contributes to the development of papillomas and carcinomas of the forestomach is not known. Although oral administration of epichlorohydrin has produced papillomas and carcinomas of the forestomach in male mice (NTP 1989), it is doubtful that Telone II® contained enough epichlorohydrin for the tumor response to be due solely to epichlorohydrin.

Two-year inhalation exposure to 1,3-dichloropropene also produced neoplastic changes in mice but not rats (Lomax et al. 1989). A statistically significant, dose-related increase in bronchioalveolar adenomas was observed in the high dose males. Hyperplastic changes were also observed, including respiratory epithelium hyperplasia, urinary bladder hyperplasia, and hyperplasia and hyperkeratosis of the forestomach in male and female mice. Similar hyperplastic changes were not observed in rats under the same exposure protocol (Lomax et al. 1989). In contrast, other studies conducted over shorter exposure periods found significant increases in nasal epithelial hyperplasia in rats or mice (Breslin et al. 1989; Lomax et al. 1989; Stott et al. 1988). Whether these hyperplastic changes were preneoplastic is not clear, because nasal neoplasms were not found in rats or mice after longer exposure periods (Lomax et al. 1989).

In contrast to the inhalation and oral studies, 1,3-dichloropropene did not initiate or promote tumor formation in mice after dermal application for 58 or 74 weeks, respectively. Subcutaneous injection of 1,3-dichloropropene did, however, cause sarcomas at the injection site in mice (Van Duuren et al. 1979).

The animal data, along with suggestive data in humans, indicate that 1,3-dichloropropene is reasonably anticipated to cause cancer in humans.

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2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism, (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1,3-dichloropropene are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,3-dichloropropene are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

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2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to 1,3-Dichloropropene

Inhalation exposure to various concentrations of 1,3-dichloropropene correlated well with the urinary level of the N-acetyl cysteine (mercapturic acid) metabolite in humans. Urinary excretion of the N-acetyl cysteine metabolite was measured in four men occupationally exposed to technical-grade 1,3-dichloropropene (Telone ITea). Exposure levels were monitored by personal dosimeters. A strong correlation was found between exposure levels of 1,3-dichloropropene and urinary excretion of the N-acetyl-cysteine metabolite ($r=0.83$, see Figure 2-3 in Section 2.3.3) (Osterloh et al. 1984).

Blood levels of the glutathione-conjugate of 1,3-dichloropropene might also be used as a biomarker. Steady-state levels of the glutathione-conjugate were reached within 15 minutes in rats exposed to 78, 155, or 404 ppm (Fisher and Kilgore 1989). In this study, however, the correlation between exposure and blood levels was not calculated.

1,3-Dichloropropene is rapidly cleared from the body. The elimination half-time, determined after a 1-hour inhalation exposure in rats, was 17 hours (Fisher and Kilgore 1989). Furthermore, less than 2% of the 1,3-dichloropropene administered by gavage to rats remained in the carcass after 4 days (Hutson et al. 1971). These data indicate that 1,3-dichloropropene does not concentrate in the body. Therefore, biomarkers based on tissue or blood levels of 1,3-dichloropropene are of limited value in assessing long-term exposure.

2.5.2 Biomarkers Used to Characterize Effects Caused by 1,3-Dichloropropene

No specific quantifiable biomarkers that characterize effects caused by 1,3-dichloropropene were identified. Consistent findings in animal studies include hyperplasia and/or degeneration of portions of the nasal epithelium after inhalation exposure, hyperplasia and/or neoplastic changes in the forestomach after oral exposure, and erythema/edema after dermal exposure. These are nonspecific effects and are, therefore, of little value as biomarkers.

2.6 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding the interaction of 1,3-dichloropropene with other chemicals to produce health effects. 1,3-Dichloropropene is widely used as a preplanting soil fumigant for the control of parasitic nematodes. The commercial product used in agriculture contains a mixture of the cis and trans isomers in approximately equal proportions, as well as stabilizers including 1,2-dichloropropane and epichlorohydrin or epoxidized soybean oil. Occupational exposure would most likely occur to this mixture. Whether interactions occur between 1,3-dichloropropene and other components is not known.

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2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No data were located regarding populations that are unusually susceptible to the toxicity of 1,3-dichloropropene; however, glutathione availability is critical for detoxification. Depletion of glutathione pools may enhance or decrease the toxicity of 1,3-dichloropropene depending on the target organ (see Section 2.8). Glutathione pools could be depleted by repeated exposures to 1,3-dichloropropene or other xenobiotics that are metabolized in whole or in part by glutathione-dependent pathways. Urinary excretion of the mercapturic acid of 1,3-dichloropropene is the primary excretory pathway; therefore, kidney disease or deficiencies in the mercapturic acid transport system may also enhance the toxicity of 1,3-dichloropropene.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,3-dichloropropene. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 1,3-dichloropropene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice,

Recommendations have been made for managing and treating persons exposed to 1,3-dichloropropene (Bronstein and Currance 1988; Stutz and Janusz 1988). Initially, the exposed persons are removed from the contaminated area, and contaminated clothing is removed and isolated. Exposed skin is decontaminated by immediately washing with copious amounts of soapy water to insure appropriate dilution of the chemical. Contaminated eyes are thoroughly flushed with water. If the victim is in respiratory distress, ventilation assistance is provided, and oxygen administered. If oral exposure occurred recently, the victim is given water or milk to dilute the chemical and activated charcoal to adsorb the chemical. Emetics are not administered (Bronstein and Currance 1988). Please refer to Bronstein and Currance (1988) and Stutz and Janusz (1988) for more complete information on treatment of specific symptoms.

No specific information was located regarding the mitigation of effects of 1,3-dichloropropene once it has entered the bloodstream. The major effects of inhalation exposure to 1,3-dichloropropene are irritation and degenerative effects on the nasal and respiratory epithelium, and hyperplasia of the urinary bladder. The major effects of oral exposure are stomach irritation, hyperplasia, and hyperkeratosis, and mild liver and kidney effects. Studies on the metabolism of 1,3-dichloropropene indicate that a major pathway occurs via conjugation of 1,3-dichloropropene with glutathione resulting in the excretion of mercapturic acids and N-acetyl-cysteine conjugates (see Section 2.3.3). Inhalation exposure of rats to 1,3-dichloropropene resulted in

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decreased levels of glutathione in the nasal tissue, kidney, and liver (Fisher and Kilgore 1988a). Oral exposure of mice to 1,3-dichloropropene resulted in decreased levels of glutathione in the forestomach, glandular stomach, liver, and kidney (Dietz et al. 1982). The decrease in glutathione levels in these tissues indicates that conjugation can occur in these tissues. If conjugation with glutathione represents a detoxification mechanism, it would seem likely that the nasal tissue and stomach damage occurs prior to conjugation. However, if 1,3-dichloropropene were detoxified in the kidney by conjugation with glutathione, it is difficult to explain the observed effects on the urinary bladder. One possible explanation is that glutathione conjugation in the kidney becomes saturated, allowing parent 1,3-dichloropropene to exert an effect. It is also possible that conjugation with glutathione could act as a toxifying mechanism. If this were the case for 1,3-dichloropropene, agents that deplete glutathione could protect against harmful effects of 1,3-dichloropropene. These agents, however, would have to be administered very soon after exposure occurred.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA as amended directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,3-dichloropropene is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,3-dichloropropene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of 1,3-Dichloropropene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,3-dichloropropene are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,3-dichloropropene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

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FIGURE 2-5. Existing Information on Health Effects of 1,3-Dichloropropene

	Death	SYSTEMIC			Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
		Acute	Intermed.	Chronic						
Inhalation		●								●
Oral										
Dermal		●		●						

HUMAN

	Death	SYSTEMIC			Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
		Acute	Intermed.	Chronic						
Inhalation	●	●	●	●		●	●	●		●
Oral	●	●	●	●		●				●
Dermal	●	●			●	●				●

ANIMAL

● Existing Studies

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Existing information regarding the health effects of 1,3-dichloropropene in humans is limited (Figure 2-5). No information was located regarding death in humans after inhalation, oral, or dermal exposure. Acute systemic effects were reported after inhalation and possible dermal exposure to 1,3-dichloropropene. No information was located regarding systemic effects in humans after intermediate or chronic duration exposures by any route. A case of delayed-type hypersensitivity after dermal exposure indicates that 1,3-dichloropropene may have immunologic effects. A clinical report that discussed a possible role for 1,3-dichloropropene in chemical carcinogenesis was located. No studies were located regarding neurological, developmental, reproductive, or genotoxic effects in humans after exposure to 1,3-dichloropropene by any route.

LC₅₀, and LD₅₀ values for 1,3-dichloropropene have been determined in rats for inhalation exposure and oral exposure, and in rats and rabbits after dermal exposure. Systemic effects of 1,3-dichloropropene in animals have been described for all routes of exposure. Development of delayed-type hypersensitivity after dermal exposure indicates that 1,3-dichloropropene has immunologic effects. Neurological effects have been observed in animals after inhalation or dermal exposure. Developmental toxicity has been assessed in pregnant rats and rabbits after inhalation exposure. Reproductive toxicity has been assessed through comprehensive histological examinations of reproductive organs and tissues and in two-generation inhalation studies. The carcinogenicity of 1,3-dichloropropene has been assessed after exposure by all routes (Lomax et al. 1989; NTP 1985; Van Duuren et al. 1979).

2.9.2 Data Needs

Information regarding the health effects of exposure to pure 1,3-dichloropropene is very limited. Virtually all toxicological studies to date have tested various commercial formulations of 1,3-dichloropropene. Many of the components of these commercial formulations alone produce serious adverse health effects; therefore, future research efforts to assess the toxicity of 1,3-dichloropropene should include assessment of the pure chemical.

Acute-Duration Exposure. Data regarding human exposures to 1,3-dichloropropene are limited to clinical reports describing isolated cases of non-Hodgkin's (histiocytic) lymphoma and acute myelomonocytic leukemia after inhalation exposure (Markovitz and Crosby 1984), delayed-type hypersensitivity after dermal exposure (Van Joost and de Jong 1988), and nonspecific clinical signs such as headache, nausea, vomiting, fatigue, impotence, and malaise after inhalation (and possibly dermal) exposure. Respiratory symptoms such as chest discomfort, breathing difficulty, coughing, and mucous membrane irritation (Flessel et al. 1978; Markovitz and Crosby 1984) indicate that the respiratory system is a target in humans. Animal studies of acute-duration exposure describe nonspecific clinical signs

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including lethargy, labored breathing, salivation, lacrimation, palpebral closure, and diarrhea. The primary target organ in animals after acute inhalation is also the respiratory tract. Lung hemorrhage and congestion, atelectasis, emphysema, pulmonary edema, and tracheal congestion have been observed (Cracknell et al. 1987; Streeter and Lomax 1988; Streeter et al. 1987). The available NOEL and LOEL values for respiratory effects (the end point on which intermediate- and chronic-duration MELs are based) and for neurological and developmental effects are higher than or too close to acute inhalation LC₅₀ values, precluding the derivation of an MRL for acute inhalation exposure.

Information regarding the effects in humans of acute oral exposure to 1,3-dichloropropene is lacking. Acute oral studies in rats have identified the stomach, lungs, and possibly the liver and kidney as targets (Jones 1988a; Jones and Collier 1986a; Mizell et al. 1988a). An acute oral MRL was not derived because the available NOEL and LOEL values for systemic and neurological effects are higher than or too close to LD₅₀ values.

Dermal exposure of humans to 1,3-dichloropropene has produced delayed type hypersensitivity (Van Joost and de Jong 1988). Delayed-type hypersensitivity to 1,3-dichloropropene has also been observed in animals (Carreon and Wal 1983; Jeffrey 1987c; Mizell 1988b). Animal studies have shown that 1,3-dichloropropene causes erythema/edema, necrosis, exfoliation, and subcutaneous hemorrhage when applied dermally (Carreon and Wall 1983; Jeffrey 1987c; Jones and Collier 1986b; Lichy and Olson 1975; Mizell et al. 1988a, 1988b). Data regarding systemic toxicity in animals are limited. Hemorrhage of the lungs and glandular stomach was reported in a few studies (Jones 1988b; Jones and Collier 1986b).

Information on the distribution of 1,3-dichloropropene following oral, inhalation, and dermal exposure is not available to help identify other target organs across routes of exposure. Intermediate and chronic duration studies in rats and mice, which included extensive histological examinations, have identified targets of inhalation and oral exposure. Additional acute studies by all routes should focus on histological examinations of major organs and tissues including the lungs, liver, kidneys, stomach, and urinary bladder, as well as the determination of threshold doses. This information is important because populations near hazardous waste sites might be exposed to 1,3-dichloropropene for brief periods.

Intermediate-Duration Exposure. Data are not available that identify target organs in humans after intermediate-duration exposure to 1,3-dichloropropene by any route.

Animal studies indicate that the primary target organs of 1,3-dichloropropene toxicity after intermediate-duration inhalation exposure are the respiratory tract and lungs, kidneys, and urinary bladder (Breslin et

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al. 1989; Coate 1979a; Lomax et al. 1989; Stott et al. 1988). Nasal hyperplasia, bronchioalveolar adenomas, cloudy swelling of the kidneys, hydronephrosis, and urinary bladder hyperplasia have been observed. These observations have been made after extensive gross and histopathological examination. An intermediate inhalation MRL based on respiratory effects in rats has been calculated, An intermediate-duration oral MRL was not derived because the available studies did not identify target organs or systems for this duration category.

No information on target organs other than the skin (Jeffrey 1987a) was located for intermediate duration dermal exposure. No distribution data following inhalation, oral, or dermal exposure were located to help identify target organs of dermal exposure. An intermediate-duration dermal study in animals that examined organs other than skin should help identify the possible effects of dermal exposure to internal tissues. Because 1,3-dichloropropene is a component of a soil fumigant, contact with soil is one way that dermal exposure of humans could occur. Furthermore, 1,3-dichloropropene may be present in the soil at hazardous waste sites, where residents may be exposed for intermediate durations.

Chronic-Duration Exposure and Cancer. There is no information in humans to identify target organs following chronic exposure by inhalation, oral, or dermal routes.

The chronic toxicity of 1,3-dichloropropene has been assessed in two animal studies: a 2-year inhalation exposure of rats and mice (Lomax et al. 1989), and a 2-year gavage study also ,in rats and mice (NTP 1985). Hyperplasia of the nasal epithelium was the only nonneoplastic toxic effect observed in rats after inhalation exposure. In contrast, mice suffered nasal epithelial hyperplasia, degeneration of the olfactory neuroepithelium, an increased incidence of bronchioalveolar adenomas, and hyperplasia and hyperkeratosis of the forestomach. Nonneoplastic and preneoplastic lesions observed in rats after a 2-year gavage study included hyperkeratosis and basal cell hyperplasia of the forestomach and pancreatic periarteritis. In mice following gavage exposure, the nonneoplastic and preneoplastic lesions included forestomach epithelial cell hyperplasia, kidney hydronephrosis, and urinary bladder hyperplasia. The data from these two studies, which included comprehensive histological examinations, are sufficient to identify the respiratory tract as the primary target organ of chronic toxicity after inhalation exposure, and the forestomach, kidney, and urinary bladder after oral exposure. Furthermore, these data are sufficient to derive a chronic inhalation MRL based on respiratory effects in mice. The data available for chronic oral exposure are not appropriate for derivation of a chronic oral MRL, because hydronephrosis, a serious effect, was observed at the same dose level that was a NOAEL value for all other systemic effects, except forestomach hyperplasia. The LOAEL for forestomach hyperplasia was lower than the serious LOAEL for nephrosis, but forestomach hyperplasia is not an

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appropriate end point for the MRL because it represents a preneoplastic lesion. Both the rats and the mice developed forestomach papilloma and carcinoma at comparable doses in this study (NTP 1985). Neither studies regarding effects of chronic-duration dermal exposure nor distribution data to identify possible targets of exposure to 1,3-dichloropropene by this route of exposure were located.

Chronic-duration dermal exposure of humans who reside near a hazardous waste site or are occupationally exposed is likely. Therefore, a chronic-duration study in animals may be warranted.

A clinical report describing three men who developed lymphoma or leukemia (Markovitz and Crosby 1984) suggests a carcinogenic potential for 1,3-dichloropropene in humans. The carcinogenicity of 1,3-dichloropropene was assessed in a 2-year inhalation study of rats and mice (Lomex et al. 1989) and a 2-year NTP gavage study also in rats and mice (NTP 1985). An increased incidence of bronchioalveolar adenomas (benign lung tumors) was observed in mice after inhalation exposure for 2 years. No other neoplasms attributable to 1,3-dichloropropene were observed in this study. In contrast, both rats and mice developed neoplasms in the 2-year gavage study. An increased incidence of forestomach squamous cell papillomas and carcinomas was noted in both species. Male rats also developed an increased incidence of liver neoplastic nodules. Mice also developed transitional cell carcinoma of the urinary bladder and bronchioalveolar adenomas. The difference in carcinogenicity observed in the two studies may be related to the stabilizer present in the technical-grade 1,3-dichloropropene tested. The oral study used a compound containing epichlorohydrin as a stabilizer. Epichlorohydrin reportedly causes nasal and forestomach tumors in rats following chronic inhalation and oral exposure, respectively. The inhalation study tested a 1,3-dichloropropene compound containing a less toxic epoxidized soybean oil as a stabilizer. It may be of value to repeat the 2-year inhalation study with Telone II® to evaluate the potential for carcinogenicity because the results in mice were equivocal. A carcinogenicity study by the oral route using a formulation without epichlorohydrin would help determine if the carcinogenicity observed in rats and mice treated with the formulation containing epichlorohydrin was due to 1,3-dichloropropene or the stabilizer.

An initiation-promotion study of cis-1,3-dichloropropene by dermal exposure in mice indicated that cis-1,3-dichloropropene was not an initiator of skin tumors (Van Duuren et al. 1979). Furthermore, cis-1,3-dichloropropene alone did not induce skin tumors after repeated dermal application for 74 weeks. No studies were located regarding the carcinogenic mechanism of action of 1,3-dichloropropene. Available data indicate, however, that 1,3-dichloropropene is mutagenic in prokaryotic and eukaryotic test systems and that it is a strong tissue irritant. Both properties may underlie the carcinogenic potential of 1,3-dichloropropene.

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Genotoxicity. No data are available regarding the genotoxicity of 1,3-dichloropropene in humans after exposure by any route. In vivo animal studies are also lacking. 1,3-Dichloropropene is mutagenic in prokaryotic (Creedy et al. 1984; De Lorenzo et al. 1977; Eder et al. 1982a, 1982b; Haworth et al. 1983; Neudecker and Henschler 1986; Neudecker et al. 1977; Stolzenberg and Hine 1980; Talcott and King 1984; Vithayathil et al. 1983; Watson et al. 1987) and eukaryotic (Eder et al. 1987; Loveday et al. 1989; Sasaki et al. 1988; Schiffman et al. 1983; von der Hude et al. 1987) systems, which indicates that the chemical may be mutagenic in humans. The carcinogenicity of 1,3-dichloropropene also supports the possibility that it would be mutagenic; however, in vitro studies that compared the mutagenicity of purified 1,3-dichloropropene with that available commercially as technical grade 1,3-dichloropropene indicated that purified 1,3-dichloropropene is not mutagenic. In contrast, the impurities removed from the technical-grade 1,3-dichloropropene were highly mutagenic. Additional in vitro studies that focus on the mutagenicity of purified 1,3-dichloropropene versus the technical grade seem warranted at this time. Furthermore, considering the development of hematological malignancies in humans exposed to 1,3-dichloropropene, it may be valuable to conduct in vivo tests for chromosomal aberrations in humans or animals exposed to 1,3-dichloropropene.

Reproductive Toxicity. No information regarding the reproductive toxicity of 1,3-dichloropropene by any route of exposure in humans is available. Pharmacokinetic data in rats indicate that 1,3-dichloropropene or its metabolites are found in low concentrations in reproductive organs and tissues (Waechter and Kastl 1988). However, no effects on reproductive parameters of rats were found in a two-generation inhalation study (Breslin et al. 1989). Furthermore, no lesions attributable to 1,3-dichloropropene were observed after gross and histologic evaluation of reproductive tissues and organs in several animal studies. These studies include a two-generation reproductive/developmental inhalation study (Breslin et al. 1989), a 10-week inhalation reproductive study (Linnett et al. 1988), a 2-year inhalation study (Lomax et al. 1989), and a 2-year oral study (NTP 1985). No studies regarding reproductive effects in animals following dermal exposure were found; however, the results of the inhalation and oral studies indicate no reason to suspect that 1,3-dichloropropene would have reproductive effects by this route. Additional reproductive studies would not be useful at this time.

Developmental Toxicity. Both acute-duration (rats and rabbits) (Kloes et al. 1983) and intermediate-duration inhalation studies (rats) (Breslin et al. 1989) of developmental and reproductive effects have shown that 1,3-dichloropropene is not teratogenic. However, fetotoxicity in the rabbits could not be assessed because significant maternal toxicity at the highest concentration tested (300 ppm) resulted in the death of six of seven rabbits (Kloes et al. 1983). Maternal toxicity in rats, also at 300 ppm, may have resulted in fetotoxicity and the subsequent decrease reported in fetuses per litter. Lower concentrations of 1,3-dichloropropene (150 ppm or less) were

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not fetotoxic in these studies, although an exposure of 120 ppm to pregnant rats resulted in delayed ossification, which may have been due to decreased body weight of the dams. Human exposures to such high concentrations of 1,3-dichloropropene are not likely; therefore, further developmental toxicity studies would not be useful at this time.

Immunotoxicity. One clinical report regarding the development of a delayed-type hypersensitivity after skin contact in a 26-year-old worker occupationally exposed to 1,3-dichloropropene (Van Joost and de Jong 1988) indicates the possibility of immunotoxicity in humans. This report is supported by animal studies that document the development of delayed-type hypersensitivity in guinea pigs (Carreon and Wall 1983; Jeffrey 1987a; Jones 1988c; Mizell 1988b). The development of hematologic malignancies in three men occupationally exposed to 1,3-dichloropropene might also indicate immunotoxicity (Markovitz and Crosby 1984). Since the immune system may be a target of 1,3-dichloropropene toxicity, a battery of immune function tests may be warranted at this time. Even so, no animal studies showed adverse hematological effects, despite exposure by inhalation or gavage for intermediate or chronic duration (Lomax et al. 1989; NTP 1985; Stott et al. 1988; Til et al. 1973; Torkelson and Oyen et al. 1977). Furthermore, gross and histological examination of the lymph nodes and the thymus in several animal studies of inhalation and oral exposure revealed no lesions attributable to 1,3-dichloropropene (Lomax et al. 1989; NTP 1985; Parker et al. 1982; Stott et al. 1988).

Neurotoxicity. No neurotoxicity was observed in humans accidentally exposed to 1,3-dichloropropene at concentrations high enough to require medical attention (Markovitz and Crosby 1984). No studies regarding the neurotoxicity of 1,3-dichloropropene in animals were located. Gross and histological examination of brain, nerves, and the spinal cord from rats and mice after inhalation (Coate 1979a; Lomax et al. 1989; Stott et al. 1988) and oral exposure (NTP 1985) revealed no lesions attributable to 1,3-dichloropropene. Clinical signs that indicate possible neurotoxicity, however, were noted in rabbits after dermal exposure to high concentrations of 1,3-dichloropropene (Jones 1988b), and in rabbits after inhalation exposure to high concentrations of 1,3-dichloropropene (Kloes et al. 1983). These signs included ataxia, loss of the righting reflex, lacrimation, salivation, and lethargy. Further studies of more subtle neurological changes, such as nerve conduction velocity, may be warranted at this time.

Epidemiological and Human Dosimetry Studies. No studies were located regarding the epidemiology of 1,3-dichloropropene exposure. One pharmacokinetic study in humans, however, described a strong correlation between exposure levels during the application of 1,3-dichloropropene on farms and urinary excretion levels of 1,3-dichloropropene metabolites (Osterloh et al. 1984). In light of the possible human carcinogenicity of 1,3-dichloropropene, epidemiological studies of carcinogenicity in, for

2. HEALTH EFFECTS

example, agricultural workers exposed occupationally, would be especially valuable. Additionally, long-term follow-up studies of chronic toxicity and carcinogenicity in people exposed to high concentrations of 1,3-dichloropropene at the site of a spill would be valuable. Chronic toxicity evaluation should focus on the lungs, liver, and kidneys, which are the primary target organs identified in animal studies. Epidemiological studies of chronic toxicity and carcinogenicity in populations residing near hazardous waste sites would also provide important information.

Biomarkers of Exposure and Effect. The only biomarker of exposure identified in the literature is the mercapturic acid metabolite of 1,3-dichloropropene found in the urine of animals exposed by inhalation (Fisher and Kilgore 1988b) and orally (Climie et al. 1979; Hutson et al. 1971) and humans exposed occupationally (Osterloh et al. 1974). In humans, a strong correlation was reported between occupational exposure levels and levels of the urinary metabolite. 1,3-Dichloropropene is rapidly cleared from the body; essentially no radioactivity was found in the carcasses of rats 48-96 hours after dosing with ¹⁴C-labeled 1,3-dichloropropene (Hutson et al. 1971). Because 1,3-dichloropropene does not appear to accumulate in the body, only short-term and possibly intermediate-duration exposures could be assessed using the urinary metabolite as a biomarker. Although no pharmacokinetic studies have investigated chronic exposure, this duration of exposure might not be reliably assessed if some period of time has passed between the last exposure and biomarker analysis. Extensive hematological and clinical chemistry analyses have been performed in animal studies of intermediate and chronic exposure. No adverse effects were observed on either parameter; therefore, attempts to develop biomarkers that use easily obtained biological fluids may not be fruitful. Research to identify a biomarker would facilitate future medical surveillance, which can lead to early detection and treatment.

The effects identified in animal studies include respiratory tract hyperplasia, lung trauma, and an increased incidence of stomach, lung, and urinary bladder neoplasms. Effects noted in humans are nonspecific clinical signs. Thus, no easily evaluated, specific biomarkers used to characterize effects are available. Development of new biomarkers of effect requires a thorough knowledge of the health effects and more subtle physiological or biochemical changes caused by 1,3-dichloropropene.

Absorption, Distribution, Metabolism, and Excretion. 1,3-Dichloropropene is absorbed by all routes of exposure. Absorption by the pulmonary (Stott and Kastle 1986) and gastrointestinal tracts (Climie et al. 1979; Hutson et al. 1971) is extensive, but quantitative information regarding dermal exposure was not located. Information regarding distribution was available only for the oral route. Following exposure of rats by gavage to radiolabeled 1,3-dichloropropene, radioactivity was widely distributed with the highest levels of radioactivity found in the nonglandular stomach and urinary bladder (Waechter and Kastl 1988). Steady-state blood levels of the

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glutathione conjugate of 1,3-dichloropropene were observed within 15 minutes of inhalation exposure in rats, indicating that the chemical is rapidly absorbed and metabolized (Fisher and Kilgore 1989). The glutathione conjugate is then converted to the corresponding mercapturic acid, which is excreted in the urine, the primary route of excretion for both inhalation (Fisher and Kilgore 1989) and oral exposure (Climie et al. 1979; Huston et al. 1971). Significant quantities are also excreted as CO₂ in the expired air, with a much smaller portion excreted in the feces (Hutson et al. 1971). Available data are insufficient to reliably assess the relative rates of absorption, distribution, metabolism, and excretion. Even so, pharmacokinetic data indicate that absorption and excretion are rapid; only 4% of a ¹⁴C-labeled dose was recovered from the carcasses of rats 48 hours after oral administration (Hutson et al. 1971). Absorption and excretion were not linear at high inhalation concentrations (300-900 ppm), indicating a saturable metabolic pathway (Stott and Kastl 1986). Comparison of the metabolism and excretion of 1,3-dichloropropene after single or repeated oral doses showed no differences (Waechter and Kastl 1988).

At this time, investigation of the absorption, distribution, metabolism, and excretion of 1,3-dichloropropene after exposure by all routes and duration categories would provide valuable information. Inhalation and dermal exposures are particularly important occupationally but are also important regarding humans residing near hazardous waste sites.

Comparative Toxicokinetics. In a study of humans occupationally exposed to 1,3-dichloropropene, the major urinary metabolite found was the mercapturic acid conjugate of 1,3-dichloropropene (Osterloh et al. 1984). A significant correlation was observed between exposure levels of 1,3-dichloropropene and excretion of the metabolite. Studies in rats (Climie et al. 1979; Fisher and Kilgore 1989; Hutson et al. 1971; Stott and Kastl 1986) and one study in mice (Dietz et al. 1982) support the identification of the mercapturic acid metabolite as the primary 1,3-dichloropropene metabolite. The excretion data in mice and rats are similar; excretion in urine is the primary route, followed by excretion of CO₂ in the expired air and then by excretion in the feces. It is reasonable to expect that excretion is similar in humans; therefore, rats would provide a good model for further pharmacokinetic and toxicity studies of 1,3-dichloropropene. Additional pharmacokinetic studies should focus on the rates of absorption, distribution, metabolism, and excretion, particularly by the dermal route, after acute, intermediate, and chronic exposures.

Mitigation of Effects. Information on the metabolism of 1,3-dichloropropene in humans (Osterloh et al. 1984) and animals (Dietz et al. 1982; Fisher and Kilgore 1988a) indicates that the major pathway occurs via conjugation with glutathione, which can occur in nasal tissue, the stomach, liver, and kidney. Since these organs and the urinary bladder are target organs of the toxicity of 1,3-dichloropropene, it is not clear whether this

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conjugation represents a detoxifying or a toxifying mechanism. Studies that determine whether the parent 1,3-dichloropropene compound or the conjugated product(s) represent the putative toxicant would be useful in planning research aimed to develop agents that could increase the conjugation (if a detoxifying mechanism) or that would deplete glutathione (if a toxifying mechanism), thereby mitigating the effects.

2.9.3 On-going Studies

No information regarding current studies of the health effects of 1,3-dichloropropene was located.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of cis- and trans-1,3-dichloropropene are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of cis- and trans-1,3-dichloropropene are presented in Table 3-2.

TABLE 3-1. Chemical Identity of the Isomers of 1,3-Dichloropropene

Characteristic	cis-1,3-Dichloropropene	trans-1,3-Dichloropropene	cis- and trans-1,3-Dichloropropene	Reference
Chemical name	cis-1,3-Dichloropropene	trans-1,3-Dichloropropene	1,3-Dichloropropene	Chemline 1989
Synonyms	cis-1,3-Dichloro-1-propene; cis-1,3-dichloropropylene	trans-1,3-Dichloro-1-propene; trans-1,3-dichloropropylene	1,3-Dichloro-1-propene; 1,3-dichloropropylene	Chemline 1989; HSDB 1989
Trade names	No data	No data	Telone [®] ; Telone II [®] (M-3993); Telone C-17 [®] ; DD [®] (Nemafene); DD-92 [®] ; Terr-O-Cide 15-D; Terr-O-Cide 30-D; Terr-O-Gas 57/43T; Vorlex (Trapex, Ditrapex, MENCS, MIC, MITC)	Yang 1986
Chemical formula	C ₃ H ₄ Cl ₂	C ₃ H ₄ Cl ₂	C ₃ H ₄ Cl ₂	Chemline 1989
Chemical structure			Cl-CH ₂ -CH=CH-Cl	
Identification numbers:				
CAS registry	10061-01-5	10061-02-6	542-75-6	Chemline 1989
NIOSH RTECS	UC8325000	UC8320000	UC8310000	SANSS 1989
EPA hazardous waste	No data	No data	No data	
OHM/TADS	8500391	8500392	8500391-2	OHM/TADS 1989
DOT/UN/NA/IMCO shipping	No data	No data	No data	
HSDB	1503	1504	1503-4	HSDB 1989
NCI	No data	No data	No data	

CAS = Chemical Abstracts Service; EPA = Environmental Protection Agency; DOT/UN/NA/IMCOP = Department of Transportation/United Nations/North America/International Maritime Consultive Organization; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials Technical Assistance Data Base; RTECS = Registry of Toxic Effects of Chemical Substances; SANSS = Structure and Nomenclature Search System

TABLE 3-2. Physical and Chemical Properties of the Isomers of 1,3-Dichloropene

Property	cis-1,3-Dichloropropene	trans-1,3-Dichloropropene	cis- and trans- 1,3-Dichloropropene	Reference
Molecular weight	110.98	110.98	110.98	Weast et al. 1988
Color	Colorless	Colorless	Colorless	Sax and Lewis 1987
Physical state	Liquid	Liquid	Liquid	Sax and Lewis 1987
Boiling point	104°C at 1 atm	112°C at 1 atm	104°C and 112°C at 1 atm	Weast et al. 1988
Density at 20°C	1.217 g/mL	1.224 g/mL	1.218-1.224 g/mL	Weast et al. 1988
Odor	Chloroform-like	Chloroform-like	Chloroform-like	Windholz et al. 1983
Odor threshold:				
Water	No data	No data	No data	
Air	1 ppm	1 ppm	1 ppm	Verschueren 1983
Solubility:				
Water at 25°C	2,700 ppm	2,800 ppm	2,700-2,800 ppm	Dilling 1977
Organic solvents	acetone; toluene; octane; ethanol benzene; chloroform	acetone; toluene; octane; ethanol benzene; chloroform	acetone; toluene; octane; ethanol benzene; chloroform	Sax and Lewis 1987; Weast et al. 1988
Partition coefficients:				
Log octanol/water	1.60 (estimated)	1.60 (estimated)	1.60 (estimated)	CLOGP-PCGEMS 1986
Log K_{oc}	1.36	1.41	1.36-1.41	Kenaga 1980
Vapor pressure at 25°C	43 mmHg	34 mmHg	34-43 mmHg	Dilling 1977
Henry's law constant:				
at 20°C	1.2x10 ⁻³ atm-m ³ /mol	8.0x10 ⁻⁴ atm-m ³ /mol	1.2x10 ⁻³ to	Leistra 1970
at 25°C			8.0x10 ⁻⁴ atm-m ³ /mol 3.55x10 ⁻³ atm-m ³ /mol	EPA 1981
Autoignition temperature	No data	No data	No data	
Flashpoint (open cup)	35°C	35°C	35°C	Sax and Lewis 1987
Flammability limits (air)	No data	No data	5.3%-14.5%	OHM/TADS 1989
Conversion factors				
in air (20°C)				
ppm (v/v) to mg/m ³	4.61	4.61	4.61	Verschueren 1983
mg/m ³ to ppm (v/v)	0.22	0.22	0.22	Verschueren 1983
Bioconcentration factor				
Log BCF	0.86 (calculated from water solubility)	0.85 (calculated from water solubility)	0.86 (calculated from water solubility)	Lyman et al. 1982
Explosive limits	No data	No data	4.3%-10.3%	OHM/TADS 1989

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

1,3-Dichloropropene is produced by either high-temperature chlorination of propylene or from 1,3-dichloro-2-propanol by dehydration with POCl_3 or P_2O_5 in benzene. All commercial preparations of 1,3-dichloropropene are mixtures of the cis- and trans- isomers. Before 1978, approximately 25 million kilograms of 1,3-dichloropropene were produced annually in the United States. Over 1 million kilograms of pesticides containing 1,3-dichloropropene were used in California alone in 1978. Recent production data are proprietary and are not available (Yang 1986).

According to USITC (1989) and SRI (1989), Dow Chemical is the only current manufacturer of 1,3-dichloropropene. It is produced under the trade name Telone II® in Freeport, Texas.

Production of Telone II®, which is 92% 1,3-dichloropropene, most likely has increased in recent years because of a 1983 suspension by EPA on the use of ethylene dibromide (EDB). Since the suspension, Telone II® and methyl bromide have become the major substitutes for EDB (Yang 1986).

4.2 IMPORT/EXPORT

Import and export data for 1,3-dichloropropene were not located in the literature.

4.3 USE

1,3-Dichloropropene is the predominant component of several formulations used in agriculture as soil fumigants for parasitic nematodes (Krijgsheld and Van der Gen 1986). To date, there have been at least 10 commercial preparations of fumigants that contain 1,3-dichloropropene. The trade names of these preparations are listed in Table 3-1. Table 4-1 contains some of the reported chemical compositions of these mixtures. Some variation may exist in the composition of these products; some of these formulations are no longer being produced. However, information as to which preparations (other than Telone II®) are presently being marketed was not available. Most of these fumigants are not diluted and are applied directly to the soil of vegetable and tobacco crops (Yang 1986).

Much smaller quantities of 1,3-dichloropropene are used as solvents and chemical intermediates (Krijgsheld and Van der Gen 1986).

4.4 DISPOSAL

1,3-Dichloropropene may be disposed of by using a sorbent media that is packaged in an epoxy-lined drum and placed in a Resource Conservation and Recovery Act (RCRA)-approved landfill. 1,3-Dichloropropene may also be

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

TABLE 4-1. Reported Compositions of Commercial Products Containing 1,3-Dichloropropene

Name (synonym)	Composition	Manufacturer	Reference
Dowfume N	50:50 ratio of 1,3-dichloropropene to 1,2-dichloropropane and related C ₃ hydrocarbons	Dow Chemical Co.	Cohen and Gilmore 1983
Vidden D	85%-93% 1,3-dichloropropene 25% 1,2-dichloropropane and related C ₃ hydrocarbons	Dow Chemical Co.	Cohen et al. 1983
Telone [•]	40.2% cis; 38.2% trans (NOS)	Dow Chemical Co.	Til et al. 1973
Telone II [•]	48%-53% cis 42%-45% trans; 1% epichlorohydrin 5% mixture of chlorinated propenes and hexenes	Dow Chemical Co.	Stott et al. 1988; Streeter et al. 1987; Yang 1986
Telone II [•]	48%-53% cis 42%-45% trans 2% epoxidized soybean oil	Dow Chemical Co.	Lomax et al. 1988 Breslin et al. 1989
M-3993	Same as Telone II		Lichy and Olson 1975
Telone C-17 [•]	40%-41% cis 38%-39% trans 19%-21% chloropicrin	Dow Chemical Co.	Mizzell et al. 1988 Streeter and Lomax 1988
DD [•] (Nemafene)	25%-28% cis 25%-27% trans 25%-29% 1,2-dichloropropane minor components: 3,3-dichloropropene 2,2-dichloropropene other related chlorinated hydrocarbons	Shell Chemical Co.	Parker et al. 1982 Linnett et al. 1988 Yang 1986
DD-92 [•]	92% cis/trans (NOS)	Shell Chemical Co.	Van Joost and de Jong 1988
Terr-O-Cide 15-D	85% DD 15% chloropicrin		Yang 1986
Terr-O-Cide 30-D	70% DD 30% chloropicrin		Yang 1986
Terr-O-Gas 57/43T	43% DD 57% chloropicrin		Yang 1986
Vorlex (Trapex, Ditrax, MENCS, MIC, MITC)	20% methylisothiocyanate 80% mixture of dichloropropenes and other related compounds		Yang 1986

NOS = not otherwise specified
cis = cis-1,3-dichloropropene
trans = trans-1,3-dichloropropene

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

disposed of in a high-temperature pesticide incinerator with a hydrochloric acid scrubber (OHM/TADS 1989) and a temperature/dwell time that will completely destroy the pesticide (HSDB 1990).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,3-Dichloropropene is not a naturally occurring compound (IARC 1986). It is produced synthetically and may be released to the atmosphere in fugitive or accidental emissions during its manufacture, storage, and transport. It is also released to air during its use as a soil fumigant. Sewage treatment facilities (Lao et al. 1982; Rawlings and Samfield 1979), petroleum refineries (Snider and Manning 1982), and electricity-generating power facilities (Bean et al. 1985) can release 1,3-dichloropropene to surface waters. Chlorination of organic substances during the treatment of drinking water also can form 1,3-dichloropropene; therefore, the compound is a potential contaminant in drinking water (Dowty et al. 1975a, 1975b; Krijgsheld and Van der Gen 1986; Otson 1987; Rogers et al. 1987).

1,3-Dichloropropene may leach into groundwater and soil from landfills and hazardous waste sites (Hauser and Bromberg 1982; Sabel and Clark 1984). The most common release of 1,3-dichloropropene to soil occurs during the application of the chemical to agricultural fields when used as a soil fumigant (Cohen 1986; Krijgsheld and Van der Gen 1986; Maddy et al. 1982a, 1982b). Accidental spills may also release 1,3-dichloropropene to the environment (Markovitz and Crosby 1984; Sterrett et al. 1986).

Possible routes of human exposure to 1,3-dichloropropene include inhalation, ingestion of contaminated foods and drinking waters, and dermal contact. High levels of exposure to 1,3-dichloropropene are most likely to occur in occupational settings where 1,3-dichloropropene is either produced or used as a soil fumigant (Albrecht 1987b; Albrecht et al. 1986; Markovitz and Crosby 1984; Nater and Gooskens 1976; Osterloh et al. 1984, 1989a, 1989b; van Joost and Jong 1988; Wang 1984). The National Occupational Exposure Survey (NOES) conducted by NIOSH between 1981 and 1983 has determined that 1,779 workers are potentially exposed to 1,3-dichloropropene (NIOSH 1989). The NOES data base does not contain information on the frequency, concentration, or duration of workers' exposure to any of the chemicals listed therein. The survey provides only estimates on the number of workers potentially exposed to chemicals in the workplace. Intake by inhalation or dermal contact is the most probable route of workplace exposure to 1,3-dichloropropene. 1,3-Dichloropropene is a volatile compound and, after soil application as a fumigant, a fraction of the compound will volatilize and escape into the atmosphere (Krijgsheld and Van der Gen 1986). Inhalation and dermal contact are probably the major sources of exposure to workers.

The EPA has identified 1,177 NPL hazardous waste sites. cis-1,3-Dichloropropene has been identified at three of the sites evaluated for the presence of this chemical (View 1989); soil, water, and air samples have not been differentiated. However, we do not know how many of the 1,177 NPL sites have been evaluated for this chemical. As more sites are evaluated by the EPA, the number may change. The frequency of these sites within the United States can be seen in Figure 5-1.

5. POTENTIAL FOR HUMAN EXPOSURE

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

1,3-Dichloropropene is produced synthetically and may be released to the atmosphere as fugitive or accidental emissions during its manufacture (Leiber and Berk 1984; van Joost and Jong 1988), transport (Markovitz and Crosby 1984; Sterrett et al. 1986), and storage (Albrecht et al. 1986). For example, on April 8, 1984, a rail accident that occurred about 45 miles southeast of Tucson, Arizona resulted in a spill of 15,000 gallons of 1,3-dichloropropene. During the clean-up, which took place between August 1984 and March 1985, approximately 19,000 pounds of 1,3-dichloropropene were released to ambient air by an aeration process (Sterrett et al. 1986).

A major anthropogenic release of 1,3-dichloropropene to the atmosphere occurs during its application as a soil fumigant (Albrecht 1987; Markovitz and Crosby 1984; Osterloh et al. 1984, 1989a, 1989b).

5.2.2 Water

Very little information regarding the release of 1,3-dichloropropene to water was found in the available literature. A survey of sewage treatment facilities demonstrated that 1,3-dichloropropene may be released to surface waters via primary and secondary effluents (Lao et al. 1982; Rawlings and Samfield 1979). Waste water effluents from petroleum refineries also release 1,3-dichloropropene to surface waters (Snider and Manning 1982). In addition, trace quantities of 1,3-dichloropropene are formed during the chlorination of cooling water, which prevents biofouling 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 and waste water from 1,3-dichloropropene production sites can also release 1,3-dichloropropene to surface waters (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, 1975b; 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 (Cohen 1986; Krijgsheld and Van der Gen 1986; Maddy et al. 1982b). 1,3-Dichloropropene may also be released to groundwater via landfills and hazardous waste sites (Hauser and Bromberg 1982; Sabel and Clark 1984).

1,3-Dichloropropene was not listed in the Contract Laboratory Program (CLP) Statistical Database.

5. POTENTIAL FOR HUMAN EXPOSURE

5.2.3 Soil

The most common release of 1,3-dichloropropene to soil occurs in agricultural fields where it is applied as a soil fumigant (Cohen 1986; Krijgsheld and Van der Gen 1986; Maddy et al. 1982a). Accidental spills may also release 1,3-dichloropropene to soil (Markovitz and Crosby 1984; Sterrett et al. 1986). For example, on April 8, 1984, a rail accident that occurred about 45 miles southeast of Tucson, Arizona resulted in a spill of 15,000 gallons of 1,3-dichloropropene (Sterrett et al. 1986).

1,3-Dichloropropene may be released to soil via the leachates of landfills and hazardous waste sites (Hauser and Bromberg 1982; Sabel and Clark 1984). The EPA has identified 1,177 NPL hazardous waste sites. cis-1,3-Dichloropropene has been identified at three of the sites evaluated for the presence of this chemical (View 1989) (soil, water, and air samples are not differentiated). However, we do not know how many of the 1,177 NPL sites have been evaluated for this chemical. As more sites are evaluated by the EPA, the number may change.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The transport and partitioning of an organic compound in the environment is a function of the physical and chemical properties of that compound and the site-specific characteristics of the environment (e.g., percent soil organic matter). Based upon similarities in their physical and chemical properties, cis- and trans-1,3-dichloropropene should behave similarly in regards to transport and partitioning within the environment.

In the atmosphere, the respective vapor pressures of cis- and trans-1,3-dichloropropene of 43 and 34 mmHg at 25°C (Dilling 1977) suggest that these compounds will exist predominantly in the vapor phase (Eisenreich et al. 1981). The water solubilities of cis- and trans-1,3-dichloropropene of 2,700 and 2,800 ppm, respectively (Dilling 1977), indicate that wet deposition may remove them from the atmosphere. This is confirmed by the detection of 1,3-dichloropropene in rainwater (Section 5.4.2).

In surface waters, volatilization of 1,3-dichloropropene should be an important fate process that will compete with the transformation processes of biodegradation or slow hydrolysis (Section 5.3.2.2). Experimentally measured Henry's law constants (the reciprocal of the solubility when the partial pressure of the solute is 1 atmosphere) for cis- and trans-1,3-dichloropropene of 1.2×10^{-3} and 8.0×10^{-4} atm-m³/mol at 20°C, respectively (Leistra 1970), indicate 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

5. POTENTIAL FOR HUMAN EXPOSURE

73m/sec are 3.8 and 4.2 hours, respectively. Using EPA's EXAMS II computer simulation model (EPA 1986a), 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.

Experimental data pertaining to the adsorption of 1,3-dichloropropene to aquatic sediments were not available in the literature. However, the relatively high water solubilities of 2,700 and 2,800 ppm for cis- and trans-1,3-dichloropropene (Dilling 1977) suggest that 1,3-dichloropropene is more likely to remain in solution than become adsorbed to suspended materials and sediment.

In soil, 1,3-dichloropropene can exist as a gas or dissolved in water. The adsorption characteristics for each form are different. Experimental K_{oc} values for cis- and trans-1,3-dichloropropene in aqueous solutions are reportedly 23 and 26, respectively (Kenaga 1980). These K_{oc} values indicate a high mobility in soil (Swann et al. 1983) and a potential for leaching. Although movement in saturated soils is possible, concurrent hydrolysis and biodegradation should attenuate the amounts of 1,3-dichloropropene that may actually leach to groundwater. Furthermore, extensive groundwater monitoring programs, conducted in California, have not demonstrated that 1,3-dichloropropene is contaminating well waters in areas of continued field applications of the pesticide (Cohen 1986; Maddy et al. 1982b).

1,3-Dichloropropene more strongly adsorbs to soil when it is in the vapor phase than when it is dissolved in water (Munnecke and Vangundy 1979). Adsorption for the vapor phase depends partly upon the soil's temperature and organic content (Leistra 1970). Soil adsorption isotherms indicate increasing adsorption with increasing organic content, and adsorption is approximately 3 times greater at 2°C than it is at 20°C. Adsorption isotherms measured for humus sand, peaty sand, and peat indicate vapor-phase K_{oc} values for 1,3-dichloropropene ranging from about 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).

Volatilization of 1,3-dichloropropene from soil is an important physical removal mechanism. After application as a soil fumigant, the amount of 1,3-dichloropropene that volatilizes can vary greatly with application methods, temperature, moisture content, soil porosity, and soil organic content (Albrecht and Chenchin 1985). During laboratory experiments conducted in jars designed to trap escaping vapors, the majority of 1,3-dichloropropene applied to a soil evaporated (Roberts and Stoydin 1976). In warm, moist, sandy loam soils, 5%-10% of the 1,3-dichloropropene applied at a depth of 0.3 meters was lost to evaporation (Munnecke and Vangundy 1979; Thomas and McKenry 1974).

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The persistence of 1,3-dichloropropene in soil has been measured by a number of investigators. Van der Pas and Leistra (1987) reported half-lives of 3-4 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. A degradation rate of 0.01/day, which corresponds to a half-life of 69 days, was reported for sandy and peat soils (Leistra 1970). Albrecht (1987) has reported half-lives of 3-25 days at 20°C for 1,3-dichloropropene. Radiolabeled cis- and trans-1,3-dichloropropene was applied to soils and stored in sealed jars for 12 weeks. In a sandy loam soil, 19% of the cis isomer and 18% of the trans isomer remained, while 10% of the cis isomer and 22% of the trans isomer persisted in a medium loam soil (Roberts and Stoydin 1976).

As discussed in Section 5.3.2.3, 1,3-dichloropropene can be removed from soils via hydrolysis, microbial degradation, and volatilization. Since the rate of these processes can vary significantly with soil conditions, the wide range of reported persistence half-lives is not surprising and demonstrates that the persistence of 1,3-dichloropropene in soil depends upon specific local conditions.

5.3.2 Transformation and Degradation

5.3.2.1 Air

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. The rate constants for the reactions of cis- and trans-1,3-dichloropropene with hydroxyl radicals have been experimentally determined to be 7.7×10^{-12} and 1.3×10^{-11} $\text{cm}^3/\text{molecule-sec}$ at 22°C, respectively (Tuazon et al. 1984). 1,3-Dichloropropene will also be removed from air via reaction with ozone; however, this reaction is expected to be secondary to photooxidation with hydroxyl radicals. The rate constants for the reactions of cis- and trans-1,3-dichloropropene with ozone molecules have been experimentally determined to be 1.5×10^{-19} and 6.7×10^{-19} $\text{cm}^3/\text{molecule-sec}$ at 22°C, respectively (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 1979), the corresponding half-lives for cis-1,3-dichloropropene in air are about 2.1 days (50 hours) and 76 days. The corresponding half-lives for trans-1,3-dichloropropene in air would be about 1.2 days (30 hours) and 17 days. Tuazon et al. (1984) calculated the respective half-lives of 52 and 12 days for cis- and trans-1,3-dichloropropene reactions with ozone based on an average background tropospheric concentration for ozone of 1.0×10^{12} molecules/ cm^3 . For the cis and trans isomers, the authors also calculated respective half-lives of 12 and 7 hours for the reactions with photochemically generated hydroxyl radicals present at an average concentration of 2.0×10^5 molecules/ cm^3 (Tuazon et al. 1984).

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The estimates of average hydroxyl radical and ozone concentrations in air used by Tuazon et al. (1984) are more indicative of urban atmospheres. In general, the hydroxyl radical and ozone concentrations in polluted air may increase by an order of magnitude over those estimates used by Atkinson (1979). Therefore, the half-life of 1,3-dichloropropene in ambient air may range between 7 and 50 hours, depending on the concentrations of cis- and trans-isomers and hydroxyl radicals in the troposphere.

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 is also 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).

5.3.2.2 Water

River die-away test data pertaining to the biodegradation of 1,3-dichloropropene in natural waters were not available in the literature. Several aerobic biological screening studies, which used settled domestic waste water for inocula, demonstrated that 1,3-dichloropropene is biodegradable (Tabak et al. 1981a, 1981b). 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, 1981b). Acclimation to a series of subcultures was also 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, 1981b). 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 than in soil-water suspensions with a soil:water ratio of 0.5 (Section 5.3.2.3).

5.3.2.3 Soil

1,3-Dichloropropene reportedly biodegrades in soil (Castro and Belser 1966, 1968; Roberts and Stoydin 1976; Tu 1988, Van der Pas and Liestra 1987). Belser and Castro (1971) reported that the microbial degradative pathway for

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both the cis and trans isomers followed a similar sequence. The initial step of the reaction involves allylic dechlorination of 1,3-dichloropropene and hydroxyl substitution to form the corresponding chloroallyl alcohol (Castro and Belser 1966; Roberts and Stoydin 1976). Again, both cis- and trans-chloroallyl alcohols 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),.

1,3-Dichloropropene may also hydrolyze in moist soils. In laboratory studies, hydrolysis rates have been measured in soil slurries and buffer solutions. For soil-water slurries with a concentration of 10^{-2} M, 1,3-dichloropropene hydrolyzed at a rate of 3.4% per day (Castro and Belser 1966). In general, soils possess a relative humidity greater than 98%. Under dry conditions, the relative humidity of soil may fall below 90% (Morrill 1985). Therefore, 1,3-dichloropropene is likely to hydrolyze in most soils. Once again, corresponding chloroallyl alcohols were reported as the products of hydrolysis for cis- and trans-1,3-dichloropropene (Castro and Belser 1966).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

1,3-Dichloropropene is not a widely occurring atmospheric pollutant. According to the National Ambient Volatile Organic Compounds (VOCs) Database, a compilation of published and unpublished air monitoring data from 1970 to 1987, the median urban atmospheric concentration of cis-1,3-dichloropropene is 23.9 ppbV (parts per billion by volume) for 148 samples collected from representative locations (Shah and Heyerdahl 1989). Information regarding the occurrence of cis-1,3-dichloropropene in suburban, rural, remote, sourcedominated (air surrounding a facility or known release of the chemical in question), workplace, and indoor and personal atmospheres was not included by the VOC database. Also, no data were reported for trans-1,3-dichloropropene (Shah and Heyerdahl 1989).

No other monitoring data on the presence of 1,3-dichloropropene in ambient air were available in the literature.

5.4.2 Water

Monitoring information pertaining to the occurrence of 1,3-dichloropropene in surface waters was unavailable in the literature. STORET (1989) did not contain any unremarked records (those data points that are not noted to be less than a given value, usually the detection limit) for cis- and trans-1,3-dichloropropene in ambient surface water.

STORET (1989) also did not contain unremarked records for cis- and trans-1,3-dichloropropene in groundwater. 1,3-Dichloropropene was detected in

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groundwater contaminated by leachates from municipal landfills in New York, Minnesota, and Wisconsin at concentrations up to 18 µg/L (Sabel and Clark 1984). In California, 1,3-dichloropropene was detected in groundwater at unspecified concentrations as a result of pesticide applications (Cohen 1986). An extensive groundwater monitoring program for agricultural chemicals in California detected cis-1,3-dichloropropene in only two groundwater samples, and trans-1,3-dichloropropene in only one groundwater sample (Cohen 1986). By comparison, dibromochloropropane, another soil fumigant, was detected in 2,522 groundwater samples. In 54 municipal wells of varying depths of 65-1,200 feet in areas of California where Telone® or DD® had been applied for over 15 years, 1,3-dichloropropene was not detected in any sample at or above the quantification limit of 0.1 ppb (Maddy et al. 1982b).

1,3-Dichloropropene was qualitatively identified in New Orleans, Louisiana, drinking water collected in August 1974 (Dowty et al. 1975a, 1975b). An analysis of 15 drinking water samples from Denver collected between October 1, 1985, and March 31, 1986, did not detect cis- or trans-1,3-dichloropropene at or above detection limits of 0.13 ppb (Rogers et al. 1987). At quantities above the detection limit of 0.1 ppb, 1,3-dichloropropene was not detected in 42 raw and 42 finished drinking water samples collected between July 1982 and May 1983 from nine municipalities along the Great Lakes (Otson 1987).

Concentrations of 10 and 2 ng of cis- and trans-1,3-dichloropropene/L, respectively, were detected in rainwater collected in Portland, Oregon, in 1982 (Mazurek and Simonetti 1986).

5.4.3 Soil

Monitoring data pertaining to 1,3-dichloropropene found in soil were not located in the available literature.

5.4.4 Other Environmental Media

1,3-Dichloropropene is not a naturally occurring product (IARC 1986). Information pertaining to the its presence in other media could not be located in the available literature.

Daft (1989) examined 231 different ready-to-eat foods (collected during the U.S. Food and Drug Administration's Market Basket Survey) for 22 fumigants and industrial residues. Although analyzed for (at a detection limit of about 1 ppb), 1,3-dichloropropene was not detected in any food sample.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Possible routes of human exposure to 1,3-dichloropropene include the inhalation of vapors, ingestion of contaminated foods and drinking water, and dermal contact.

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Monitoring data regarding the presence of 1,3-dichloropropene in foods were not located (see Section 5.4.4). It has been suggested that chlorination of water can lead to the formation of 1,3-dichloropropene, and that the detection of 1,3-dichloropropene in various water samples confirm this (Krijgsheld and Van der Gen 1986). However, information pertaining to the occurrence of 1,3-dichloropropene in drinking water is also very limited.

Very few atmospheric monitoring data for 1,3-dichloropropene exist in the literature. Because substantial quantitative information for air, food, and drinking water is not available, the respective average daily intakes were not calculated.

Occupational exposures to 1,3-dichloropropene, mainly during handling and application as a soil fumigant, have been documented (Albrecht 1987; Albrecht et al. 1986; Markovitz and Crosby 1984; Nater and Gooskens 1976; Osterloh et al. 1984, 1989a, 1989b; Schenker and McCurdy 1986; van Joost and Jong 1988; Wang 1984). According to the NOES conducted by NIOSH between 1980 and 1983, it has been estimated that 1,779 workers were potentially exposed to 1,3-dichloropropene in the workplace in 1980 (NIOSH 1989). The NOES data base does not contain information on the frequency, concentration, or duration of workers' exposure to any of the chemicals listed therein. The survey provides only estimates on the number of workers potentially exposed to chemicals in the workplace. The most probable routes of occupational exposure are inhalation and dermal contact at places where 1,3-dichloropropene- and/or 1,3-dichloropropene-containing compounds are produced or used as a soil fumigant. Albrecht (1987) studied the inhalation exposure of 1,3-dichloropropene to workers involved in applying Telone II to pineapple fields in Hawaii. Exposures were predominantly below 1 ppm.

The Monsanto Agricultural Products Company conducted research to ensure that workers in the workplace were not being exposed to unacceptable levels of 1,3-dichloropropene in the air during its manufacture. Under laboratory conditions simulating the workplace environment, atmospheric levels of 1,3-dichloropropene ranged from 0.4 to 4.0 ppm (Leiber and Berk 1984).

Populations that live near hazardous waste sites may be exposed to 1,3-dichloropropene; however, only three hazardous waste sites of an unknown number of evaluated sites have been found to contain it.

Pertinent monitoring data regarding the dermal exposure of 1,3-dichloropropene were not located in the available literature. Dermal exposure is possible for workers involved in fumigant applications of 1,3-dichloropropene.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

High levels of exposure to 1,3-dichloropropene are most likely to occur in occupational settings where 1,3-dichloropropene is either produced or used

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as a soil fumigant. Intake by inhalation or dermal contact is the most probable route of high exposure to 1,3-dichloropropene. 1,3-Dichloropropene is a volatile compound and, after soil application as a fumigant, a fraction of the compound will volatilize and escape into the atmosphere (Krijgsheld and Van der Gen 1986).

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA as amended directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,3-dichloropropene is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,3-dichloropropene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Data Needs

Physical and Chemical Properties. The physical and chemical properties of both cis- and trans-1,3-dichloropropene have been described and are readily available in the literature (CLOGP-PCGEMS 1989; Dilling 1977; EPA 1981; Kenaga 1980; Leistra 1970; OHM/TADS 1989; Sax and Lewis 1987; Verschueren 1983; Weast et al. 1988; Windholz et al. 1983). Some of these physical properties were required for assessing the fate and transport of 1,3-dichloropropene in the environment because experimental data were not available. The literature values were sufficient for performing the necessary estimates (Lyman et al. 1982).

Production, Import/Export, Use, and Disposal. Current production and import/export volumes are unavailable in the literature. Much of the information regarding 1,3-dichloropropene has been included in combination with other chemicals. For example, USITC (1989) data for 1,3-dichloropropene are grouped with other soil fumigants. Historical production volumes are well documented (Yang 1986), but information regarding future domestic production, and past, present, and future imports and exports are lacking in the literature. With up-to-date and accurate production/import/export data, the extent of release into the environment and the subsequent potential for human exposure could be more realistically determined.

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According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxic Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Literature pertaining to the use of 1,3-dichloropropene as a agricultural soil fumigant is readily available (Krijgsheld and Van der Gen 1986). Yet, monitoring data that showed the existence of 1,3-dichloropropene in food were not located. 1,3-Dichloropropene has been monitored in drinking water supplies with a low frequency of occurrence (Dowty et al. 1975a, 1975b; Otson 1987; Rodger et al. 1987). Disposal methods have been described and appear to be satisfactory. Information concerning the numbers of persons potentially exposed to 1,3-dichloropropene near waste sites and manufacturing, production, and use facilities, however, is not available. In these areas and those of widespread use, the potential for human exposure is high.

Environmental Fate. Information concerning the partitioning of 1,3-dichloropropene in the environment is available (Cohen 1986; Dilling 1977; EPA 1986a; Kenaga 1980; Leistra 1970; Maddy et al. 1982; Munnecke and Vangundy 1979; Roberts and Stoydin 1976; Thomas and McKenry 1974; Van der Pas and Leistra 1987); 1,3-dichloropropene occurs in all environmental media. Information on the transport of 1,3-dichloropropene in environmental media is also available (Albrecht 1981; Cohen 1986; Dilling 1977; EPA 1986a; Leistra 1970; Maddy et al. 1982; Munnecke and Vangundy 1979; Roberts and Stoydin 1976; Swann et al. 1983; Thomas 1982; Van der Pas and Leistra 1987); however, precisely and accurately predicting the behavior of 1,3-dichloropropene in the environment is difficult because of the influence of site-specific environmental characteristics and the effects of competing fate processes, such as volatilization and adsorption. Likewise, we do not know if 1,3-dichloropropene is transported long distances from its point of release in air, nor do we know the rate of photolysis in the presence of atmospheric particulate matter. A better understanding in these areas will enable scientists to more accurately assess the extent of human exposure to 1,3-dichloropropene, especially among populations living near points of release to the environment.

Bioavailability from Environmental Media. Case reports of people who have experienced 1,3-dichloropropene poisoning following oral, dermal, and inhalation exposure indicate that 1,3-dichloropropene can be absorbed by these routes (Albrecht 1987; Markovitz and Crosby 1984; Hater and Gooskens 1976; Osterloh et al. 1984, 1989). However, no information is available regarding oral or dermal absorption of 1,3-dichloropropene in water, soil, or plant material. Studies of absorption of 1,3-dichloropropene from air, water, soil, and plant material would allow determination of the rate and extent of

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absorption from each of these media, and allow comparison of the potential hazard posed by 1,3-dichloropropene contained in each.

Food Chain Bioaccumulation. Few data are available describing the food chain bioaccumulation of 1,3-dichloropropene. Experimental data are unavailable; therefore, we do not know if the bioconcentration potential is consistent with estimated values obtained from regression equations (Lyman et al. 1982). Information concerning the potential for food chain biomagnification has not been described. Knowledge in this area would enable scientists to assess the dangers of human exposure to 1,3-dichloropropene via food such as fish and seafoods.

Exposure Levels in Environmental Media. Information on exposure levels in environmental media is largely unavailable. Data describing the exposure levels in air, surface water, and groundwater (sources of groundwater contamination include hazardous waste sites) are lacking. For 1,3-dichloropropene, estimates of human intake via air, water, and food are not available. Additional information, particularly for waste sites, would be helpful in describing the potential dangers of human exposure to 1,3-dichloropropene in the environment.

Exposure Levels in Humans. 1,3-Dichloropropenes are not naturally occurring substances (IARC 1986). Available information shows that N-acetyl cysteine is present in the urine of people who were occupationally exposed to 1,3-dichloropropene (Osterloh et al. 1984, 1989a, 1989b). Additional information regarding the utility of this biomarker as an indicator of general population exposure to the compound may be useful in monitoring the frequency of human exposure to 1,3-dichloropropene.

Exposure Registries. No exposure registries for 1,3-dichloropropene were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to the compound.

Populations near hazardous waste sites and manufacturing, production, and use facilities may be exposed both from elevated air concentrations and from drinking contaminated groundwater (Bean et al. 1985; Cohen 1986; Dowty et al. 1975; Hauser and Bromberg 1982; Krijgsheld and Van der Gen 1986; Lao et al. 1982; Maddy et al. 1982; Markovitz and Crosby 1984; Otson 1987; Rawlings and Samfield 1979; Rodgers et al. 1987; Sabel and Clark 1983; Sterrett et al. 1986). No registries are available that document the exposure of these populations to 1,3-dichloropropene. An exposure registry would provide a reference for assessing exposure levels and frequencies of exposure to

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1,3-dichloropropene. It will also facilitate the conduct of epidemiological or health studies that evaluate any adverse health effects resulting from 1,3-dichloropropene exposure. In addition, a registry based upon exposure sources will allow the assessment of variations in exposure levels between sources and the effects of geographical, seasonal, and regulatory actions on the level of exposure within a certain source.

5.7.2 On-going Studies

For 1,3-dichloropropene, as well as other halogenated hydrocarbons, the reactions and movement in soil are a concern of ongoing investigations (Federal Research in Progress 1988). The U.S. Dept. of Agriculture-Cooperative State Research Service (USDA-CSRS) is sponsoring research at New Haven, Connecticut, regarding the sorption of 1,3-dichloropropene by sterile and nonsterile soils under anaerobic and aerobic conditions. The rate of desorption is being examined with the leaching of water and other solvents through the soils. Similar studies, dealing with soil retention and leachability among field soils, are in progress at the University of Florida, Gainesville, Florida.

The USDA-CSRS, at the University of Clemson in South Carolina, is studying ways to more effectively use chemical nematicides in the field. The goal is to develop more efficient means in which to apply soil fumigants (Federal Research in Progress 1988).

Worker exposure to 1,3-dichloropropene and other pesticides is currently being assessed by the USDA-CSRS, at the University of California in Davis, California (Federal Research in Progress 1988). Worker exposure levels of 1,3-dichloropropene are being monitored in the soil and air during the handling, storage, and application of the chemical. Local distributors and warehouse employees are being monitored in addition to the field applicators.

A remedial investigation and feasibility study conducted at the three NPL sites known to be contaminated with 1,3-dichloropropene will add to the available database on exposure levels in environmental media, exposure levels in humans, and exposure registries; this will also increase the current knowledge regarding the transport and transformation of 1,3-dichloropropene in the environment.

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing human blood samples for 1,3-dichloropropene and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring 1,3-dichloropropene in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify 1,3-dichloropropene. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect 1,3-dichloropropene in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

The available literature produced only one recent method for determining levels of cis- and trans-1,3-dichloropropene in biological materials. Kastl and Hermann (1983) developed an analytical procedure for determining the level of cis- and trans-1,3-dichloropropene in whole rat blood. Blood is extracted, 200 μ L n-hexane is added, and the sample is vortexed and centrifuged at 800 g for 1 minute. Samples are either directly injected onto a GC column for GC/MS analysis or diluted with hexane for GC/ECD (electron capture detection) analysis. Percent recoveries of the GC analysis range from 80.8 to 98.5 for the cis isomer and 81.3 to 98.2 for trans-1,3-dichloropropene. For GC/MS analysis, percent recoveries are between 83.1 and 94.9 for cis- and 88.7 and 98.8 for trans-1,3-dichloropropene. The GC/ECD method is sensitive to cis and trans isomeric concentrations in rat blood of $5.88-1.17 \times 10^4$ and $5.35-1.07 \times 10^4$ ng/mL, respectively. The GC/MS method is sensitive to cis- and trans-1,3-dichloropropene concentrations in rat blood of 5.18×10^1 to 1.29×10^4 and 4.71×10^1 to 1.18×10^4 ng/mL, respectively.

Table 6-1 summarizes the methods used to detect 1,3-dichloropropene in biological materials, including a procedure for detecting 1,3-dichloropropene in foods (Daft 1989).

In addition, the detection of N-acetyl cysteine conjugate in urine has been used to indicate human exposure to 1,3-dichloropropene (Osterloh et al. 1984, 1989a, 1989b).

6.2 ENVIRONMENTAL SAMPLES

Procedures for detecting cis- and trans-1,3-dichloropropene in water, soil, and sediment samples at hazardous waste sites are outlined in the method for semivolatiles in the CLP Statement of Work for Organics Analysis (EPA 1988). The required quantification limits for both cis- and

TABLE 6-1. Analytical Methods for Determining cis- and trans-1,3-Dichloropropene in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Rat blood	Extract with hexane vortex and centrifuge	GC/MS	51.8 ng/mL (cis) 4.71 ng/mL (trans)	83.1-94.9 (cis) 88.7-98.8 (trans)	Kastl and Hermann 1983
Rat blood	Extract with hexane vortex and centrifuge	GC/ECD	5.88 ng/mL (cis) 5.35 ng/mL (trans)	80.8-98.5 (cis) 81.3-98.2 (trans)	Kastl and Hermann 1983
Food	Extract composited, table-ready foods with isooctane or acetone-aqueous phosphoric acid-isooctane mixture	GC-ECD/HECD	No data	45-112	Daft 1989

ECD = electron capture detection

GC = gas chromatography

HECD = Hall electron capture detection

MS = mass spectrometry

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trans 1,3-dichloropropene are 5 ppb for water samples and 5 ppb for soil and sediment samples in this monitoring program.

For the most part, soil and sediment samples are analyzed in a similar manner to water samples, with the exception that a small amount of water is added to soil and sediment samples. At this point, all three matrices are subjected to a purge-and-trap cycle. An inert gas is bubbled through the sample, volatilizing 1,3-dichloropropene. The gas stream is then passed through an adsorbent tube, which recollects the 1,3-dichloropropene. The sorbent tube is attached to a GC, heated, and backflushed with an inert gas to desorb the halocarbons onto a GC column. Quantification can be accomplished using either a flame ionization detector or an MS, depending on the total concentration of organics in the sample.

EPA's Test Methods for Organic Chemical Analysis of Municipal and Industrial Wastewater (EPA 1982) and Test Methods for Solid Waste (EPA 1986a) are very similar to those already outlined. However, the purge-and-trap cycle may be bypassed for aqueous process wastes with expected concentrations in excess of 10,000 µg/L. In these instances, the sample may be directly injected into the GC system with a 10 mL syringe (EPA 1986a). No other standardized methods for determining 1,3-dichloropropene in environmental samples were located.

It is important to note the discrepancies in detection limits between the standardized methods. CLP cites a detection limit of 5 ppb, yet gives no information regarding the percent recoveries (EPA 1988a). The U.S. EPA procedures for solid wastes (EPA Method 8010) and municipal and industrial waste waters (EPA Method 601), however, maintain a detection limit of 0.34 ppb. The percent recovery, according to the Solid Waste Manual, ranges from 22 to 178 (EPA 1986a). Therefore, results from EPA Method 8010 must be interpreted with caution. For municipal and industrial waste waters, the average percent recoveries for the cis- and trans-isomers are reportedly 86.7 and 73.5 with standard deviations of 6.0 and 17.2%, respectively (EPA 1982). Again, the precision at which the trans-isomer can be measured is questionable

No other standardized methods for the detection of 1,3-dichloropropene in environmental samples were located. However, a few methods have appeared in the available literature. Leiber and Berk (1984) outlined a method for determining 1,3-dichloropropene in ambient air. Tenax-GC sampling tubes are used for sample collection. Solvent desorption is accomplished with isoctane containing 4.0 µg/L of 1,3,5-tribromobenzene, followed by heat treatment at 90°C for 15 minutes; the mixture is then left to stand for 12 hours. After centrifugation, an aliquot of the resulting solution is injected onto the GC column. Sample analysis by capillary GC/ECD was validated for the range of 0.4-4.0 ppm, with a mean percent recovery of 100. Table 6-2 summarizes the methods for detecting cis- and trans-1,3-dichloropropene in environmental media.

TABLE 6-2. Analytical Methods for Determining 1,3-Dichloropropene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Adsorb (Tenax-GC); desorb (isooctane); inject aliquot	GC/ECD	2.3 mg/m ³	98	Leiber and Berk 1984
Water	Purge and trap	GC/FID GC/MS (EPA CLP Method)	5 ppb	No data	EPA 1988
Water	Purge and trap	GC/MS (EPA Method 8010)	0.34 ppb	22-178	EPA 1986a
Wastewater	Purge and trap	GC/MS (EPA Method 601)	0.20 ppb 0.34 ppb	86.7(cis) 73.5(trans)	EPA 1982
Soil	Add water, heat to 40°, purge and trap, thermal desorption	GC/FID GC/MS (EPA CLP Method)	5 ppb	No data	EPA 1988
Sediment	Add water, heat to 40°, purge and trap, thermal desorption	GC/FID GC/MS (EPA CLP Method)	10 ppb	No data	EPA 1988

ECD = electron capture detector
 FID = flame ionization detector
 GC = gas chromatography
 MS = mass spectrometry

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6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA as amended directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,3-dichloropropene is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,3-dichloropropene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Data Needs

Methods for Determining Biomarkers of Exposure and Effect. There are no known biomarkers of exposure that are unique to 1,3-dichloropropene. Therefore, standardized analytical methods for their determination are not warranted.

There are no known biomarkers of effect that are unique to 1,3-dichloropropene. Therefore, standardized analytical methods for their determination are not warranted.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining of 1,3-dichloropropene in environmental matrices have appeared in the literature. Of these, standardized methods exist only for the analysis of surface water, soil, or sediment samples (EPA 1982, 1986a, 1988). For sediments and soils, the levels of accuracy have not been reported. Both the accuracy and precision at which the trans-isomer can be measured in water is questionable. Therefore, refinement of the current procedures and establishing standardized methods for analyzing other media such as air will aid in determining levels of human exposure to 1,3-dichloropropene.

A limited number of methods is available to determine 1,3-dichloropropene in biological materials (Daft 1989; Kastl and Hermann 1983) and none of the methods have been standardized. The establishment of standardized methods for determining of 1,3-dichloropropene in biological materials, together with methods that are unique to 1,3-dichloropropene exposure, would be helpful in determining the levels of and exposure to the general population.

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6.3.2 On-going Studies

The Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of 1,3-dichloropropene and other volatile organic compounds in blood. These methods use purge and trap methodology and magnetic mass spectrometry which gives detection limits in the low parts per trillion range.

Other on-going studies developing new analytical methods for determining 1,3-dichloropropene in environmental matrices and/or biological materials were not located.

7. REGULATIONS AND ADVISORIES

International, national, and state regulations and guidelines pertinent to human exposure to 1,3-dichloropropene are summarized in Table 7-1.

1,3-Dichloropropene is regulated by the Clean Water Effluent Guidelines for the following industrial point sources: electroplating, organic chemicals production, steam electricity power generation, asbestos product manufacturing, timber products processing, metal finishing, paving, roofing, paint formulating, ink formulating, gum and wood chemicals manufacturing, and carbon black manufacturing (EPA 1988).

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to 1,3-Dichloropropene

Agency	Description	Information	References
<u>INTERNATIONAL</u>			
IARC	Carcinogen classification	Group 2B ^a	IARC 1987
<u>NATIONAL</u>			
Regulations:			
a. Air:			
OSHA	PEL TWA (skin)	1 ppm ^b	OSHA 1989 (29 CFR 1910)
b. Water:			
EPA OWRS	Groundwater monitoring requirements	Yes	EPA 1987a (40 CFR 264)
c. Other:			
EPA OTS	Toxic chemical release reporting: community right-to-know (proposed)	Yes	EPA 1987b (40 CFR 372.45)
EPA OERR	RQ 100 lbs	EPA 1986b	(40 CFR 302.4)
Guidelines:			
a. Air:			
ACGIH	TWA-TLV	1 ppm	ACGIH 1989
EPA	RfC (inhalation)	0.02 mg/m ³	IRIS 1991
b. Water:			
EPA OWRS	Ambient water quality criteria for protection of human health	87 ng/L ^c 14.1 mg/L ^d	EPA 1980
c. Other:			
EPA	RfD (oral) Carcinogen classification	0.0003 mg/kg/day Group B2 ^e	IRIS 1991
<u>STATE</u>			
Regulations and Guidelines:			
a. Air:			
Connecticut	Acceptable ambient air concentrations	100 ng/m ³	NATICH 1988
Kentucky	Acceptable ambient limits	10 mg/m ³	State of Kentucky 1986
North Dakota		0.05 mg/m ³	NATICH 1988
Nevada		0.009 mg/m ³	NATICH 1988
Virginia		80 mg/m ³	NATICH 1988
b. Water:			
Connecticut	Drinking water quality standards	10 g/L	FSTRAC 1988
Kansas		89 µg/L	
California	(New standard)	Yes	

^aGroup 2B: Possible human carcinogen^bBased on avoidance of kidney toxicity^cIngesting water and contaminated aquatic organisms^dIngesting contaminated aquatic organisms^eGroup B2: Probable human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; RfC = Reference Concentration; RfD = Reference dose; RQ = Reportable Quantity; TLV = Threshold Limit Value; TWA = Time-weighted Average

8. REFERENCES

*ACGIH. 1989. Threshold limit values and biological exposure indices for 1989-1990. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

Albrecht WN. 1987. Toxicology and hazard assessment of 1,3-dichloropropene (11). Arch Environ Health 42:292-296.

*Albrecht W. 1987. Occupational exposure to 1,3-dichloropropene (Telone II') in Hawaiian pineapple culture. Arch Environ Health 42:236-291.

*Albrecht WN, Chenchin K. 1985. Dissipation of 1,2-Dibromo-3-chloropropane (DBCP), cis-1,3-dichloroprop (1,3-DCP), and dichloropropenes from soil to atmosphere. Bull Environ Contam Toxicol 34:824-831.

*Albrecht WN, Hagadone MR, Chenchin K. 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.

*Atkinson R, Darnall KR, Lloyd AC, 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.

*Barnes D, Bellen J, DeRosa C, et al. 1988. Reference dose (RfD): Description and use in health risk assessments. Volume I, Appendix A: Integrated risk information system supportive documentation. Washington, DC: US Environmental Protection Agency, Office of Health and Environmental Assessment. EPA/600/8-86/032a.

*Bean RM, Thomas BL, Neitzel DA. 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.

*Belser NO, Castro CE. 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.

*Breslin W, Kirk H, Streeter C, et al. 1989. 1,3-Dichloropropene: Twogeneration inhalation reproduction study in Fischer 344 rats. Fundam Appl Toxicol 12:129-143. .

*Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. Washington, DC: The C.V. Mosby Company, 53, 155-156.

* Cited in text

8. REFERENCES

- *Carreon R, Wall J. 1983. Telone II®: Skin sensitization potential in the guinea pig. Dow Chemical Company, Midland, Michigan.
- *Castro CE, Belser NO. 1966. Hydrolysis of cis- and trans-1,3-dichloropropene in wet soil. J Agric Food Chem 14:69-70.
- *Castro CE, Belser NO. 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.
- *Chemline. 1989. National Library of Medicine Chemline Database. July 8, 1989.
- *Climie I, Hutson D, Morrison B, et al. 1979. Glutathione conjugation in the detoxication of (Z)-1,3-dichloropropene (a component of the nematocide DD') in the rat. Xenobiotica 9:149-156.
- *CLOGP-PCGEMS. 1987. PCGEMS Graphical Exposure Modeling System. U.S. Environmental Protection Agency, Washington, DC.
- *Coate W. 1979a. Addendum to final report on the go-day inhalation toxicity study in rats and mice - Telone II". Hazleton Laboratories: Vienna, Virginia, for Dow Chemical Company, Midland, Michigan.
- *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.
- *Cohan DB, Gilmore D, Fisher C, et al. 1983. 1,3-Dichloropropene (1,2-D)-1,3-dichloropropene (1,3-D). California State Water Resources Control Board.
- *Cohen DB. 1986. Groundwater contamination by toxic substances. A California assessment. In: American Chemical Society Symposium Series 315, 499-529.
- *Cracknell S, Jackson G, Hardy C. 1987. Telone II® (1,3-dichloropropene) - Acute inhalation study in rats - 0-hour exposure. Huntingdon Research Centre: Cambridgeshire, England, for Dow Chemical Europe, Horgen, Switzerland.
- *Greedy C, Brooks T, Dean B, 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.
- *Daft JL. 1989. Determination of fumigants and related chemicals in fatty and non-fatty foods. J Agric Food Chem 37:560-564.

8. REFERENCES

- *De Lorenzo F, Degl'innocenti S, Ruocco A, et al. 1977. Pesticides containing 1,3-dichloropropene. *Mutagenicity of Cancer Res* 37:1915-1917.
- *Dietz F, Dittenber D, Kastl P. 1982. 1,3-Dichloropropene: Effects on tissue non-protein sulfhydryl content and blood concentration time profileprobe study. Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Company, Midland, MI.
- *Dietz F, Hermann E, Kastl P, 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. Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Company, Midland, MI.
- *Dilling WL. 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.
- *Dowty BJ, Carlisle DR, Laseter JL. 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.
- *Dowty B, Carlisle D, Laseter J, et al. 1975b. Halogenated hydrocarbons in New Orleans drinking water and blood plasma. *Science* 187:75-77.
- *Eder E, Henschler D, Neudecker T. 1982a. Mutagenic properties of allylic and α,β -unsaturated compounds: Consideration of alkylating mechanisms. *Xenobiotica* 12:831-848.
- *Eder E, Neudecker T, Lutz D, et al. 1982b. Correlation of alkylating and mutagenic activities of allyl and allylic compounds: Standard alkylation test vs. kinetic investigation. *Chem Biol Interact* 38:303-315.
- *Eder E, Dornbusch K, Fischer G. 1987. The role of biotransformation in the genotoxicity of allylic compounds. *Arch Toxicol* 60:182-186.
- *Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. *Environ Sci Technol* 15:30-38.
- *EPA. 1980. Water quality criteria documents; availability. *Federal Register* 45:79333.
- *EPA. 1981. Treatability manual. Washington, DC: Office of Research and Development, U.S. Environmental Protection Agency, 1.12.14-1 to 1.12.14-5

8. REFERENCES

- *EPA. 1982. Test methods. Methods for organic chemical analysis of municipal and industrial wastewater: Test method purgeable halocarbons-method 601. Environmental Monitoring and Support Laboratory, Cincinnati, OH. EPA 600/42-82-057
- EPA. 1983. Reportable quantity document for 1,3-dichloropropene. Prepared for Office of Solid Waste and Emergency Response by Environmental Criteria and Assessment Office, Cincinnati OH.
- EPA. 1985. Health and environmental effects profile for 1,3-dichloropropene. Prepared for Office of Solid Waste and Emergency Response by Environmental Criteria and Assessment Office, Cincinnati, OH.
- *EPA. 1986a. 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, Washington, DC. 8010-1 to 8010-13.
- *EPA. 1986b. Superfund programs; reportable quantity adjustments; final rule. Federal Register 51:34542.
- *EPA. 1987a. List (phase 1) of hazardous constituents for ground-water monitoring; final rule. Federal Register 52:25949.
- *EPA. 1987b. Toxic chemical release reporting; community right-to-know; proposed rule. Federal Register 52:21170.
- *EPA. 1988. Contract laboratory program statement of work for organic analysis, multi-media, multi-concentration. Methods for determining volatile organics. U.S. Environmental Protection Agency, Washington, DC.
- *EPA. 1989. Interim methods for development of inhalation reference doses. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. Washington, DC. EPA 600/8-88-066F.
- EPA. 1989. Health and environmental effects document for 1,3-dichloropropene. Prepared for Office of Solid Waste and Emergency Response by Environmental Criteria and Assessment Office, Cincinnati, OH.
- *Federal Research in Progress. 1988. Federal Research in Progress Database. December 13, 1988.
- .
- *Fisher G, Kilgore W. 1988a. Tissue levels of glutathione following acute inhalation of 1,3-dichloropropene. J Toxicol Environ Health 23:171-182.
- *Fisher G, Kilgore W. 1988b. Mercapturic acid excretion by rats following inhalation exposure to 1,3-dichloropropene. Fundam Appl Toxicol 11:300-307.

8. REFERENCES

- *Fisher G, Kilgore W. 1989. Pharmacokinetics of S-[3-chloroprop-2-enyl] glutathione in rats following acute inhalation exposure to 1,3-dichloropropene. *Xenobiotica* 19:269-278.
- *Flessel P, Goldsmith J, Kahn E, et al. 1978. Acute and possible long-term effects of 1,3-dichloropropene--California. *Morbidity and Mortal Weekly Report* 27:5-55.
- *FSTRAC. 1988. Summary of state and federal drinking water standards and guidelines. Prepared by Chemical Communication Subcommittee, Federal-State Toxicology and Regulatory Alliance Committee (FSTRAC).
- *Hanley T Jr., John-Greene J, Young J, et al. 1987. Evaluation of the effects of inhalation exposure to 1,3-dichloropropene on fetal development in rats and rabbits. *Fundam Appl Toxicol* 8:562-570.
- *Hauser TR, Bromberg SM. 1982. EPA's monitoring program at Love Canal 1980. *Environ Monit Assess* 2:249-272.
- *Haworth S, Lawlor T, Mortelmans K, et al. 1983. Salmonella mutagenicity test results for 250 chemicals. *Environ Mutagen Suppl* 1:3-142.
- *HSDB. 1990. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. January 8, 1990.
- *Hutson D, Moss J, Pickering B. 1971. of the soil fumigant DD®
Excretion and retention of components and their metabolites in the rat. *Food Cosmet Toxicol* 9:677.
- *IARC. 1986. IARC monographs of the evaluation of the carcinogenic risk of chemicals to humans. Vol. 41: 1,3-Dichloropropene. World Health Organization, Lyon, France.
- *IARC. 1987. IARC monographs on the evaluation of carcinogenic risks to humans. Volumes 1-42, Supplement 7. Lyon, France.
- *IRIS. 1991. Integrated Risk Information System. Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.
- *Jeffrey M. 1987a. Telone II® soil fumigant: Dermal sensitization potential in the Hartley albino guinea pig. Dow Chemical Company, Midland, Michigan.
- *Jeffrey M. 1987b. Telone II® soil fumigant: Primary eye irritation study in New Zealand white rabbits. Dow Chemical Company, Midland, Michigan.
- *Jeffrey M. 1987c. Telone II® soil fumigant: Primary dermal irritation study in New Zealand white rabbits. Dow Chemical Company, Midland, Michigan.

8. REFERENCES

- *Jeffrey M, Schuetz D, Lomax L. 1987. Telone II® soil fumigant: Acute dermal toxicity study in New Zealand white rabbits. Dow Chemical Company, Midland, Michigan.
- *Jones JR. 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. [Unpublished study to be peer reviewed].
- *Jones JR. 1988b. 1,3-Dichloropropene cis-isomer: Acute dermal toxicity test in the rat. Project Number 44/247. Performed by Safepharm Laboratories Limited, Derby, U.K., for Dow Chemical Company Limited, Oxfordshire, U.K. [Unpublished study to be peer review].
- *Jones JR. 1988c. 1,3-Dichloropropene cis-isomer: Modified nine-induction Buehler contact sensitization study in the guinea pig. Project Number 44/249. Performed by Safepharm Laboratories Limited, Derby, U.K., for Dow Chemical Company Limited, Oxfordshire, U.K. [Unpublished study to be peer review].
- *Jones J, Collier T. 1986a. Telone II®: OECD 401 acute oral toxicity test in the rat. Safepharm Laboratories Limited: Derby, U.K., for Dow Chemical Europe, Horgen, Switzerland.
- *Jones J, Collier T. 1986b. Telone II®: OECD 401 acute dermal toxicity test in the rat. Safepharm Laboratories Limited: Derby, U.K., for Dow Chemical Europe, Horgen, Switzerland.
- *Kastl PE, Hermann EA. 1983. Determination of cis- and trans-1,3-dichloropropene in whole rat blood by gas chromatography and gas chromatography - chemical ionization mass spectrometry with selected-ion monitoring. J Chromatogr 265:277-283.
- *Kenaga EE. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol Environ Safety 4:26-38.
- *Kloes P, Calhoun L, Young J, et al. 1983. Telone II®: Inhalation teratology probe study in Fischer 344 rats and New Zealand white rabbits. Dow Chemical Company, Midland, Michigan.
- *Krijgsheld KR, Van der Gen A. 1986. Assessment of the impact of the emission of certain organochlorine compounds on the aquatic environment. Part II: Allylchloride, 1,3- and 2,3-dichloropropene. Chemosphere 15:861-880.
- *Lao RC, Thomas RS, Bastien P, 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, 107-118.

8. REFERENCES

- *Leiber MA, Berk HC. 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-1-01 and 1,1,2,2,3-pentachloropropane. Anal Chem 56:2134-2137.
- *Leistra M. 1970. Distribution of 1,3-dichloropropene over the phases in soil. J. Agric Food Chem 18:1124
- *Lichy C, Olson K. 1975. Acute toxicological properties of experimental nematicide formulation M-3993 containing 1,3-dichloropropene. Dow Chemical Company, Midland, Michigan.
- *Linnett S, Clark D, Blair D, et al. 1988. Effects of subchronic inhalation of DD' (1,3-dichloropropene/1,2-dichloropropane) on reproduction in male and female rats. Fundam Appl Toxicol 10:214-223.
- *Lomax L, Stott W, Johnson K, 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.
- *Loveday, KS, Lugo MH, Resnick MA, et al. 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.
- *Lyman WJ. 1982. Adsorption coefficient for soils and sediments. In: Lyman WJ, Reehl WF, Rosenblatt EH, Ed. Handbook of chemical property estimation methods. (Chapter 4). New York, NY: McGraw Hill Book Co.
- *Mabey WR, Smith JH, Pod011 RT, et al. 1981. Aquatic fate process data for organic priority pollutants. U.S. Environmental Protection Agency, Washington, DC. EPA 440/4-81-014.
- *Maddy KT, Busick B, Richmond D. 1980. applications of Telonee Studies concerning the field and DD® in California in 1979 and the ambient air concentrations of these pesticides during the following application by shank injection into soil in fields. HS-686. Sacramento, CA: California Department of Food and Agriculture, Division of Pest Management, Environmental Protection and Worker Safety. (cited in Albrecht 1987).
- *Maddy KT, Schnieder F, Frederickson S. 1982a. 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).

8. REFERENCES

- *Maddy KT, Fong HR, Howe JA. 1982b. A study of well water in selected California communities for residues of 1,3-dichloropropene, chloroallyl alcohol and 49 organophosphate or chlorinated hydrocarbon pesticides. Bull Environ Contam Toxicol 29:354-359.
- *Markovitz A, Crosby WH. 1984. Chemical carcinogenesis. A soil fumigant, 1,3-dichloropropene, as possible cause of hematologic malignancies. Arch Intern Med 144:1409-1411.
- *Mazurek MA, Simoneit BRT. 1986. Organic components in bulk and wet-only precipitation. CRC Crit Rev Environ Control 16:140.
- *Mizell M. 1988a. Telone C-17® soil fungicide and nematicide: Primary dermal irritation study in New Zealand white rabbits. Dow Chemical Company, Midland, Michigan.
- *Mizell M. 1988b. Telone C-17® soil fungicide and nematicide: Dermal sensitization potential in the Hartley albino guinea pig. Dow Chemical Company, Midland, Michigan.
- *Mizell M, Yano BL, Battjes JE. 1988a. Telone C-17® soil fungicide and nematicide: Acute oral toxicity study in Fischer 344 rats. Dow Chemical Company, Midland, MI.
- *Mizell M, Johnson K, Battjes J. 1988b. Telone C-17® soil fungicide and nematicide: Acute dermal toxicity study in New Zealand white rabbits. Dow Chemical Company, Midland, Michigan.
- *Merrill LG, Reed LW, Chinn KSK. 1985. Toxic chemicals in the soil environment. Vol. 2: Interactions of some toxic chemicals/chemical warfare agents and soils. Defense Technical Information Center Dugway Proving Ground, Utah. NTIS AD-A158 215.
- *Munnecke DE, Vangundy SD. 1979. Movement of fumigants in soil, dosage, responses, and differential effects. Ann Rev Phytopathol 17:405-429.
- *Nater JP, Gooskens VHJ. 1976. Occupational dermatosis due to a soil fumigant. Contact Dermatitis 2:227-229.
- *NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.
- *NATICH. 1988. National Air Toxics Information Clearinghouse. NATICH Data Base Report on State, Local and EPA Air Toxics Activities. Office of Air Quality Planning and Standards. Environmental Protection Agency. Research Triangle Park, NC.

8. REFERENCES

- *Neudecker T, Henschler D. 1986. Mutagenicity of chloroolefins in the Salmonella/mammalian microsomes 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.
- *Neudecker T, Stefani A, Henschler D. 1977. In vitro mutagenicity of the soil nematicide 1,3-dichloropropene. *Experientia* 33:1084-1085.
- *NIOSH. 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.
- *NTP. 1985. Toxicology and carcinogenesis studies of Telone II® (technical grade 1,3-dichloropropene [Cas No. 542-75-61 containing 1.0% epichlorohydrin as a stabilizer]) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program Technical Report Series 269:1-159.
- *NTP. 1989. Fifth annual report on carcinogens summary. NTP 89-239. U.S. Department of Health and Human Services. Prepared for the National Institute of Environmental Health Sciences, Research Triangle Park, NC by Technical Resources, Inc., Rockville, MD. 114-115, 139-141.
- *OHM/TADS. 1989. Oil and Hazardous Materials Technical Assistance Data System. December 12, 1989
- *OSHA. 1989. Air Contaminants. Final Rule. U.S. Department of Labor, Occupational Safety and Health Administration. Federal Register 54:2933.
- *Osterloh J, Letz G, Pond S, et al. 1983. An assessment of the potential testicular toxicity of 10 pesticides using the mouse-sperm morphology assay. *Mutat Res* 116:407-415.
- *Osterloh JD, Cohen B-S, Popendorf W, 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.
- *Osterloh JD, Wang R, Schneider F, et al. 1989a. Biological monitoring of dichloropropene: Air concentrations, urinary metabolite, and renal enzyme excretion. *Arch Environ Health* 44:207-213.
- *Osterloh JD, Wang R, O'Connell L, et al. 1989b. Pilot study for biological monitoring of 1,3-dichloropropene. In: American Chemical Society Symposium Series 382, 218-230.
- *Otson R. 1987. Purgeable organics in Great Lakes raw and treated water. *Int J Environ Anal Chem* 31:41-53.

8. REFERENCES

- *Parker C, Coate W, Voelker R. 1982. Subchronic inhalation toxicity of 1,3-dichloropropene/1,2-dichloropropane (DD®) in mice and rats. *J Toxicol Environ Health* 9:899-910.
- *Pellizzari ED, Hartwell TD, Harris BSH, et al. 1982. Purgeable organic compounds in mothers milk. *Bull Environ Contam Toxicol* 28:322-328.
- *Rawlings GD, Samfield M. 1979. Toxicity of secondary effluents from textile plants. U.S. Environmental Protection Agency, Washington, DC. EPA 600/7-78-168.
- *Roberts TR, Stoydin G. 1976. The degradation of (Z)- and (E)-1,3-dichloropropenes and 1,2-dichloropropane in soil. *Pestic Science* 7:325-335.
- *Rogers SE, Peterson DL, Lauer WC. 1987. Organic contaminants removal for potable reuse. *J Water Pollut Control Fed* 59:722-732.
- *Sahel GV, Clark TP. 1984. Volatile organic compounds as indicators of municipal solid waste leach contamination. *Waste Management Res* 2:119-130.
- *SANSS . 1989. Structure and Nomenclature Search System.
- Sasaki YFX, Imanishi H, Matsumoto K, et al. 1988. 1,3-Dichloropropene: In vitro cytogenetics test. IET 88-0038. Prepared by Dow Chemical Japan Limited and Shell Kagaku K.K., by the Institute of Environmental Toxicology, Tokyo, Japan. [Unpublished study to be peer reviewed].
- *Sax NI, Lewis RJ. 1987. *Hawley's condensed chemical dictionary*. 11th ed. New York, NY: Van Nostrand Reinhold Co.
- *Schenker M, McCurdy S. 1986. Pesticides, viruses and sunlight in the etiology of cancer among agricultural workers. In: Becker CE, Coye MJ, Ed. *Cancer prevention: Strategies in the workplace*. Washington, DC: Hemisphere Publishing Corporation, 29-37.
- *Schiffmann D, Eder E, Neudecker T, et al. 1983. Induction of unscheduled DNA synthesis in HeLa cells by allylic compounds. *Cancer Lett* 20:263-269.
- *Shah JJ, Heyerdahl EK. 1989. National ambient volatile organic compound data base update. Nero and Associates. EPA 600/3-88/010(a).
- *Snider EH, Manning FS. 1982. A survey of pollutant emission levels in waste waters and residuals from the petroleum refining industry. *Environ Int* 7:237-258.
- *SRI. 1989. 1989 Directory of chemical producers. Menlo Park, CA: Stanford Research Institute, International.

8. REFERENCES

- *State of Kentucky. 1986. New or modified sources emitting toxic air pollutants. 401 KAR 63:022.
- *Sterrett RJ, Ransom ME, Barnhill GD. 1986. Site assessment and on-site treatment of a pesticide spill in the vadose zone. In: Proceedings of the Conference on Hazardous Material Spills, Preparedness, Prevention, Control, and Cleanup of Releases, Association of American Railroads, United States Coast Guard.
- *Stolzenberg SJ, Hine CH. 1980. Mutagenicity of 2- and 3-carbon halogenated compounds in the Salmonella/mammalian-microsome test. Environ Mutagen 2:59-66.
- *STORET. 1989. Database. December 19, 1989.
- *Stott W, Kastl P. 1986. Inhalation pharmacokinetics of technical grade 1,3-dichloropropene in rats. Toxicol Appl Pharmacol 85:332-341.
- *Stott W, Young J, Calhoun L, et al. 1988. Subchronic toxicity of inhaled technical grade 1,3-dichloropropene in rats and mice. Fundam Appl Toxicol 11:207-220.
- *Streeter C, Lomax L. 1988. Telone C-17® soil fungicide and nematocide: A one-hour acute vapor inhalation study in Fischer 344 rats. Dow Chemical Company, Midland, Michigan.
- *Streeter C, Battjes J, Lomax L. 1987. Telone II® soil fumigant: An acute vapor inhalation study in Fischer 344 rats. Dow Chemical Company, Midland, Michigan.
- *Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, v, 300-301.
- *Swarm RL, Laskowski DA, McCall PJ, et al. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio and water solubility. Research Review 85:17-28.
- *Tabak HH, Quave SA, Mashni CI, et al. 1981a. Biodegradability studies with organic priority pollutant compounds. J Water Pollut Control Fed 53:1503-1518.
- *Tabak HH, Quave SA, Mashni CI, 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, 267-328.

8. REFERENCES

- *Talcott R, King J. 1984. Mutagenic impurities in 1,3-dichloropropene preparations. *J Natl Cancer Inst* 72:1113-1116.
- *Thomas RG. 1982. Volatilization from water. In: Lyman WJ, Reehl WF, Rosenblatt DH, Ed. (Chapter 15). New York, NY: McGraw Hill Book Co.
- *Thomas IJ and McKenry MV. 1974. Part I: Movement and fate as affected by various conditions in several soils. *Hilgardia* 42:393-421.
- *Til H, Spanjers T, Feron V, et al. 1973. Sub-chronic (go-day) toxicity study with Telonee in albino rats (final report). Central Institute for Nutrition and Food Research: The Netherlands, for Dow Chemical Company, Norfolk, England.
- *Torkelson TR, Oyen F. 1977. The toxicity of 1,3-dichloropropene as determined by repeated exposure of laboratory animals. *Am Ind Hyg Assoc J* 38:217-223.
- *Tu CM. 1988. Effects of selected pesticides on activities of invertase, amylase and microbial respiration in sandy soil. *Chemosphere* 17:159-163.
- *Tuazon EC, Atkinson R, Winer AM, 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.
- *USITC. 1989. Synthetic organic chemicals, United States production and sales, 1988. USITC Publication #2219. Washington, DC: United States International Trade Commission, 3-2 and 3-13.
- *Valencia R, Mason J, Woodruff R, 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.
- *Van der Pas LJT, Leistra M. 1987. Movement and transformation of 1,3-dichloropropene in the soil of flower-bulb fields. *Arch Environ Contam Toxicol* 16:417-422.
- *Van Duuren B, Goldschmidt B, Loewengart G, et al. 1979. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. *J Natl Cancer Inst* 63:1433.
- *Van Joost T, de Jong G. 1988. Sensitization to DD soil fumigant during manufacture. *Contact Dermatitis* 18(5):307-308.
- *Verschueren K. 1983. Handbook of environmental data on organic chemicals. 2nd ed. New York, NY: Van Nostrand Reinhold Company, 507-508.

8. REFERENCES

- *View Database. 1989. Agency for Toxic Substances and Disease Registry (ATSDR), Office of External Affairs, Exposure and Disease Registry Branch, Atlanta, GA.
- *Vithayathil AJ, McClure C, Myers JW. 1983. Salmonella/microsome multiple indicator mutagenicity test. *Mutat Res* 121:33-37.
- *van der Hude W, Scheutwinkel M, Gramlich U, et al. 1987. Genotoxicity of three-carbon compounds evaluated in the SCE test in vitro. *Environ Mutagen* 9:401-410.
- *van der Hude W, Behm C, Guertler R, et al. 1988. Evaluation of the SOS chromatest. *Mutat Res* 203:81-94.
- *Waechter J, Kastl P. 1988. 1,3-Dichloropropene: Pharmacokinetics and metabolism in Fischer 344 rats following repeated oral administration. Dow Chemical Company, Midland, Michigan.
- *Wang GM. 1984. Decision making. *Reg Toxicol Pharmacol* 4:316-371.
- *Watson W, Brooks T, Huckle K, et al. 1987. Microbial mutagenicity studies with (Z)-1,3-dichloropropene. *Chem Biol Interact* 61(1):17-30.
- *Weast RC, Astle MJ, Beyer WH. 1988. CRC Handbook of chemistry and physics. 69th ed. Boca Raton, FL: CRC Press, Inc.
- *Windholz M, Budavari S, Blumetti RF, et al. 1983. The Merck index. Rahway, NJ: Merck and Co.
- *Yang R. 1986. 1,3-Dichloropropene. *Residue Rev* 97:19-35.
- *Yakel H, Kociba R. 1977. Acute inhalation toxicity of M-3993 (Telone II®) in rats. Dow Chemical Company, Midland, Michigan.

9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

9. GLOSSARY

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration_(LO) (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose (LD_(LO) (LD_{LO}) -- The lowest dose of a chemical introduced by a route animals. other than inhalation that is expected to have caused death in humans or

Lethal Dose₍₅₀₎ (LD₅₀) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

9. GLOSSARY

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1^* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu\text{g}/\text{L}$ for water, $\text{mg}/\text{kg}/\text{day}$ for food, and $\mu\text{g}/\text{m}^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

APPENDIX A**USER'S GUIDE****Chapter 1****Public Health Statement**

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2**Tables and Figures for Levels of Significant Exposure (LSE)**

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND**See LSE Table 2-1**

- (1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist,

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three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively); LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

- (2) Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.
- (3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.
- (4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-1).
- (5) Species The test species, whether animal or human, are identified in this column.
- (6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.
- (7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.
- (8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "c").
- (9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to

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quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

- (10) Reference The complete reference citation is given in Chapter 8 of the profile.
- (11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. GELS are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.
- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND**See LSE Figure 2-1**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

- (13) Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.
- (15) Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

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- 18). Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).
- 19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure ^a	Species	Exposure frequency/duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5 ↓	6 ↓	7 ↓	8 ↓	9 ↓		10 ↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3 ^b	10 (hyperplasia)		Nitschke et al. 1981

CHRONIC EXPOSURE							
Cancer							
38	Rat	18 mo 5d/wk 7hr/d				11 ↓ 20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

^a The number corresponds to entries in Figure 2-1.

12 → ^b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

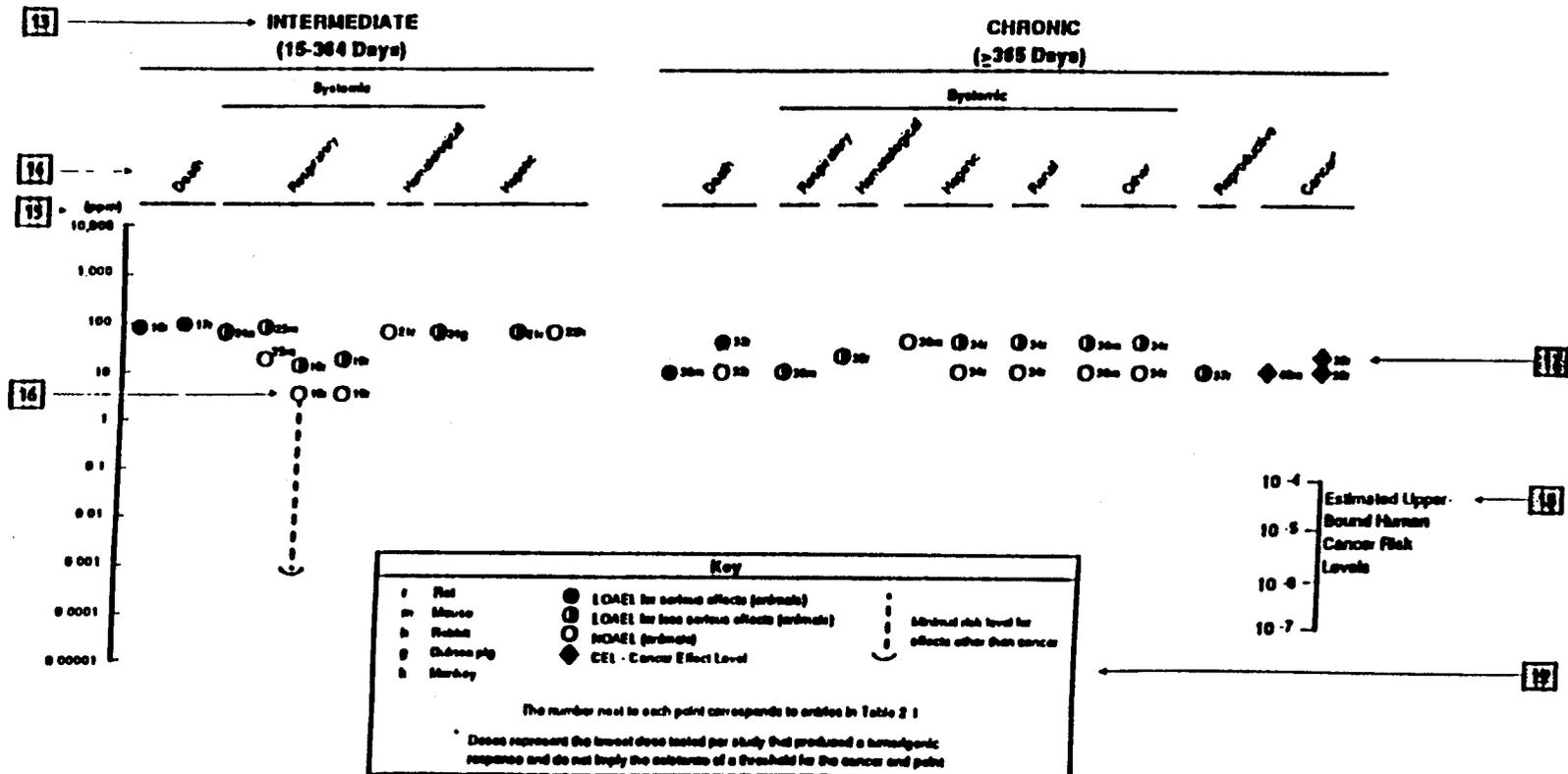


FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

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Chapter 2 (Section 2.4)**Relevance to Public Health**

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, -chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

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MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f ₁	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
K _d	adsorption ratio
kg	kilogram
K _{oc}	octanol-soil partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC _{Lo}	lethal concentration low
LC ₅₀	lethal concentration 50 percent kill
LD _{Lo}	lethal dose low
LD ₅₀	lethal dose 50 percent kill

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LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSH TIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	<u>STORAGE</u> and <u>RETRIEVAL</u>
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States

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UF	uncertainty factor
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram
μmol	micromole

APPENDIX C

PEER REVIEW

A peer review panel was assembled for 1,3-dichloropropene. The panel consisted of the following members: Dr. Nancy Tooney, Polytechnic University, Brooklyn, New York; Dr. Michael Norvell, Private Consultant, Ringoes, New Jersey; and Dr. Ronny Woodruff, Bowling Green State University, Bowling Green, Ohio. These experts collectively have knowledge of 1,3-dichloropropene's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Comprehensive Environmental Response, Compensation, and Liability Act of 1986, Section 104.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

