TOXICOLOGICAL PROFILE FOR
1,2,3-TRICHLOROPROPANE

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

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DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

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.

William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about 1,2,3-trichloropropane and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,300 National Priorities List (NPL) sites. 1,2,3-Trichloropropane has been found at 8 of these sites. However, we do not know how many of the 1,300 NPL sites have been evaluated for 1,2,3-trichloropropane. As EPA evaluates more sites, the number of sites at which 1,2,3-trichloropropane is found may change. The information is important for you because 1,2,3-trichloropropane may cause harmful health effects and because these sites are potential or actual sources of human exposure to 1,2,3-trichloropropane.

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 to it 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 1,2,3-trichloropropane, 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 1,2,3-TRICHLOROPROPANE?

1,2,3-Trichloropropane is a colorless, heavy liquid with a sweet but strong odor. It evaporates almost as fast as water does at normal temperatures. Small amounts of 1,2,3-trichloropropane will dissolve in water. 1,2,3-Trichloropropane can dissolve several substances, such as oils and waxes, the way water dissolves salt. For this reason, it has been and may continue to be used as an industrial solvent, paint remover, and cleaner. We do not know exactly how much of it is made or used now, but it may be a large amount. Most of the 1,2,3-trichloropropane is used to make other substances.

In sunlight, 1,2,3-trichloropropane in the air will break down. Most of the 1,2,3-trichloropropane that is released to the air will disappear in a month. In water, half of it will evaporate into the air within hours or several days. Very little of it will stick to the soil at the bottom of rivers, lakes, or ponds, and very little of it will be expected to concentrate in fish or other seafoods. 1,2,3-Trichloropropane will not stick to soil. If it is spilled onto most soils, some will evaporate and some will travel through the soil into the groundwater, where it may stay for a long time. It

may slowly change to a simpler form in water and soil by natural biological and chemical processes.

You will find more information on the properties of 1,2,3-trichloropropane in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO 1,2,3-TRICHLOROPROPANE?

If you live near a hazardous waste disposal site in which 1,2,3-trichloropropane is not stored properly, you could be exposed to 1,2,3-trichloropropane from breathing air or drinking water. Because 1,2,3-trichloropropane easily changes into a vapor, you are more likely to be exposed from breathing air than from drinking water. A child playing in this waste disposal site could be exposed by drinking liquids containing 1,2,3-trichloropropane, by eating soil coated with 1,2,3-trichloropropane, or getting this soil or liquid on his or her skin.

You could be exposed to 1,2,3-trichloropropane in other ways that have nothing to do with hazardous waste sites. For example, you may be exposed to higher levels of 1,2,3-trichloropropane if you are using paint- and varnish-removers that contain it; however, some of these products may no longer contain this chemical. If you breathe air near an accidental spill of 1,2,3-trichloropropane, you can be exposed to higher levels of the chemical. Exposure in the workplace may result from spills or other accidents or from normal operations in the workplace.

1,2,3-Trichloropropane is not common in the environment (air, water, and soil), but it has been found in a few rivers, bays, drinking water, groundwater, and hazardous waste sites at low levels. This is because 1,2,3-trichloropropane can enter the environment while it is being made, where it is used to make or to dissolve other substances, or where it is released in the waste that is made during these processes. Although 1,2,3-trichloropropane is usually not found in the environment, disposal at hazardous waste sites in the past, or release during spills and accidents have lead to higher levels in nearby water, soil, and groundwater. Although we do not know exactly how much 1,2,3-trichloropropane the general public or workers are exposed to, the information that we have shows that the levels are probably low and exposure probably does not occur often.

You can find more information in Chapter 5 on how much 1,2,3-trichloropropane is in the environment and how you can be exposed to it.

1.3 HOW CAN 1,2,3-TRICHLOROPROPANE ENTER AND LEAVE MY BODY?

If you were to drink water containing 1,2,3-trichloropropane, most of the chemical would pass into your body from your stomach and intestines within the same day. 1,2,3-trichloropropane would also pass into your body from your lungs if you were to breathe in air containing it or from your skin if you

were to touch it. However, we do not know how quickly or completely 1,2,3-trichloropropane passes into your body from your lungs or skin. 1,2,3-Trichloropropane that enters your body leaves your body almost completely within a few days in your breath, urine, and feces. More information on how 1,2,3-trichloropropane can enter and leave your body is presented in Chapter 2.

1.4 HOW CAN 1,2,3-TRICHLOROPROPANE AFFECT MY HEALTH?

Some people who breathed air containing high levels of 1,2,3-trichloropropane for several minutes had eye and throat irritation. These levels of 1,2,3-trichloropropane are ikely to be much higher than levels usually found in outdoor air, including air at hazardous waste sites. We do not know what effects might occur in people who breath 1,2,3-trichloropropane for days, weeks, or longer durations. We also do not know the possible effects of 1,2,3-trichloropropane in people who swallow 1,2,3-trichloropropane or get 1,2,3-trichloropropane on their skin.

Animals that breathed air containing 1,2,3-trichloropropane at levels higher than those usually found in the environment developed other health effects. Rats and mice died after they breathed air containing high levels of 1,2,3-trichloropropane for several hours, but we do not know the exact cause of death. These levels of 1,2,3-trichloropropane are several times higher than those that can cause eye and throat irritation in humans. Rats that breathed 1,2,3-trichloropropane for a few months at levels lower than those that affected humans developed eye, nose, and lung irritation and liver and kidney disease.

Rats and mice usually died from damage to the liver and kidney within a few days after they swallowed a large amount of 1,2,3-trichloropropane. Most rats and mice that swallowed small amounts of 1,2,3-trichloropropane every day for a few months also died from liver and kidney damage. Rats that swallowed even smaller amounts of 1,2,3-trichloropropane every day for a few months did not die but developed stomach irritation, blood disorders, and minor liver and kidney damage.

Rabbits had severe skin irritation and even injury to internal organs, including the liver, kidneys, and stomach after 1,2,3-trichloropropane was applied to their skin in large amounts for 1 day. These injuries can result in death. 1,2,3-Trichloropropane also caused eye irritation in rabbits and rats when it was applied to the eyes.

We have limited knowledge of the effects in animals exposed to very small amounts of 1,2,3-trichloropropane by breathing, swallowing, or skin contact for many months or years leads to serious disease or death. Rats that breathed low levels of 1,2,3-trichloropropane for several weeks or swallowed large amounts of 1,2,3-trichloropropane for a few days did not develop fertility problems, but we do not know whether breathing high levels of

1,2,3-trichloropropane or swallowing 1,2,3-trichloropropane for more than a few days affects fertility in animals. 1,2,3-Trichloropropane has not been found to cause birth defects when injected in rats. We do not know whether 1,2,3-trichloropropane causes cancer in humans, but animals that swallowed low doses of 1,2,3-trichloropropane for most of their lives developed cancer in a number of organs.

More information on how 1,2,3-trichloropropane can affect health can be found in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 1,2,3-TRICHLOROPROPANE?

Scientists can measure 1,2,3-trichloropropane in blood, urine, and breath, but there are no readily available tests to determine whether you have been exposed. We do not think these tests would be adequate to allow doctors to predict harmful health effects. More information about tests for exposure and effects can be found in Chapters 2 and 6.

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

The federal government has a rule designed to protect workers who may be exposed to 1,2,3-trichloropropane. The Occupational Safety and Health Administration (OSHA) states that workers may not be exposed to average levels of 1,2,3-trichloropropane greater than 10 ppm in air during an 8-hour workday. The federal government has no recommendations on environmental exposure to 1,2,3-trichloropropane. More information on regulations and advisories can be found in Chapter 7.

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 1,2,3-trichloropropane 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 1,2,3-trichloropropane based on toxicological studies and epidemiological investigations.

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 (more than 365 days).

Levels of significant exposure for each route and duration are presented in Tables 2-1, 2-2 and 2-3 and illustrated in Figures 2-1 and 2-2. The points in the figures showing no-observed-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 1989a), 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 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 1,2,3-trichloropropane.

Exposure to 1,2,3-trichloropropane of unknown purity for 4-6 hours caused death in mice at concentrations as low as 343 ppm (Gushow and Quast 1984) and rats at concentrations as low as 500 ppm (Union Carbide 1958). An intermediate-duration study showed that intermittent exposure to 297 ppm and higher concentrations of 1,2,3-trichloropropane for 4 weeks was lethal in rats (Johannsen et al. 1988). The available data suggest that 1,2,3-trichloropropane concentrations producing death in rodents may be similar (i.e., approximately 300 ppm) for acute- and intermediate-duration exposures of several weeks. The cause of death is unclear, but signs suggestive of central nervous system (CNS) impairment (e.g., incoordination and convulsions) have been observed prior to death in both species. The highest NOAEL values and all reliable LOAEL values for death in both species and duration categories are recorded in Table 2-l and plotted in Figure 2-1.

2.2.1.2 Systemic Effects ,

Systemic effects of inhaled 1,2,3-trichloropropane are discussed below. The highest NOAEL values and all reliable LOAEL values for these effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-l.

Respiratory Effects. Limited information indicates that brief exposure (15 minutes) to 100 ppm 1,2,3-trichloropropane (purity unknown) can cause throat irritation in humans (Silverman et al. 1946).

Repeated exposure of animals to 1,2,3-trichloropropane concentrations much lower than 100 ppm causes respiratory system effects that are indicative of irritant action. Intermittent 4-hour exposures for 11 days produced alterations in nasal tissues of rats and mice, particularly of the olfactory epithelium (Miller et al. 1986a, 1986b). These changes included decreased thickness of the olfactory epithelium in rats at 3 ppm, degeneration of the

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

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 d 4 hr/d		343		697	Gushow and Quast 1984
2	Rat	1 d 4 hr/d				1,000	Smyth et al. 1962
3	Rat	1 d 1-4 hr/d				500	Union Carbide 1958
4	Rat	1 d 6 hr/d				888	Johannsen et al. 1988
5	Mouse	1 d 4 hr/d		126		343	Gushow and Quast 1984
Systemic							
6	Human	1 d 15 min/d	Resp Derm/oc		100 (throat irritation) 100 (eye irritation)		Silverman et al. 1946
7	Rat	1 d 4 hr/d	Derm/oc		126 (eye irritation)		Gushow and Quast 1984
8	Rat	11 d 5 d/wk 6 hr/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Other	 132 132 132 132 40 132 132	13 (nasal olfactory degeneration) 132 (increased liver weight)		Miller et al. 1986a
9	Rat	11 d 5 d/wk 6 hr/d	Resp	1[b]	3 (decreased thickness of olfactory epithelium)		Miller et al. 1986b

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
10	Mouse	11 d 5 d/wk 6 hr/d	Resp		13 (decreased thickness of olfactory epithelium)		Miller et al. 1986a
			Cardio	132			
			Gastro	132			
			Hemato	132			
			Musc/skel	132			
			Hepatic	40	132 (increased liver weight)		
			Renal	132			
			Other	132			
11	Mouse	1 d 4 hr/d	Derm/oc		126 (eye irritation)		Gushow and Quast 1984
12	Mouse	11 d 5 d/wk 6 hr/d	Resp	3	10 (nasal olfactory inflammation)		Miller et al. 1986b
INTERMEDIATE EXPOSURE							
Death							
13	Rat	4 wk 5 d/wk 6 hr/d		95		297	Johannsen et al. 1988
Systemic							
14	Rat	13 wk 5 d/wk 6 hr/d	Resp	1.54	4.5 (peribronchial hyperplasia)		Johannsen et al. 1988
			Cardio	49			
			Gastro	49			
			Hemato	49			
			Musc/skel	49			
			Hepatic	1.54	4.5 (increased liver weight)		
			Renal	15	49 (increased kidney		

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
15	Rat	4 wk 5 d/wk 6 hr/d	Hepatic		95 (increased liver weight)		Johannsen et al. 1988
			Renal		297 (increased kidney weight)		
			Other		297 (decreased weight gain)		
Reproductive							
16	Rat	Premating: 10 wk, 5 d/wk, 6 hr/d Mating: 30-40 d, 5 d/wk, 6 hr/d Gestation: 6 hr/d, gd 0-14		15			Johannsen et al. 1988

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an acute inhalation Minimal Risk Level (MRL) of 0.0003 ppm; dose adjusted for intermittent exposure, converted to an equivalent concentration in humans, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

Cardio = cardiovascular; d = day; Derm/oc = dermal/ocular; Gastro = gastrointestinal; gestat = gestation; gd = gestation day; Hemato = hematological; hr = hour; LOAEL = lowest-observed-adverse-effect level; min = minute; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week

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

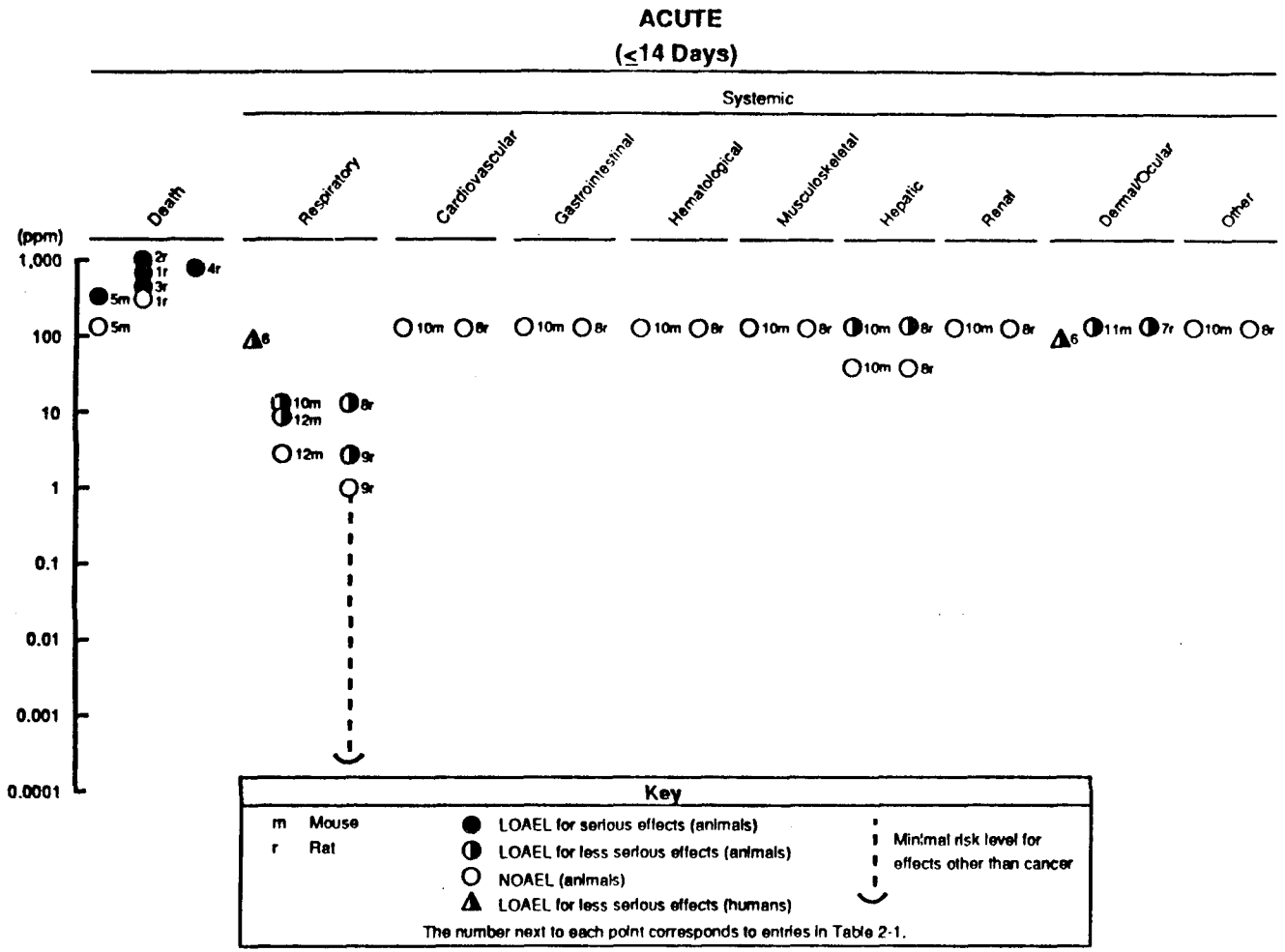
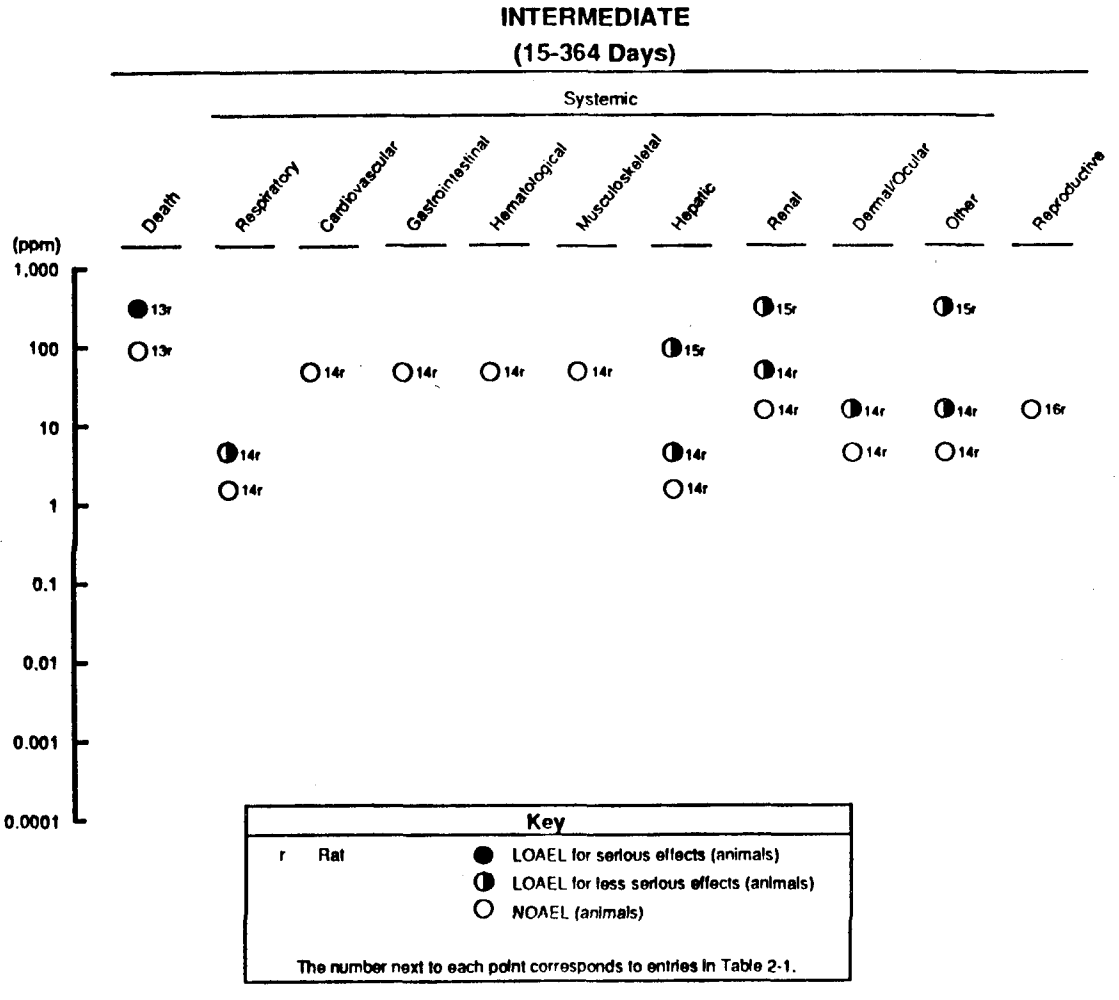


FIGURE 2-1 (Continued)



olfactory epithelium in rats at 10 ppm and higher concentrations, and inflammation and decreased thickness of the olfactory epithelium in mice at lo-13 ppm with degeneration at higher concentrations. Based on the NOAEL of 1 ppm for these effects in rats, an acute inhalation MEL of 0.0003 ppm was calculated as described in the footnote in Table 2-l. Intermittent exposure to slightly higher concentrations of 1,2,3-trichloropropane (4.5 ppm) or more for 13 weeks caused focal peribronchial hyperplasia in rats (Johannsen et al. 1988). Intermittent exposure to 132 ppm for 11 days caused nasal submucosal fibrosis in rats (Miller et al. 1986a).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after inhalation exposure to 1,2,3-trichloropropane.

There were no histopathological changes in the hearts of rats and mice that were intermittently exposed to concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a) or rats that were similarly exposed to up to 49 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to 1,2,3-trichloropropane.

There were no histopathological changes in the stomach and intestines of rats and mice that were intermittently exposed to concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a) or rats that were similarly exposed to up to 49 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988).

Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to 1,2,3-trichloropropane.

Hematological evaluations were normal in rats and mice that were intermittently exposed to concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a). Hematological evaluations of rats that were similarly exposed to up to 49 ppm 1,2,3-trichloropropane for 13 weeks also were normal, but splenic hematopoiesis was increased at 4.5 ppm or more (Johannsen et al. 1988). Although increased splenic hematopoiesis was observed, other hematology parameters were unremarkable. Spleen weights were decreased in rats that were intermittently exposed to 579 ppm 1,2,3-trichloropropane for 4 weeks, but the hematological significance of this effect cannot be determined because evaluation of hematology and histology was not performed (Johannsen et al. 1988).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to 1,2,3-trichloropropane.

There were no histopathological changes in the skeletal muscle or bone of rats and mice that were intermittently exposed to concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a) or rats that were similarly exposed to up to 49 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988).

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to 1,2,3-trichloropropane.
Acute and intermediate duration inhalation exposure to 1,2,3-trichloropropane causes increased liver weight in rats and mice. Increased liver weight was produced by intermittent exposure to 132 ppm for 11 days (Miller et al. 1986a), 95 ppm or more for 4 weeks (Johannsen et al. 1988), and 4.5 ppm or more for 13 weeks (Johannsen et al. 1988). Mild hepatocellular hypertrophy occurred in most of the rats exposed to 4.5 ppm or more in the 13-weeks study. Although not accompanied by serious histological alterations, the increased liver weight may represent an adverse effect because oral exposure studies (see discussion of Hepatic Effects *in* Section 2.2.2.2) indicate that this effect is a manifestation of 1,2,3-trichloropropane-induced hepatotoxicity.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to 1,2,3-trichloropropane.

Intermittent exposure to 297 ppm or more 1,2,3-trichloropropane for 4 weeks and 49 ppm for 13 weeks caused increased kidney weights without histopathology in rats (Johannsen et al. 1988). As with liver weight changes, the increased kidney weight may represent an adverse effect because oral exposure studies indicate that the increased weight is a manifestation of 1,2,3-trichloropropane-induced nephrotoxicity (see discussion of Renal Effects in Section 2.2.2.2.).

Dermal/Ocular Effects. Limited information indicates that brief (15-minute) exposure to 100 ppm 1,2,3-trichloropropane vapor causes eye irritation in humans (Silverman et al. 1946).

A single 4-hour exposure to vapor concentrations as low as 126 ppm 1,2,3-trichloropropane (Gushow and Quast 1984) caused eye irritation in rats and mice. Repeated intermittent exposure to vapor concentrations as low as 15 ppm for 13 weeks (Johannsen et al. 1988) caused eye irritation in rats.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to 1,2,3-trichloropropane.

Intermittent exposure to 1,2,3-trichloropropane concentrations as high as 132 ppm for 11 days did not adversely affect body weight gain in rats or mice (Miller et al. 1986a). Body weight gain was decreased in rats that were intermittently exposed to lethal concentrations (297 ppm or more) of 1,2,3-trichloropropane for 4 weeks and concentrations as low as 15 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988). The decreased weight gain was more severe at higher concentrations and there was initial weight loss at 600 ppm in the 4-week study.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans after inhalation exposure to 1,2,3-trichloropropane.

There were no histopathological alterations in the thymus, spleen, lymphoid tissue, or bone marrow of rats and mice that were intermittently exposed to concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a) or rats that were similarly exposed to up to 49 ppm for 13 weeks (Johannsen et al. 1988). Intermittent exposure to a higher (lethal) concentration (579 ppm) for 4 weeks caused decreased spleen weight in rats (Johannsen et al. 1988). Due to the lack of histological examinations and immunoassays, the immunological significance of the decreased spleen weight cannot be determined.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to 1,2,3-trichloropropane.

No histopathological effects were observed in the brain, spinal cord, and peripheral nerves of rats and mice that were intermittently exposed to concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a). No effect was observed on brain and spinal cord histology and brain weight in rats that were intermittently exposed to up to 49 ppm for 13 weeks (Johannsen et al. 1988). These data do not necessarily mean that 1,2,3-trichloropropane is not neurotoxic, however, due to a lack of neurological evaluations. Brain weight was increased in rats exposed to 297 or 579 ppm 1,2,3-trichloropropane for 4 weeks (Johannsen et al., 1988), but it is unclear if absolute or relative brain weight was increased. The rats in the 4-week study were hypoactive and had labored breathing, but were not subjected to histological and neurological evaluations. Due to the lack of histological and neurological evaluations, signs attributable specifically to CNS impairment, and sufficient information to determine if relative brain weight was increased (which could reflect decreased body weight), the neurological significance of the increased brain weight cannot be determined.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to 1,2,3-trichloropropane.

Limited information regarding developmental effects of inhaled 1,2,3-trichloropropane in animals is available from a reproduction study in which male and female rats were intermittently exposed to concentrations as high as 15 ppm prior to mating, during mating, and during gestation (Johannsen et al. 1988). There were no effects on gestation length, and pup viability and weight at birth and during lactation were normal. These data incompletely characterize developmental toxicity because the fetuses were not examined for teratogenicity.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to 1,2,3-trichloropropane.

In the only inhalation reproductive study of 1,2,3-trichloropropane, male and female rats were intermittently exposed to concentrations of 0.49-15 ppm prior to mating, during mating, and during gestation (Johannsen et al. 1988). There were no effects on mating performance or fertility in either sex, but the data for the males at 4.5 ppm and higher concentrations are inconclusive because the control group for these males had low mating performance compared to another male control group. The highest NOAEL value is recorded in Table 2-l and plotted in Figure 2-l.

Studies with animals exposed to higher concentrations of 1,2,3-trichloropropane have examined effects on reproductive organs. Intermittent expcsure to less than or equal to 132 ppm for 11 days (Miller et al. 1986b) and less than or equal to 49 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988) had no effect on the weights or histology of the reproductive organs of male and female rats. Intermittent exposure to 1,2,3-trichloropropane for 4 weeks at concentrations that caused some deaths decreased ovary weights (greater than or equal to 297 ppm) and testes weights (579 ppm) in rats, but these organs were not examined histologically (Johannsen et al. 1988). Reproductive function was not evaluated in any of these studies. Because of incomplete information on reproductive organ histology and lack of information regarding sperm counts and reproductive function, conclusions regarding the reproductive toxicity of 1,2,3-trichloropropane cannot be drawn from these studies.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxicity in humans or animals after inhalation exposure to 1,2,3-trichloropropane. Other mutagenicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding carcinogenicity in humans or animals after inhalation exposure to 1,2,3-trichloropropane.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to 1,2,3-trichloropropane.

Oral LD_{50} values as low as 150 mg/kg have been determined for rats (Alpert 1982; Smyth et al. 1962). Variations in LD_{50} values are apparent, which could be due to differences in animal strain, sex, fed/fasted state or compound purity. The cause of death is unclear, but signs suggestive of CNS impairment (e.g., piloerection, salivation, ataxia, coma) prior to death and hemorrhagic damage in visceral tissues (e.g., liver, kidney) were observed. Daily gavage administration of 1,2,3-trichloropropane caused death due to liver and kidney toxicity in 15% of female rats by the 13th week at a dose of 125 mg/kg, in 100% of female rats by week 2 at 250 mg/kg, and in 80% of female mice by week 4 at 250 mg/kg (NTP 1983a, 1983b). Mortality occurred at a lower rate or occurred later in similarly treated male rats and mice. Lethal gavage doses of 1,2,3-trichloropropane in rodents, therefore, appear to be similar for acute exposures and intermediate-duration exposures of several weeks. Doses as high as 149 mg/kg/day were not lethal in rats, however, when administered in the drinking water for the 13 weeks (Villeneuve et al. 1985). Although absorption of 1,2,3-trichloropropane from drinking water could have been decreased due to use of a solubilizer, this suggests that 1,2,3-trichloropropane may be less toxic when ingested gradually throughout the day than when administered as a bolus. The highest NOAEL values and all reliable LOAEL values for death for both species and duration categories are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

Systemic effects resulting from oral exposure to 1,2,3-trichloropropane are discussed below. The highest NOAEL values and all reliable LOAEL values for these effects in 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 1,2,3-trichloropropane. Two animal studies showed that 1,2,3-trichloropropane produced pathologic changes in the nasal turbinates of rats and mice when administered by oral intubation (NTP 1983a, 1983b). These changes were produced by daily

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

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(G)	1x				444 (LD_{50})	Smyth et al. 1962
2	Rat	(G)	1x				150 (LD_{50})	Alpert 1982
3	Rat	(GO)	2 wk 5 d/wk		125		250	NTP 1983a
4	Mouse	(GO)	2 wk 5 d/wk		125		250	NTP 1983b
Systemic								
5	Rat	(GO)	2 wk 5 d/wk	Resp Hepatic Renal		250 (nasal necrosis)	 250 (necrosis) 250 (necrosis)	NTP 1983a
6	Rat	(GO)	14 d 1x/d	Renal Other	60 15	60 (decreased weight gain)		Dix 1979
7	Mouse	(GO)	2 wk 5 d/wk	Resp Hepatic Renal		250 (inflammation, necrosis) 250 (tubular casts)	 250 (necrosis)	NTP 1983b
Reproductive								
8	Rat	(GO)	5 d 1x/d		80			Saito-Suzuki et al. 1982
INTERMEDIATE EXPOSURE								
Death								
9	Rat	(W)	13 wk 7 d/wk		149			Villeneuve et al. 1985
10	Rat	(GO)	17 wk 5 d/wk		63		125	NTP 1983a
11	Mouse	(GO)	17 wk 5 d/wk		125		250	NTP 1983b

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Systemic								
12	Rat	(W)	13 wk 7 d/wk	Cardio	149			Villeneuve et al. 1985
				Hemato	149			
				Hepatic	17.6	113 (mild histology)		
				Renal	17.6	113 (mild histology)		
				Other	17.6	113 (mild thyroid histology, reduced body weight gain)		
13	Rat	(GO)	17 wk 5 d/wk	Resp	63	125 (nasal necrosis)		NTP 1983a
				Cardio	125			
				Gastro	63	125 (hyperkeratosis, acanthosis)		
				Hemato	8	16 (anemia)		
				Musc/skel	125			
				Hepatic	8[b]	16 (increased liver weight)	125 (necrosis)	
				Renal	16	32 (increased kidney weight)	125 (necrosis)	
				Derm/oc	32	63 (alopecia)		
				Other	32	63 (decreased weight gain)		
14	Mouse	(GO)	17 wk 5 d/wk	Resp	32	63 (bronchiole epithelial changes)		NTP 1983b
				Cardio	250			
				Gastro	32	63 (hyperkeratosis, acanthosis)		
				Hemato	250			
				Musc/skel	250			
				Hepatic	63	125 (necrotic changes)	250 (necrosis)	
				Renal	125	250 (necrotic changes)		
				Derm/oc	250			
				Other	125	250 (decreased weight gain)		
Reproductive								
15	Rat	(GO)	17 wk 5 d/wk		125			NTP 1983a

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
16	Mouse	(GO)	17 wk 5 d/wk		125			NTP 1983b
CHRONIC EXPOSURE								
Cancer								
17	Rat	(GO)	2 yr 5 d/wk				3 (CEL - tumors of forestomach, pancreas)	NTP 1991
18	Mouse	(GO)	2 yr 5 d/wk				6 (CEL - tumors of forestomach, liver, uterus)	NTP 1991

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an intermediate oral minimal risk level (MRL) of 0.06 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; d = day; Derm/oc = dermal/ocular; (G) = gavage; Gastro = gastrointestinal; (GO) = gavage in oil vehicle; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; LD_{50} = lethal dose 50% kill; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = water; wk = week; x = time; yr = year(s)

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

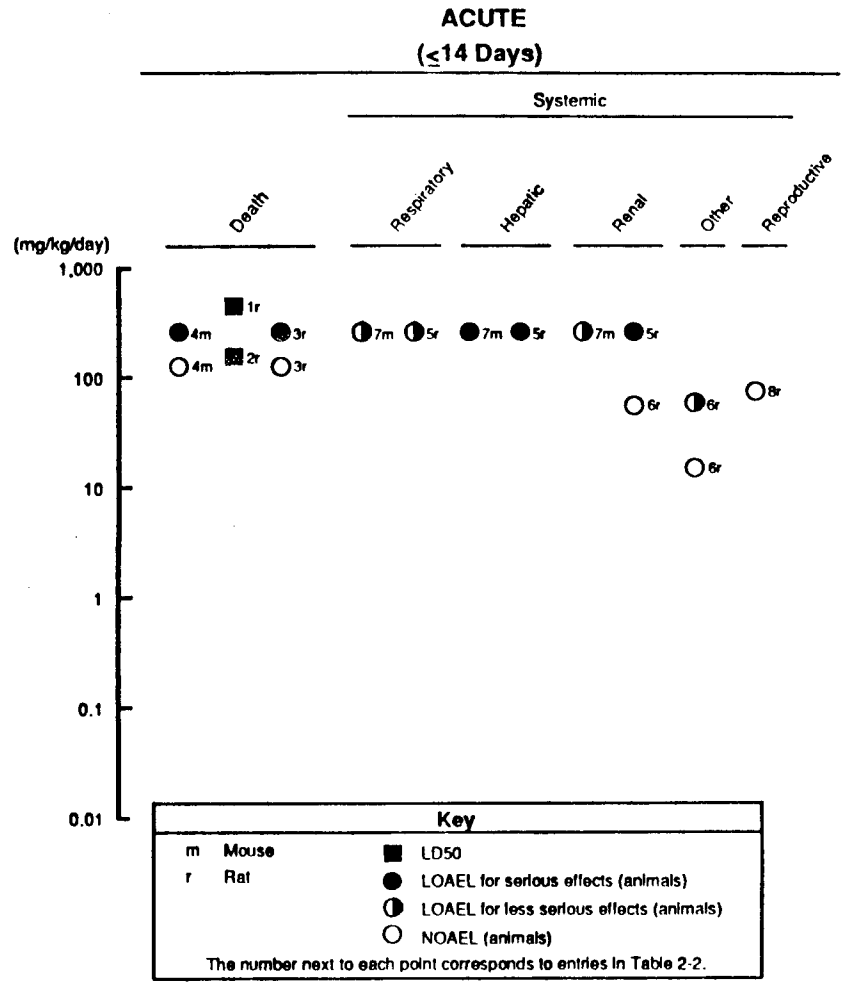


FIGURE 2-2 (Continued)

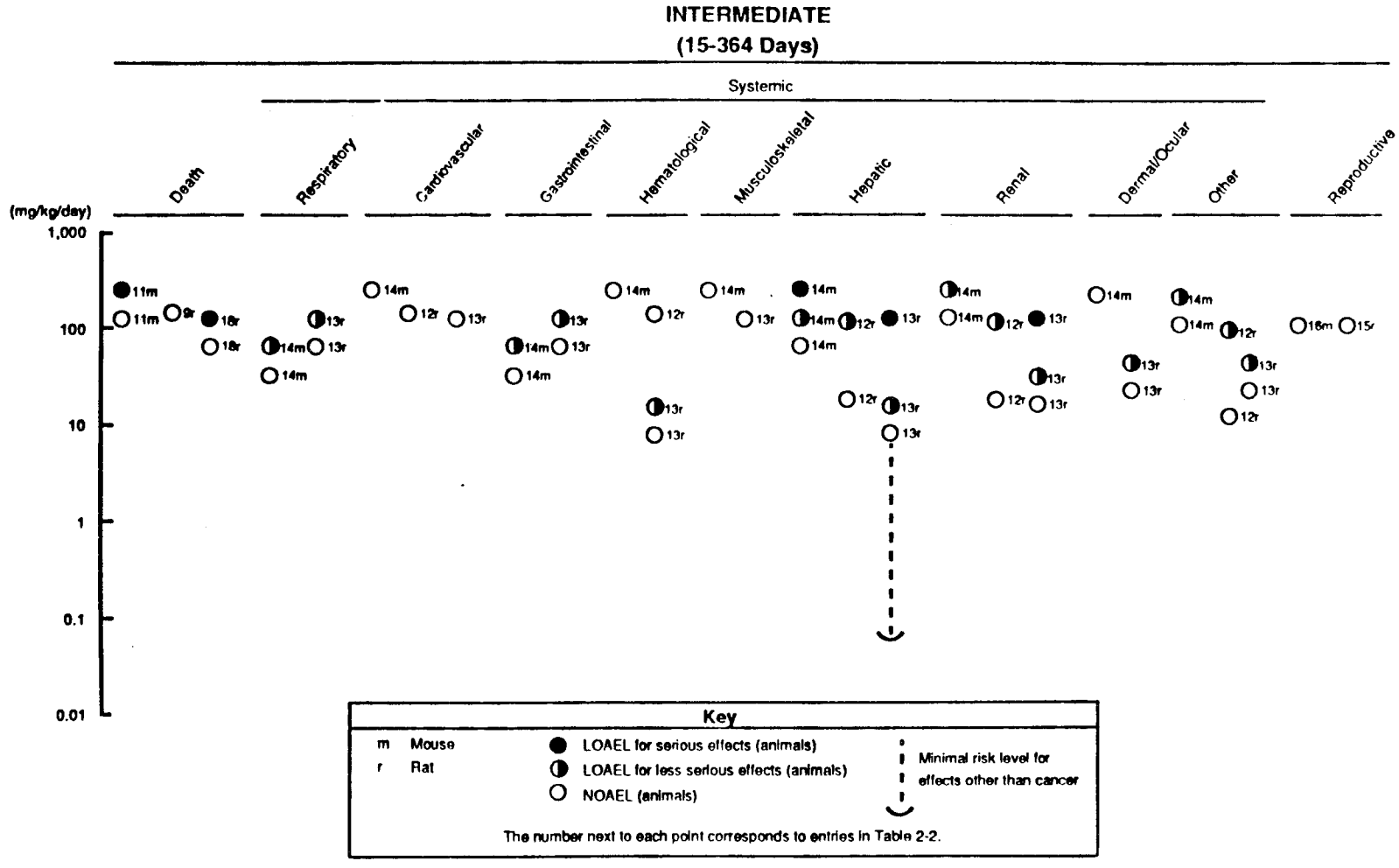
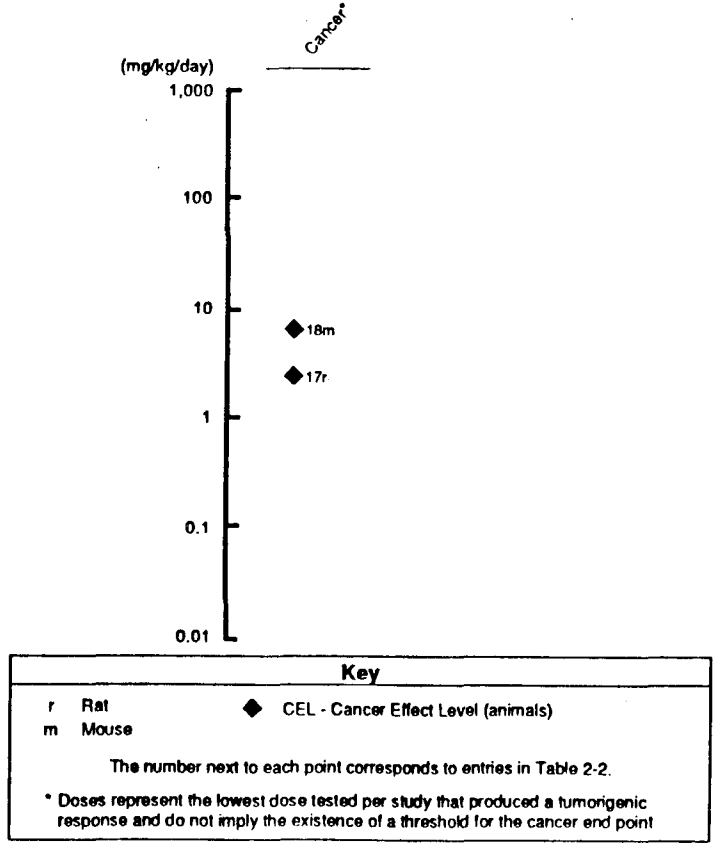


FIGURE 2-2 (Continued)

CHRONIC
(≥ 365 Days)



doses of 250 mg/kg (rats and mice) for 2 weeks and 125 mg/kg (rats) or 250 mg/kg (mice) for up to 17 weeks. Effects were similar in both species; these typically included inflammation, attenuation of the epithelial lining, ' and necrotic alterations, and principally occurred in the dorsal posterior of the nasal passages. These effects are similar to those caused by inhalation exposure to 1,2,3-trichloropropane (see discussion of Respiratory Effects in Section 2.2.1.2.) The oral doses that produced the nasal alterations were in the near lethal range. Repeated daily exposure of mice to lower doses of 1,2,3-trichloropropane (as low as 63 mg/kg) by oral intubation over a period of 17 weeks caused regenerative changes (e.g., hyperplasia) in the bronchiolar epithelium that did not progress or regress with continued exposure. It is possible that the nasal and pulmonary effects caused by oral treatment were due to inadvertent local exposure (see discussion of Systemic Effects in Section 2.4.) or excretion of 1,2,3-trichloropropane or its metabolites in the breath (see Section 2.3.4).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to 1,2,3-trichloropropane.

Two animal studies found that daily administration of 1,2,3-trichloropropane by gavage over a period of 17 weeks caused decreased heart weight without histological alterations in rats and mice at doses up to 125 and 250 mg/kg, respectively (NTP 1983a, 1983b). This effect is not considered adverse, due to the lack of histopathology. There was no effect on heart weight or histology in rats that were administered 1,2,3-trichloropropane in the drinking water at doses as high as 149 mg/kg/day for 13 weeks (Villeneuve et al. 1985).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to 1,2,3-trichloropropane.

Two animal studies found that daily administration of 1,2,3-trichloropropane over a period of 17 weeks caused gastrointestinal effects indicative of irritant action, particularly increased hyperkeratosis and/or acanthosis of the esophagus and stomach (NTP 1983a, 1983b). These effects occurred at doses of 63 mg/kg/day and higher in mice and 125 mg/kg/day in rats.

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to 1,2,3-trichloropropane.

One study found evidence of anemia, indicated by decreased hematocrit, hemoglobin, and erythrocyte counts, in rats that were administered 1,2,3-trichloropropane by gavage at doses as low as 16 mg/kg/day over a period of 17 weeks (NTP 1983a). The anemia was mild at the lower doses and appears to be nonregenerative and associated with depressed erythropoiesis. Higher

doses (63 mg/kg/day or more) in this gavage study produced histological alterations in the spleen (lymphoid depletion) of rats, and mice similarly treated with 250 mg/kg/day 1,2,3-trichloropropane had splenic lymphoid depletion with occasional lymphoid necrosis (NTP 1983b). The hematological significance of these splenic effects is unknown because hematology was normal except for the anemia in rats. 1,2,3-Trichloropropane did not produce significant hematological alterations in rats when administered in the drinking water at doses as high as 149 mg/kg/day for 13 weeks (Villeneuve et al. 1985).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,2,3-trichloropropane.

There were no pathological effects in bone or skeletal muscle of rats and mice that were administered 1,2,3-trichloropropane at doses as high as 125 and 250 mg/kg, respectively, over a period of 17 weeks (NTP 1983a, 1983b).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to 1,2,3-trichloropropane.
Liver toxicity is a major systemic effect of orally administered 1,2,3-trichloropropane in animals. Daily gavage doses of 250 mg/kg produced hepatotoxicity (e.g., necrosis) severe enough to contribute to death in rats and mice within 2 weeks (NTP 1983a, 1983b). Necrotic changes also occurred in the livers of rats and mice treated with daily gavage doses as low as 125 mg/kg over a period of 17 weeks (NTP 1983a, 1983b). Similar doses of 1,2,3-trichloropropane (113 or 149 mg/kg) administered in drinking water for 13 weeks produced mild hepatic changes (e.g., occasional fatty vacuolization and biliary hyperplasia) in rats (Villeneuve et al., 1985), suggesting that 1,2,3-trichloropropane may be less toxic when ingested gradually throughout the day than when administered as a bolus. One study found hepatic effects in rats treated by gavage with doses as low as 16 mg/kg/day over a period of 17 weeks (NTP 1983a). These effects included decreased serum pseudocholinesterase activity and increased liver weight. It is likely that the decreased serum pseudocholinesterase activity is attributable to depressed synthesis resulting from hepatocellular damage, but it could indicate that 1,2,3-trichloropropane inhibits pseudocholinesterase. Based on the NOAEL (8 mg/kg) for these effects, which is the same as the NOAEL for anemia in rats (see discussion of Hematologic Effects in Section 2.2.2.2), an intermediate oral MRL of 0.06 mg/kg/day was calculated as described in a footnote to Table 2-2.

Renal Effects. No studies were located regarding renal effect in humans after oral exposure to 1,2,3-trichloropropane.

Kidney toxicity is a major systemic effect of orally administered 1,2,3-trichloropropane in animals. Daily gavage doses of 250 mg/kg produced

serious renal toxicity (e.g., tubular nephropathy, necrosis) in rats and mice within 2 weeks (NTP 1983a, 1983b). The kidney damage in rats was severe enough to contribute to death. Necrotic changes occurred in the kidneys of rats and mice treated with daily gavage doses as low as 125 mg/kg over a period of 17 weeks (NTP 1983a, 1983b). Similar doses of 1,2,3-trichloropropane (113 or 149 mg/kg) administered in drinking water for 13 weeks produced mild renal changes (e.g., pyknosis, fine glomular adhesions, and occasional histologic proteinuria) in rats (Villeneuve et al. 1985). The term "histologic proteinuria" presumably refers to protein in the lumen of tubules. The mild renal changes suggest that 1,2,3-trichloropropane may be less toxic when ingested gradually throughout the day than when administered as a bolus. Daily gavage doses as high as 60 mg/kg for 2 weeks did not produce renal histological alterations in rats (Dix 1979), but rats treated with gavage doses as low as 32 mg/kg/day over a period of 17 weeks displayed less serious renal effects consisting of increased kidney weight and minimal inflammation (NTP 1983a).

Dermal/Ocular Effects. No studies were located regarding dermal or ocular effects in humans after oral exposure to 1,2,3-trichloropropane.

Daily gavage administration of 1,2,3-trichloropropane at doses of 63 mg/kg or more for up to 17 weeks caused alopecia but no gross eye irritation in rats (NTP 1983a). Mice that were similarly treated with up to 250 mg/kg 1,2,3-trichloropropane had no macroscopic skin lesions or gross eye irritation (NTP 1983b).

Other Systemic Effects. No studies were located regarding other systemic effects in humans after oral exposure to 1,2,3-trichloropropane.

Reduced body weight gain occurred in rats treated with 1,2,3-trichloropropane by gavage at doses of 60 mg/kg/day for 2 weeks (Dix 1979) or 63 or 125 mg/kg/day for up to 17 weeks (NTP 1983a). Thyroid histology, evaluated in the rats treated for up to 17 weeks, was normal. Doses of 113 or 149 mg/kg/day, when administered in the drinking water for 13 weeks, caused reduced body weight gain and thyroid histological alterations in rats (Villeneuve et al. 1985). Decreased weight gain without abnormal thyroid histology occurred in mice that were treated with 250 mg/kg/day by gavage for up to 17 weeks (NTP 1983b).

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans after oral exposure to 1,2,3-trichloropropane.

Lymphoid depletion was observed in the spleen and thymus of rats that were administered 1,2,3-trichloropropane at doses greater than or equal to 63 mg/kg/day over 17 weeks (NTP 1983a). Mice that were similarly treated with lethal doses (250 mg/kg) showed splenic lymphoid depletion with occasional

lymphoid necrosis and increased thymus weight. The immunological significance of these effects are not known.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to 1,2,3-trichloropropane.

There were no treatment-related changes in brain weight or brain histology in rats and mice that were administered 1,2,3-trichloropropane doses as high as 250 mg/kg/day for periods as long as 17 weeks (NTP 1983a, 1983b). These data do not necessarily mean that 1,2,3-trichloropropane is not neurotoxic, however, due to a lack of neurological evaluations.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to 1,2,3-trichloropropane.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 1,2,3-trichloropropane.

No effects on mating, fertility, or histological appearance of the testes were found in male rats that were treated with 80 mg/kg/day 1,2,3-trichloropropane for 5 days in a dominant lethal mutation study (Saito-Suzuki et al. 1982). Testis and epididymis weights were decreased in rats and mice that were administered 1,2,3-trichloropropane doses as high as 125 mg/kg for 60-120 days, but testicular histology, sperm counts, and sperm morphology were normal or inconclusive (NTP 1983a, 1983b). Although a definite conclusion regarding the reproductive toxicity of 1,2,3-trichloropropane in this study is precluded by a lack of information on reproductive function and the short exposure duration, the doses are considered NOAELs because the lack of testicular histological lesions and effects on sperm reduces concern that the decreased testicular and epididymal weights reflect a biologically significant change. The NOAEL values for reproductive effects in both species and duration categories are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to 1,2,3-trichloropropane.

As indicated in Section 2.2.2.6, orally administered 1,2,3-trichloropropane did not produce dominant lethal mutations in male rats (Saito-Suzuki et al. 1982). Other mutagenicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding carcinogenicity in humans after oral exposure to 1,2,3-trichloropropane.

1,2,3-Trichloropropane has been demonstrated to be carcinogenic in a variety of organs in Fischer-344 rats and B6C3Fl mice when administered by gavage in corn oil in a 2-year study (NTP 1991). In male rats treated with 23 mg/kg/day, clear evidence of carcinogenicity was found, based on increased incidences of squamous cell papilloma and carcinoma of the oral mucosa and/or forestomach, pancreatic acinar adenoma, renal tubule adenoma, and preputial gland adenoma and carcinoma. In female rats similarly treated, clear evidence of carcinogenicity was also found, based on increased incidences of squamous cell papilloma and carcinoma of the oral mucosa and forestomach, clitoral gland adenoma and carcinoma, and mammary gland adenocarcinoma. High incidences of Zymbal's gland carcinoma and intestinal adenocarcinoma were also found in the male and female rats, and may be related to the 1,2,3-trichloropropane exposure.

Clear evidence of carcinogenicity was also found in male and female mice treated with 6 mg/kg/day or greater (NTP 1991). The evidence consisted of increased incidences of squamous cell carcinoma of the oral mucosa (females), squamous cell papilloma and carcinoma of the forestomach (males and females), hepatocellular adenoma or carcinoma (males and females), Harderian gland adenoma (male and female), and uterine adenoma, adenocarcinoma, and stromal polyp (females). High dose male mice (60 mg/kg/day) also had squamous cell papilloma of the oral mucosa, which occurred in low incidence, but was probably related to 1,2,3-trichloropropane treatment.
The lowest doses associated with cancer in rats and mice are recorded in Table 2-2 and plotted in Figure 2-2 as Cancer Effect Levels (CELs).

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to 1,2,3-trichloropropane.

Single dermal doses as low as 250 mg/kg caused death in rabbits (Alpert 1982). A dermal LD_{50} of 836 mg/kg has been determined for rats using 1,2,3-trichloropropane of relatively low purity (92%) (Clark 1977). The treated skin of the animals in these studies was covered with an impervious barrier for 24 hours to prevent evaporation of the volatile compound. The cause of death is unclear, but symptoms suggestive of CNS impairment (e.g., ataxia, tremors, coma) and internal hemorrhage have been observed. Lethal

dermal doses of 1,2,3-trichloropropane in these species are recorded in Table 2-3.

2.2.3.2 Systemic Effects

Systemic effects resulting from dermal exposure to 1,2,3-trichloropropane are discussed below. The highest NOAEL values and all reliable LOAEL values for these effects in each species and duration category are recorded in Table 2-3.

No studies were located regarding cardiovascular, hematological, or musculoskeletal effects in humans or animals after dermal exposure to 1,2,3-trichloropropane.

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to 1,2,3-trichloropropane. Lung hemorrhage and apparently related effects (e.g., discoloration of the lungs and liquid in the thoracic cavity) have been observed in rabbits exposed to lethal dermal doses of 1,2,3-trichloropropane (Alpert 1982; Union Carbide 1958).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after dermal exposure to 1,2,3-trichloropropane.

Ulceration of the stomach wall was observed in rabbits exposed to lethal dermal doses of 1,2,3-trichloropropane (Alpert 1982).

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to 1,2,3-trichloropropane.

Turgid and discolored livers were observed in rabbits exposed to lethal dermal doses of 1,2,3-trichloropropane (Alpert 1982; Union Carbide 1958). These macroscopic alterations are consistent with oral and inhalation evidence of hepatotoxicity.

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to 1,2,3-trichloropropane.

Discolored kidneys and hematuria were observed in rabbits exposed to lethal dermal doses of 1,2,3-trichloropropane (Alpert 1982; Union Carbide 1958). These macroscopic alterations are consistent with oral and inhalation evidence of renal toxicity.

Dermal/Ocular Effects. No studies were located regarding dermal effects in humans after dermal exposure to 1,2,3-trichloropropane. Limited information indicates that brief (15-minute) exposure to 100 ppm

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

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect) Less serious	LOAEL (effect) Serious (mg/kg)	Reference
ACUTE EXPOSURE						
Death						
Rat	24 hr		278 mg/kg		836 (LD_{50})	Clark 1977
Rabbit	24 hr				250	Alpert 1982
Systemic						
Human	1 d 15 min/d	Derm/oc		100 ppm (eye irritation)		Silverman et al. 1946
Rabbit	24 hr	Derm/oc		174 mg/kg/day (skin irritation)		Clark 1977
Rabbit	24 hr	Resp			250 (lung discoloration)	Alpert 1982
		Gastro			250 (stomach ulceration)	
		Hepatic			250 (liver discoloration)	
		Renal			250 (discoloration of kidneys and bladder contents)	
Rabbit	10x in 15d	Derm/oc		2 mL (intense skin irritation, subdermal bleeding)		McOmie and Barnes 1949
Rabbit	24 hr	Derm/oc		278 mg/kg/day (skin irritation)		Alpert 1982
Rabbit	1x	Derm/oc		0.1 mL (eye irritation)		Alpert 1982
Rabbit	1x	Derm/oc		0.1 mL (eye irritation)		Clark 1977
Rat	1 d 4 hr/d	Derm/oc		126 ppm (eye irritation)		Gushow and Quast 1984
Rat	13 wk 5 d/wk 6 hr/d	Derm/oc	4.5 ppm	15 ppm (eye irritation)		Johannsen et al. 1988
Mouse	1 d 4 hr/d			126 ppm (eye irritation)		Gushow and Quast 1984

TABLE 2-3. (Continued)

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect) Less serious	LOAEL (effect) Serious (mg/kg)	Reference
Gn pig	3 wk 1d/wk 6hr/day	Derm/oc	0.51 mL[b]			Alpert 1982

[a]Two 0.1 mL injections followed 1 week later by covered topical application for 48 hours. Challenge conducted 2 weeks later by covered topical application for 24 hours.
[b]Challenge dose applied to sensitized and virgin skin for 6 hours 14 days after the last sensitizing dose. Both sensitizing and challenge doses were covered.

d = day; Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gn pig = guinea pig; hr = hour; LOAEL = lowest-observed-adverse-effect level; LD_{50} = lethal dose 50% kill; mg/kg/day = milligrams per kilogram per day; mL = milliliter; min = minute; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week; x = times

1,2,3-trichloropropane vapor causes eye irritation in humans (Silverman et al. 1946).

1,2,3-Trichloropropane vapor caused eye irritation in rats and mice exposed for 4 hours to concentrations as low as 126 ppm (Gushow and Quast 1984) and in rats exposed intermittently to concentrations as low as 15 ppm over a period of 13 weeks (Johannsen et al. 1988). Ocular application of 1,2,3-trichloropropane caused eye irritation in rabbits (Alpert 1982; Clark 1977).

Dermal application of 1,2,3-trichloropropane causes severe skin irritation in rabbits. Evidence suggests that prolonged exposure (e.g., for 24 hours) or repeated daily application (e.g., for 2 weeks) may be necessary to cause irritation (Clark 1977; McOmie and Barnes 1949). The results of one study suggest that 1,2,3-trichloropropane in corn oil vehicle was a very mild skin sensitizer in guinea pigs (Clark 1977). Another study that used a less sensitive procedure found no evidence of skin sensitization by undiluted 1,2,3-trichloropropane in guinea pigs (Alpert 1982). This study also found that corn oil itself was a mild skin sensitizer in guinea pigs, indicating that there is a possibility that the vehicle may enhance the weak effect observed by Clark (1977).

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans after dermal exposure to 1,2,3-trichloropropane.

As indicated in the discussion of Dermal/Ocular Effects in Section 2.2.3.2, one study provides limited evidence that 1,2,3-trichloropropane may be a very weak dermal sensitizer in animals (Clark 1977).

No studies were located regarding the following effects in humans or animals after dermal exposure to 1,2,3-trichloropropane:

2.2.3.4 Neurological Effects
2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects

Other mutagenicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding carcinogenicity in humans or animals after inhalation exposure to 1,2,3-trichloropropane.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No quantitative information was located regarding absorption of 1,2,3-trichloropropane in humans or animals following inhalation exposure; however, since liver and kidney toxicity has been reported in animals exposed by the inhalation route (see discussions of Hepatic Effects and Renal Effects in Section 2.2.1.2), it can be concluded that absorption occurs to some extent.

2.3.1.2 Oral Exposure

No quantitative information was located regarding absorption of 1,2,3-trichloropropane in humans following oral exposure.

The results of studies performed in rats indicate that near complete absorption (greater than 80%) from the gastrointestinal tract occurs within the first day following oral exposure (Sipes et al. 1982; Volp et al. 1984).

2.3.1.3 Dermal Exposure

No quantitative information was located regarding absorption of 1,2,3-trichloropropane in humans or animals following dermal exposure. However, internal pathology and death have been reported in animals exposed by the-dermal route (see Sections 2.2.3.1 and 2.2.3.2). Since vapor exposure was unlikely due to occlusive covering of the treatment area, it can be concluded that dermal absorption occurs to some extent.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No information was located regarding the distribution of 1,2,3-trichloropropane in humans or animals following inhalation exposure.

2.3.2.2 Oral Exposure

No information was located regarding the distribution of 1,2,3-trichloropropane in humans following oral exposure.

Muscle, blood, liver, skin, and adipose tissue contained the largest amounts of 1,2,3-trichloropropane following oral exposure in rats (Sipes et al. 1982). Retention in all tissues was low, however, as elimination of 1,2,3-trichloropropane-derived radioactivity from tissues was nearly complete (greater than 97%) within 8 days after exposure.

Elimination of 1,2,3-trichloropropane from tissues is nearly complete (greater than 97%) within 8 days after oral exposure in rats (Sipes et al. 1982).

2.3.2.3 Dermal Exposure

No information was located regarding the distribution of 1,2,3-trichloropropane in humans or animals following dermal exposure.

2.3.2.4. Other Routes of Exposure

No information was located regarding the distribution of 1,2,3-trichloropropane in humans following exposure by other routes.

Distribution studies of intravenously injected 1,2,3-trichloropropane in rats have provided a quantitative description of the distribution kinetics from which predictions can be made regarding other routes of exposure (Sipes et al. 1982; Volp et al. 1984). Intravenously injected 1,2,3-trichloropropane rapidly distributes to many tissues. The major sites of accumulation are liver, kidney, small and large intestine, adipose tissue, muscle, and skin. Peak concentrations are achieved within l-2 hours after intravenous injection.

Elimination of 1,2,3-trichloropropane from tissues in the rat is also rapid and a two-phase process (Volp et al. 1984). Elimination half-times for greater than 90% of the 1,2,3-trichloropropane in tissues ranged from 20 minutes in kidney to 2 hours in adipose tissue (first phase). A small fraction of the 1,2,3-trichloropropane in these tissues (less than 10%) was eliminated more slowly, with half-times ranging from 23 to 45 hours (second phase). Elimination of total radioactivity from the tissues after intravenous injection of radiolabeled 1,2,3-trichloropropane (phase one half-times between 2-5 hours, phase two half-time between 87-182 hours) is slower than elimination of parent 1,2,3-trichloropropane. This suggests that metabolites of 1,2,3-trichloropropane are eliminated slower than the parent compound.

Based on the results of studies in the rat, it can be concluded that 1,2,3-trichloropropane absorbed by any route is likely to be widely distributed in the body. Most of the 1,2,3-trichloropropane that enters tissues is eliminated within hours to days.

2.3.3 Metabolism

No information was located regarding the metabolism of 1,2,3-trichloropropane in humans; however, studies in animals have provided information about metabolic pathways and rates of metabolism that are likely to occur in humans. Intravenously injected 1,2,3-trichloropropane is extensively metabolized within hours in rats. Metabolic products in rats include carbon dioxide, which is expired, and numerous unidentified

metabolites that are excreted in urine and enter the bile to be excreted in feces or absorbed in the intestines (Sipes et al. 1982; Volp et al. 1984). Although the nonvolatile metabolites of 1,2,3-trichloropropane that are formed in the rat have not been identified, dehalogenation products, glutathione conjugates, and subsequent metabolites (e.g., mercapturic acids) can be anticipated, based on the metabolic pathways that have been identified for other halogenated alkanes.

Chloroalkanes such as 1,2,3-trichloropropane undergo dehalogenation reactions catalyzed by cytochrome P-450 (Ivanetich et al. 1978; Salmon et al. 1981; Van Dyke et al. 1971). Depending on the reaction mechanism, highly reactive intermediates (e.g., radicals) can be formed from these reactions leading to protein and DNA adducts or lipid peroxidation. Conjugation with glutathione could result in formation of sulfur mustard-like compounds that are potential alkylating agents.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No information was located regarding the excretion of 1,2,3-trichloropropane in humans or animals following inhalation exposure.

2.3.4.2 Oral Exposure

No information was located regarding the excretion of 1,2,3-trichloropropane in humans following oral exposure.

Studies conducted with rats showed that 1,2,3-trichloropropane and its metabolites were excreted in urine, feces, and exhaled breath after oral exposure (Sipes et al. 1982). Excretion was nearly complete (95-96%) within 2 days. Most of the dose was excreted in the urine and feces (up to 56% and 25%, respectively), with the remainder in the breath.

2.3.4.3 Dermal Exposure

No information was located regarding the excretion of 1,2,3-trichloropropane in humans or animals following dermal exposure.

2.3.4.4 Other Routes of Exposure

No information was located regarding the excretion of 1,2,3-trichloropropane in humans following other routes of exposure.

Studies of the excretion of intravenously injected 1,2,3-trichloropropane in rats have provided a quantitative description of the excretion kinetics from which predictions can be made about other routes of exposure (Sipes et al. 1982; Volp et al. 1984). Excretion of intravenously injected

1,2,3-trichloropropane and metabolites is nearly complete within 2 days. Unchanged 1,2,3-trichloropropane and its major metabolite, carbon dioxide, are expired in exhaled breath. Nonvolatile metabolites are excreted in the urine. Extensive biliary excretion of nonvolatile metabolites also occurs, resulting in fecal excretion as well as reabsorption of metabolites from the gastrointestinal tract. Based on the results of studies in rats, exhaled breath, urine, and feces are likely to be significant routes of excretion of absorbed 1,2,3-trichloropropane and its metabolites in humans.

2.4 RELEVANCE TO PUBLIC HEALTH

The only information that is available on the health effects of 1,2,3-trichloropropane in humans indicates that exposure to 1,2,3-trichloropropane of unknown purity in air can produce eye and throat irritation. Effects in the respiratory system, eyes and skin, gastrointestinal tract, liver, kidneys, blood, and spleen have been observed in animals exposed to 1,2,3-trichloropropane by air, mouth, and/or skin. 1,2,3-Trichloropropane also induced tumors at multiple sites in animals exposed orally.

Sufficient information is available on the health effects of 1,2,3-trichloropropane to derive MRLs for acute duration inhalation exposure and intermediate duration oral exposure. Based on a NOAEL of 1 ppm for histological changes in the nasal olfactory epithelium of rats (Miller et al. 1986b), an acute inhalation MEL of 0.0003 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 olfactory epithelium (decreased thickness) in rats is 3 ppm (Miller et al. 1986b). Supporting studies show that similar nasal effects occurred in mice at 10 ppm, and more pronounced changes in nasal tissues occurred in rats and mice at higher concentrations (Miller et al. 1986a, 1986b). An intermediate duration inhalation MEL for 1,2,3-trichloropropane cannot be derived due to a lack of information on effects on the nasal olfactory epithelium which, based on the acute data, is the critical target of inhalation exposure. A chronic inhalation MEL is precluded by a lack of data on chronic toxicity. Insufficient information is available on the systemic effects of acute oral exposure to 1,2,3-trichloropropane at sublethal doses to derive an acute oral MEL. Based on a NOAEL of 8 mg/kg/day for hepatic effects in rats (NTP 1983a), an oral MEL of 0.06 mg/kg/day was calculated for intermediate duration exposure by dividing the NOAEL by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability). The LOAEL for hepatic effects (increased liver weight, decreased serum cholinesterase) is 16 mg/kg/day (NTP 1983a). The NOAEL and LOAEL for anemia in rats are the same as the NOAEL and LOAEL for hepatic effects, but other data that lend support to the intermediate oral MEL are not available. A chronic oral MEL is precluded by lack of information on chronic toxicity.

Acute-duration, intermediate-duration, and chronic duration dermal MRLs were not derived for 1,2,3-trichloropropane due to the lack of an appropriate methodology for the development of dermal MRLs.

Death. Information regarding death in humans following exposure to 1,2,3-trichloropropane by any route was not found.

Studies with rats and mice suggest that 1,2,3-trichloropropane is similarly toxic following acute- and intermediate-duration exposure by either the inhalation or oral route. Lethal concentrations as low as approximately 300 ppm for inhalation exposure and lethal doses in the range of 125-250 mg/kg for gavage exposure indicate that the 1,2,3-trichloropropane is likely to be moderately toxic for humans. However, 1,2,3-trichloropropane may be less toxic when ingested gradually throughout the day, such as in the drinking water, than when taken as a bolus. Acute dermal and oral lethal doses of 1,2,3-trichloropropane in animals appear to be similar in magnitude, suggesting that skin contact with liquid 1,2,3-trichloropropane at waste sites could be toxic for humans. The dermal doses may actually overestimate lethality, however, because the testing methods may have prevented evaporation of 1,2,3-trichloropropane from the skin.

Systemic Effects.

Respiratory Effects. The respiratory tract is a principal target of inhaled 1,2,3-trichloropropane in studies with humans and animals. Human subjects experienced objectionable throat and eye irritation at 100 ppm. Some subjects found 50 ppm unacceptable for an 8-hour day, but information on irritation in humans at lower concentrations is not available. Rodent data showing that 1,2,3-trichloropropane causes irritative effects in the respiratory tract, eyes, and skin following vapor exposure, and in the gastrointestinal tract following oral exposure support the fact that 1,2,3-trichloropropane is a local irritant in humans. Effects indicative of local irritation have occurred in rats and mice at air concentrations as low as 3 ppm (rats); these effects consisted of microscopic alterations in the nasal cavity (inflammatory and degenerative changes) and bronchi (lymphoid hyperplasia). The animal evidence suggests that the nasal olfactory epithelium is more sensitive than the respiratory epithelium to inhaled 1,2,3-trichloropropane, but most inhalation studies, including the only intermediate-duration study in animals (rats), did not examine the nasal cavity. Because rodents are obligate nose breathers (Miller et al. 1986a, 1986b), histologicai alterations in rodent olfactory mucosa might be pronounced in comparison to humans, who are capable of breathing via the mouth. However, because the effects on the olfactory tissue are progressive and show the potential for olfactory impairment in humans, they are an appropriate basis for the acute inhalation MRL.

Histological effects have also been observed in the nasal cavity and bronchiolar epithelium of rats and/or mice that were exposed to

1,2,3-trichloropropane for acute and intermediate durations by oral intubation at doses of 63 mg/kg/day and more. These effects seem to be generally consistent with those found in the inhalation studies and confirm that 1,2,3-trichloropropane is a probable respiratory tract toxicant in humans. The nasal effects ranged from inflammation to mucosal necrosis at lethal doses, but appear to have occurred principally in the dorsal posterior nasal mucosa rather than the olfactory mucosa. The pathogenesis of the nasal lesions in orally treated animals is unclear since the principal location of the nasal effects in these animals (dorsal posterior) may suggest a local rather than systemic effect. This could possibly result from small amounts of residual compound in the pharynx after dosing, escape of volatile material from the stomach into the nasal passages, or elimination of 1,2,3-trichloropropane or metabolites in expired air. Therefore, the respiratory effects seen in animals after gavage exposure may be relevant to human exposure to 1,2,3-trichloropropane via drinking water because 1,2,3-trichloropropane could also escape from the pharynx and stomach into the nasal passages or be eliminated in expired air after exposure by this route. The relevance of the effects in the bronchiolar epithelium, which were primarily regenerative changes such as hyperplasia in mice, is uncertain because it is possible that they were caused by exposure due to improper gavage treatment. This possibility may be substantive since there were a number of deaths resulting from faulty intubation techniques in the same study. Based on the overall evidence from animal studies, it appears that continued exposure to 1,2,3-trichloropropane in air or water at sufficiently high levels may be capable of producing adverse changes in nasal tissues of humans.

Hematological Effects. 1,2,3-Trichloropropane has not been reported to produce hematological effects in humans. Nonregenerative anemia occurred in rats orally exposed to 1,2,3-trichloropropane for intermediate durations. This is one of most sensitive effects of 1,2,3-trichloropropane in animals. Effects in the spleen (increased hematopoiesis, decreased spleen weight or lymphoid depletion) in rats and mice exposed orally or by inhalation may indicate hematological effects of 1,2,3-trichloropropane, but the biological significance of these changes is uncertain because anemia was the only abnormal hematology measurement in the rats and hematology was normal in the mice. Overall, the animal data suggest some potential for adverse hematological effects in humans exposed to 1,2,3-trichloropropane.

Hepatic Effects. Adverse effects on the liver in humans have not been reported; however, the liver is a major target organ of 1,2,3-trichloropropane in animals. 1,2,3-Trichloropropane causes dose-related hepatic toxicity that is severe enough at high doses to contribute to death in rats and mice following acute- or intermediate-duration gavage administration. 1,2,3-Trichloropropane appears to be less hepatotoxic when ingested throughout the day (i.e., in drinking water) than when taken as a bolus. Hepatic effects other than increased liver weight and hepatocellular hypertrophy have not been observed in rats and mice exposed by inhalation, but examinations were not

performed on animals exposed for periods longer than 13 weeks. Gavage studies show that the changes in the liver are progressive, with increased organ weights, minimal histological alterations, and/or clinical chemistry alterations occurring at lower doses. The most sensitive hepatic effect observed appears to be decreased serum pseudocholinesterase activity which, in the absence of known inhibitors, suggests depressed synthesis due to hepatocellular damage (NTP 1983a). The oral MRL for intermediate-duration exposure is based on this effect. There was macroscopic evidence of liver damage in rabbits that died following acute dermal exposure to 1,2,3-trichloropropane. Although effects on the liver have not been observed in humans, the studies in animals indicate that such hepatic effects might occur in humans at sufficiently high or prolonged exposures.

Renal Effects. Adverse effects on the kidneys in humans have not been reported, but the kidneys are a major target of 1,2,3-trichloropropane toxicity in animals. 1,2,3-Trichloropropane causes dose-related renal toxicity that is severe enough at high doses to contribute to death in rats and mice following acute- or intermediate-duration gavage administration. 1,2,3-Trichloropropane appears to be less toxic to the kidneys when ingested throughout the day (i.e., in drinking water) than when taken as a bolus. Renal effects other than increased kidney weights have not been observed in rats exposed by inhalation, but examinations were not performed on animals exposed for longer than 13 weeks. Gavage studies indicate that the renal effects are progressive, with increased organ weight and clinical chemistry alterations occurring at lower doses. Macroscopic evidence of kidney damage was observed in rabbits that died following acute dermal exposure to 1,2,3-trichloropropane. Although effects on kidneys have not been observed in humans, the studies in animals indicate that renal effects might occur in humans at sufficiently high or prolonged exposures.

Other Systemic Effects. Other systemic effects observed in rats following intermediate-duration oral exposure to 1,2,3-trichloropropane included weight loss, alopecia, and histological changes in the thyroid (reduced follicular size, increased epithelial height). Insufficient information is available to determine if 1,2,3-trichloropropane is likely to produce these effects in exposed humans.

Immunological Effects. Immunological effects of 1,2,3-trichloropropane have not been reported in humans. Intermediate-duration studies with rats and mice have shown effects in the spleen and thymus (lymphoid depletion and/or decreased organ weight) following oral or inhalation exposure. The effects occurred at high levels of exposure, frequently in the lethal range. These effects cannot be used to infer immunotoxicity of 1,2,3-trichloropropane in humans because immune function has not been evaluated.

Neurological Effects. Neurological effects of 1,2,3-trichloropropane have not been reported in humans. Signs suggestive of CNS impairment occur in rodents exposed to lethal levels of 1,2,3-trichloropropane by the inhalation,

oral, and dermal routes, but these effects do not necessarily indicate that 1,2,3-trichloropropane is neurotoxic because they could be due to indirect causes (e.g., asphyxiation, kidney failure) in dying animals. Brain weights were reported to have increased in rats that inhaled lethal concentrations of 1,2,3-trichloropropane in an intermediate-duration study, but this could simply reflect a decrease in body weight (i.e., if relative brain weight was increased). Since the studies that reported the aforementioned effects did not perform neurological or behavioral evaluations, insufficient information is available to determine if 1,2,3-trichloropropane is likely to produce neurological effects in humans at sublethal levels.

Developmental Effects. Developmental effects of 1,2,3-trichloropropane have not been reported in humans. 1,2,3-Trichloropropane did not produce effects on survival or growth during gestation or lactation in offspring of rats exposed by inhalation, but teratogenicity was not evaluated. Developmental toxicity of 1,2,3-trichloropropane has not been evaluated in animals exposed orally or dermally. There was no evidence of teratogenicity or fetal toxicity in rats treated with a maximum tolerated dose of 1,2,3-trichloropropane (37 mg/kg) by intraperitoneal injection on days l-15 of gestation (Hardin et al. 1981). Although the available data provide some assurance that 1,2,3-trichloropropane is not developmentally toxic in animals, additional information, particularly teratogenicity evaluations in animals by environmentally relevant routes of exposure, would be needed to prove that 1,2,3-trichloropropane is not a likely developmental toxicant in humans.

Reproductive Effects. Reproductive effects of 1,2,3-trichloropropane in humans have not been reported. There were no effects on mating performance or fertility in rats exposed orally for 5 days or by inhalation at relatively low concentrations (less than or equal to 15 ppm) for 10 weeks. Oral administration for up to 4 months at lethal levels caused decreased testes and epididymis weights in rats and mice, but no effects on testicular histology or sperm. Rats exposed by inhalation for 4 weeks at lethal levels experienced decreased testes and ovary weights, but histology and sperm were not evaluated. Although effects of 1,2,3-trichloropropane on reproductive function have not been evaluated in animals treated at high (near maximum tolerated) doses or concentrations, the normal testicular histology and sperm counts and morphology at lethal levels in the 4-week inhalation study are consistent with normal reproductive function. Overall, the available data suggest that 1,2,3-trichloropropane will not be a reproductive toxicant in humans.

Genotoxic Effects. Genotoxic effects of 1,2,3-trichloropropane in humans have not been reported. 1,2,3-trichloropropane was mutagenic in certain strains of Salmonella typhimurium when assayed with exogenous metabolic activation preparation, and it induced sister chromatid exchanges in cultured hamster cells (Table 2-4). 1,2,3-trichloropropane did not induce dominant lethal mutations when administered orally to rats (Saito-Suzuki et al. 1982) (see Section 2.2.2.7). Although only limited data are available,

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

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium (plate incorporation test)	Gene mutation	+	-	Stolzenberg and Hine 1980
S. typhimurium (liquid preincubation test)	Gene mutation	+	-	Haworth et al. 1983
S. typhimurium (plate incorporation test)	Gene mutation	+	-	Ratpan and Plaumann 1988
Eukaryotic organisms:				
Mammalian cells:				
Chinese hamster V79 cells	Sister-chromatid exchange	+	-	Von Der Hude et al. 1987

+ = positive result; - = negative result

this evidence indicates that 1,2,3-trichloropropane is genotoxic in animals and may be genotoxic in humans.

Cancer. Information regarding the carcinogenicity of 1,2,3-trichloropropane in humans by any route of exposure was not located. Clear evidence of carcinogenicity was found for 1,2,3-trichloropropane in male and female rats at doses of 3 mg/kg/day or more and in male and female mice at doses of 6 mg/kg/day or more in a 2-year gavage study (NTP 1991). Increased incidences of squamous cell papilloma and/or carcinoma were found in the oral mucosa and/or the forestomach of both sexes of both species. These tumors were morphologically similar in the oral mucosa and forestomach, forming a continuum. Other tumors that were considered to be related to 1,2,3-trichloropropane exposure consisted of pancreatic acinar adenoma, renal tubule adenoma, adenoma and carcinoma of the preputial gland in male rats; clitoral gland adenoma and carcinoma, mammary gland adenocarcinoma in female rats; hepatocellular adenoma and carcinoma and Harderian gland adenoma in male and female mice; and uterine neoplasms in female mice. Zymbal's gland carcinoma and intestinal adenocarcinoma also found in the male and female rats may be related to the 1,2,3-trichloropropane exposure. The carcinogenicity of 1,2,3-trichloropropane is consistent with the positive genotoxicity findings in the presence of bioactivation (see Table 2-4) and with its metabolism to reactive intermediates, such as alkylating agents, which can lead to protein and DNA adducts (see Section 2.3.3). NTP, IARC, and EPA have not yet classified 1,2,3-trichloropropane with respect to its potential carcinogenicity for humans, but the evidence in both sexes of two species of animals strongly suggests a public health concern.

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

2.5.1 Biomarkers Used,to Identify and/or Quantify Exposure to 1,2,3-Trichloropropane

Biomarkers of exposure to 1,2,3-trichloropropane cannot be identified because information on levels of 1,2,3-trichloropropane or its metabolites in human tissues, fluids, or excreta or information on effects specific for 1,2,3-trichloropropane is not available. Studies with rats indicate that excretion of 1,2,3-trichloropropane in the breath or urine may be sufficient for monitoring purposes (see Section 2.3.4). Mild anemia and serum enzyme alterations associated with liver toxicity, particularly decreased serum pseudocholinesterase activity, occurred in rats exposed to 1,2,3-trichloropropane. The enzyme alterations were used as the basis for the intermediate-duration oral MRL. Although the anemia and enzyme alterations are sensitive indicators of toxicity in rats, they are not specific indicators of exposure to 1,2,3-trichloropropane and may not occur in humans.

2.5.2 Biomarkers Used to Characterize Effects Caused by 1,2,3-Trichloropropane

Effects in humans that are specifically attributable to 1,2,3-trichloropropane exposure are not known. Principal targets of 1,2,3-trichloropropane in animals are the respiratory tract, blood, liver, and kidneys (see Section 2.4). One study with rats suggests that alterations of serum enzymes (e.g., decreased serum pseudocholinesterase activity) and anemia might be

useful biomarkers for hepatic and hematologic effects, respectively, of 1,2,3-trichloropropane. Insufficient data exist, however, to determine whether 1,2,3-trichloropropane is likely to cause anemia in humans, and substances other than 1,2,3-trichloropropane could also cause similar hematologic and hepatic effects.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Rats were exposed by inhalation to 500 ppm 1,2,3-trichloropropane and 1,000 ppm dichloropropane alone and in combination for 4 hours (Drew et al. 1978). Activities of liver-associated serum enzymes (serum glutamicoxaloacetic transaminase, serum glutamic-pyruvic transaminase, ornithine carbamyl transferase) were increased 24-48 hours following exposure to each chemical alone. The combined exposure resulted in higher enzyme activities than with either chemical alone, but the increases were less than additive.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No populations with unusual susceptibility to health effects of 1,2,3-trichloropropane have been identified. The respiratory tract, blood, liver, and kidneys are principal targets of 1,2,3-trichloropropane in animals (see Section 2.4). It is therefore possible that people with chronic respiratory, liver, or kidney disease, or possibly people with compromised pulmonary, hepatic, or renal function (e.g., alcoholics), might be unusually susceptible to 1,2,3-trichloropropane.

2.8 MITIGATION OF TOXICOLOGICAL EFFECTS

This section will describe the clinical practice and research methods for reducing toxic effects of exposure to 1,2,3-trichloropropane. However, because some the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 1,2,3-trichloropropane. When specific exposures have occurred poison control centers and medical toxicologists should be consulted for medical advice.

Human exposure to 1,2,3-trichloropropane may occur by inhalation, ingestion, or by dermal contact. Specific information on the management and treatment of toxicological effects following acute exposure to 1,2,3-trichloropropane were not located in the literature. However, since effects of 1,2,3-trichloropropane are consistent with those produced by other halogenated aliphatic hydrocarbons compounds, general information on mitigation for this chemical class pertains to 1,2,3-trichloropropane (Stutz and Janusz 1988). Mitigation approaches to reduce absorption of 1,2,3-trichloropropane have included general recommendations of separating contaminated food, water, air, and clothing from the exposed individual. Externally, 1,2,3-trichloropropane can produce irritation and injury to the skin and mucous membranes. Exposed eyes are flushed with a clean neutral

solution such as water or normal saline. The skin is immediately washed with large amounts of soapy water.

If oral exposure has occurred, inducing emesis may be indicated within the first 30 minutes following substantial ingestion unless the patient is or could rapidly become obtunded, comatose, or convulsing (HSDB 1992). The victim is then given water or milk to dilute the chemical and activated charcoal to adsorb the chemical (Stutz and Janusz 1988). Although of unproven value in all cases of ingestion, administration of a cathartic such as magnesium sulfate may stimulate fecal excretion of the chemical before it is completely absorbed by the body (Stutz and Janusz 1988).

Little information specific to enhancing excretion or reducing body burden of 1,2,3-trichloropropane was available. However, animal data indicate that once absorbed orally in rats, 95-96% of 1,2,3-trichloropropane is excreted within 2 days. Most of the dose (56%) was excreted in the urine and 25% in the feces, with the remainder exhaled in the breath. (Sipes et al. 1982). Mitigation strategies to increase urinary output and dilute the chemical in humans might include flushing the gastrointestinal and circulatory systems with fluid while carefully monitoring fluid and electrolyte balances. Muscle, blood, liver, skin, and adipose tissue contained the largest amounts of radiolabled 1,2,3-trichloropropane following oral exposure in rats (Sipes et al. 1982).

Based on metabolic pathways for other chloroalkanes, 1,2,3-trichloropropane probably undergoes dehalogenation reactions via cytochrome P-450 dependent microsomal metabolism, resulting in the formation of highly reactive intermediates that may lead to protein and DNA adducts or lipid peroxidation (Ivanetich et al. 1978; Salmon et al. 1981; Van Dyke et al. 1971). If the mechanism of 1,2,3-trichloropropane induced toxicity involves the action of reactive intermediates, administration of chemicals that interfere with these metabolic processes might be effective in reducing adverse health effects.

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

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 1,2,3-Trichloropropane

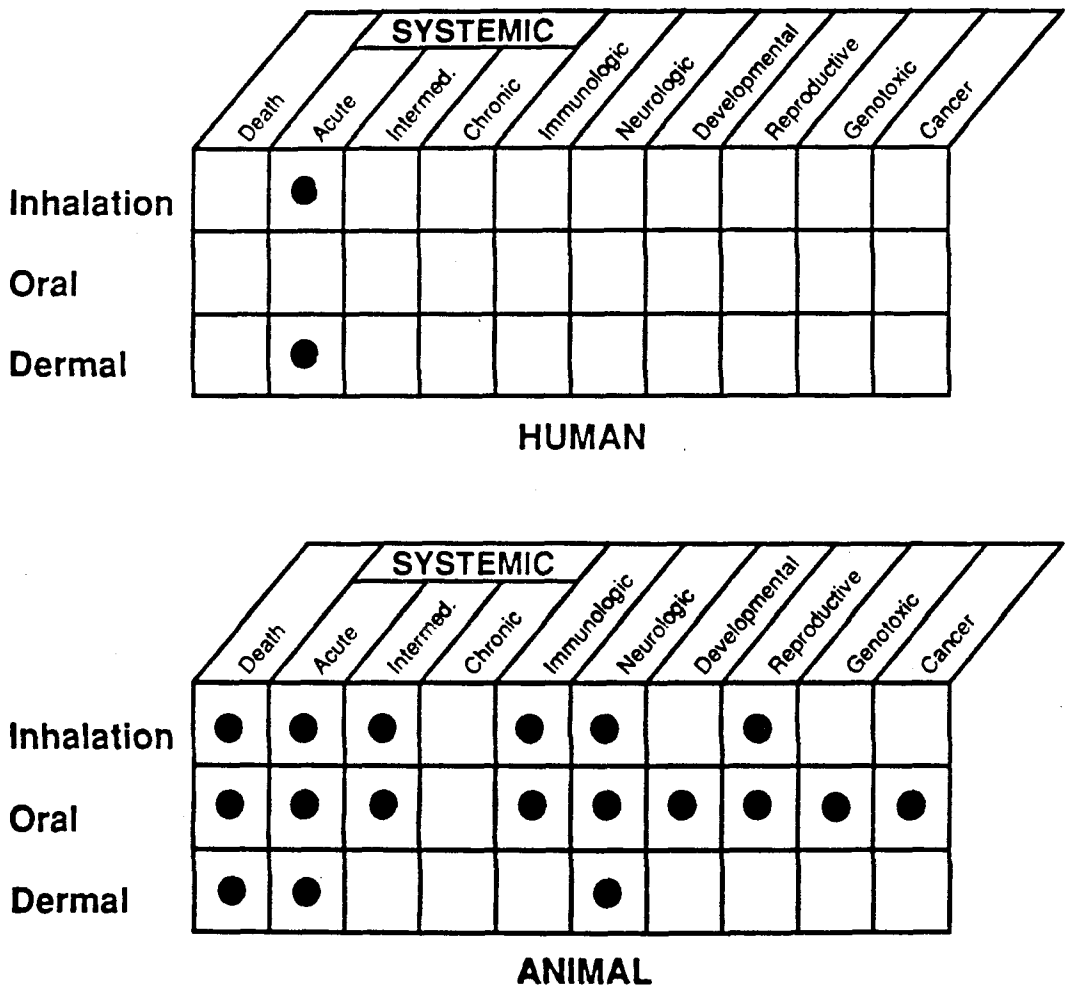
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2,3-trichloropropane are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,2,3-trichloropropane. Each dot in the figure 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).

Information on health effects of 1,2,3-trichloropropane in humans is limited to one report of systemic effects (eye and throat irritation) resulting from acute vapor exposure (Silverman et al. 1946). As indicated in Figure 2-3, data are available for the lethality, acute systemic toxicity, intermediate systemic toxicity, and reproductive effects of 1,2,3-trichloropropane in animals exposed by the oral and inhalation routes. Limited information is available for immunologic and neurologic effects by the inhalation and oral routes, and developmental and genotoxic effects by the oral route. Information is also available on the carcinogenicity of 1,2,3-trichloropropane in animals exposed by the oral route. Dermal toxicity studies of 1,2,3-trichloropropane provide acute lethality data and limited information on acute systemic and neurologic effects.

2.9.2 Data Needs

Acute-Duration Exposure. There is evidence that 1,2,3-trichloropropane vapor irritates the eyes and throat of humans (Silverman et al. 1946), but information on other targets of acute 1,2,3-trichloropropane toxicity in humans is not available. The respiratory tract, liver, and kidneys appear to be principal targets of 1,2,3-trichloropropane toxicity in rats and mice following inhalation or oral exposure for approximately 2 weeks (Miller et al. 1986a, 1986b; NTP 1983a, 1983b), and are likely targets of acute exposure in humans. Sufficient respiratory (nasal) effects data are available on which to base an acute MRL for inhalation exposure (Miller et al. 1986b). Respiratory effects of 1,2,3-trichloropropane, however, have been investigated in only two animal species (rats and mice). Studies with other species could confirm that the respiratory system is the most sensitive target of acute-duration inhalation exposure to 1,2,3-trichloropropane. Additional acute oral studies could help characterize the systemic effects of 1,2,3-trichloropropane at sublethal doses to enable determination of an acute-duration oral MRL. Information is available for effects of 1,2,3-trichloropropane on the skin and

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



● Existing Studies

eyes (Alpert 1982; Clark 1977; Gushow and Quast 1984), but not on other tissues, following acute nonlethal dermal exposure. There are no pharmacokinetic data available to support the identification of target organs across routes of exposure. Dermal studies may not be necessary to provide information on systemic toxicity since it appears, based on inhalation and oral data, that systemic effects of 1,2,3-trichloropropane, other than respiratory effects, may not be route-specific.

Intermediate-Duration Exposure. Information is not available on systemic effects of 1,2,3-trichloropropane in humans following intermediate-duration exposure by any route. The respiratory system, blood, liver, and kidneys appear to be principal targets of 1,2,3-trichloropropane in rats and mice exposed by inhalation or orally for intermediate durations (Johannsen et al. 1988; NTP 1983a, 1983b; Villeneuve et al. 1985), but studies longer than 2-4 months have not been performed (inhalation) or are not completed (NTP oral bioassay; see Section 2.8.3). The spleen and thyroid are less sensitive targets of intermediate-duration oral exposure in animals (NTP 1983a; Villeneuve et al. 1985), but the biological significance of effects observed in these organs is uncertain. Although intermediate-duration inhalation studies with animals are consistent with acute data in showing the respiratory system to be a target of 1,2,3-trichloropropane toxicity, intermediate-duration exposure levels that do not cause adverse respiratory (nasal) effects have not been determined. Although the respiratory system does not appear to be the most sensitive target for intermediate-duration oral exposure, drinking water studies could help ascertain if the pulmonary effects observed in gavage studies are a consequence of the method of treatment. Sufficient information is available from one study (NTP 1983a) to determine a dose that does not cause adverse hepatic and hematologic effects and to derive an MRL for intermediate-duration oral exposure based on these effects. Confidence in this MRL could be strengthened by additional studies. Additional information would be useful to determine if intermediate-duration exposure to 1,2,3-trichloropropane is capable of causing biologically significant alterations to the spleen and thyroid, particularly at doses in the range for nonadverse liver and hematologic effects. Information is not available on effects of intermediate-duration dermal exposure to 1,2,3-trichloropropane in animals, and there are no pharmacokinetic data to support the identification of target organs across routes of exposure. Acute-duration toxicity data, however, suggest that systemic effects of 1,2,3-trichloropropane, other than respiratory effects, may not be route-specific.

Chronic-Duration Exposure and Cancer. Information is not available regarding the chronic toxicity of 1,2,3-trichloropropane in humans or animals exposed by any route. Chronic studies in animals could provide information on progression or reversibility of effects caused by subchronic exposure, particularly respiratory system effects following inhalation exposure and liver and hematological effects following oral exposure. Chronic studies in animals also could enable identification of effects produced by low-level exposure that might not be detected in shorter-duration studies.

The carcinogenicity of 1,2,3-trichloropropane in humans or animals exposed by any route has not been evaluated. 1,2,3-trichloropropane induced multiple site tumors in both sexes of rats and mice exposed orally (NTP 1991). The most frequently induced tumors were found in the oral and forestomach mucosa, suggesting local reactivity, in addition to systemic reactivity. As discussed in Section 2.8.3, there is evidence that 1,2,3-trichloropropane is metabolized to reactive intermediates that can bind to DNA (Weber and Sipes 1988). Since these intermediates can interact with DNA, and respiratory effects of inhaled 1,2,3-trichloropropane could be due to local reactivity, it is reasonable to assume that prolonged inhalation exposure to 1,2,3-trichloropropane would produce local and systemic tumors. An inhalation bioassay would be useful to confirm this expectation and to determine the airborne concentrations necessary to produce a carcinogenic response. 1,2,3-Trichloropropane could also be tested to determine whether it is carcinogenic by the dermal route.

Genotoxicity. Information on the genotoxicity of 1,2,3-trichloropropane in humans is not available. The genotoxicity of 1,2,3-trichloropropane has been evaluated in several assays that provide limited evidence of mutagenicity in bacteria and clastogenicity (sister chromatid exchanges) in cultured hamster cells (Haworth et al. 1983; Ratpan and Plaumann 1988; Stolzenberg and Hine 1980; Von der Hude et al. 1987). 1,2,3-Trichloropropane did not induce dominant lethal mutations in rats exposed orally for 5 days (Saito-Suzuki et al. 1982). Additional studies in mammalian cells in vitro and in animals would more fully characterize the genotoxicity of 1,2,3-trichloropropane.

Reproductive Toxicity. Information on reproductive effects of 1,2,3-trichloropropane in humans is not available. There were no reproductive effects in rats exposed to a moderately high oral dose for 5 days or by inhalation to a relatively low concentration (near the lowest concentrations producing respiratory effects) for 10 weeks prior to mating (Johannsen et al. 1988; Saito-Suzuki et al. 1982). Oral exposure to lethal doses for 4 months caused decreased testes and epididymis weights and no effects on testicular histology or sperm in rats and mice, but reproductive function was not evaluated (NTP 1983a, 1983b). Inhalation exposure to lethal concentrations of 1,2,3-trichloropropane for 4 weeks caused decreased testes and ovary weights in rats, but reproductive organ histology and sperm and reproductive function were not evaluated (Johannsen et al. 1988). Insufficient toxicokinetic data are available to determine if 1,2,3-trichloropropane is likely to produce similar reproductive effects by different routes of exposure. Evaluation of reproductive function in animals following prolonged low dose oral exposure and inhalation exposure at high (near maximum tolerated) concentrations, therefore, would more fully assess the potential reproductive toxicity of 1,2,3-trichloropropane. Multigeneration or continuous-breeding studies in animals would provide a better basis for evaluating reproductive toxicity but may not be desirable unless other studies indicate that the reproductive

system is a target organ. Reproductive toxicity data are particularly desirable prior to developing MRLs.

Developmental Toxicity. Information on the developmental toxicity of 1,2,3-trichloropropane in humans is not available. There were no effects on growth or viability of offspring of rats exposed by inhalation to low concentrations of 1,2,3-trichloropropane prior to mating and during gestation, but teratogenicity was not evaluated (Johannsen et al. 1988). 1,2,3-Trichloropropane was not teratogenic in rats treated by intraperitoneal injection (Hardin et al. 1981). Insufficient toxicokinetic data are available to determine if 1,2,3-trichloropropane is likely to produce similar developmental effects by different routes of exposure. Additional evaluations using natural routes of exposure and higher doses, particularly inhalation and oral teratogenicity studies, would more fully evaluate the developmental toxicity potential of 1,2,3-trichloropropane. Developmental toxicity data are particularly desirable prior to developing MRLs.

Immunotoxicity. Information on the immunological effects of 1,2,3-trichloropropane in humans is not available. Effects such as lymphoid depletion and decreased weight of the spleen of rats and mice exposed orally and by inhalation to near-lethal levels of 1,2,3-trichloropropane for several weeks could have immunological significance (Johannsen et al. 1988; NTP 1983a). Limited evidence from one study suggests that 1,2,3-trichloropropane may be a weak dermal sensitizer in guinea pigs (Clark 1977). The only other skin sensitization study of 1,2,3-trichloropropane (Alpert 1982), also performed with guinea pigs, was negative and provides evidence that the vehicle may have accounted for the effect observed by Clark (1977). Sensitization by 1,2,3-trichloropropane from other routes of exposure has not been evaluated. Immunoassays and additional sensitization tests would help assess the immunotoxic potential of 1,2,3-trichloropropane.

Neurotoxicity. Information on the neurological effects of 1,2,3-trichloropropane in humans is not available. Signs suggestive of CNS impairment occur only in animals exposed to acute lethal levels of 1,2,3-trichloropropane by the inhalation, oral, and dermal routes (Alpert 1982; Clark 1977; Gushow and Quast 1984; Union Carbide 1958), but these do not necessarily indicate that 1,2,3-trichloropropane is neurotoxic because they could be due to other causes in dying animals. There is evidence that exposure to 1,2,3-trichloropropane does not cause histopathological lesions in the CNS (Johannsen et al. 1988; Miller et al. 1986a; NTP 1983a, 1983b), but this does not necessarily indicate that 1,2,3-trichloropropane is nonneurotoxic because behavioral, neurochemical, and neurophysiological examinations were not performed. Overall, there is evidence that neurotoxicity is a critical effect of 1,2,3-trichloropropane.

Epidemiological and Human Dosimetry Studies. Health effects of 1,2,3-trichloropropane in humans have only been described as a consequence of intentional vapor exposure in a study of sensory response. As indicated in

Chapter 5, there is probably no identifiable subpopulation with exclusive or predominant exposure to 1,2,3-trichloropropane in the general populace or workplace. If such a population is identified, excreted 1,2,3-trichloropropane or its metabolites could probably be correlated with exposure or health effects. Metabolites specifically attributable to 1,2,3-trichloropropane, however, are presently unknown.

Biomarkers of Exposure and Effect. There are no known biomarkers of exposure for 1,2,3-trichloropropane in humans. Studies with rats suggest that respiratory or urinary excretion of 1,2,3-trichloropropane may be sufficient for monitoring purposes (Sipes et al. 1982). Additional studies could help determine the feasibility of using 1,2,3-trichloropropane in the breath or urine as a biomarker of exposure. Mild anemia and alterations in liverassociated serum enzymes occurred in rats treated with 1,2,3-trichloropropane (NTP 1983a) but are not useful as biomarkers of exposure because they can be due to many causes and might not occur in humans. Information on effects specific for 1,2,3-trichloropropane would be helpful for developing a biomarker of exposure for 1,2,3-trichloropropane.

There are no known biomarkers of effects for 1,2,3-trichloropropane in humans. One study with rats (NTP 1983a) suggests that anemia and alterations of serum enzymes (e.g., decreased serum pseudocholinesterase activity) might be sensitive biomarkers for hematologic and hepatic effects of 1,2,3-trichloropropane, respectively. Additional animal studies or examination of humans with known exposure to 1,2,3-trichloropropane would help determine if 1,2,3-trichloropropane is likely to cause anemia or consistent serum enzyme alterations in humans.

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

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

Mitigation of Effects. Based on limited toxicokinetic data for 1,2,3-trichloropropane and information on the metabolism of other halogenated alkanes, it is anticipated that 1,2,3-trichloropropane can undergo dehalogenation reactions catalyzed by microsomal mixed function oxidases. Depending on the reaction mechanism(s), reactive intermediates could be formed. Also it is possible that 1,2,3-trichloropropane itself contributes to toxicity. Studies elucidating the mechanism of action and identity of reactive intermediates of 1,2,3-trichloropropane would be useful in planning research aimed at developing agents that could interfere with the mechanism of toxicity, thereby mitigating the effects.

2.9.3 On-going Studies

A bioassasy in which rats and mice were treated by gavage for 2 years has been completed and recently approved (NTP 1991). The doses of 1,2,3-trichloropropane used in the bioassay were 0, 3, 10, and 30 mg/kg in rats and 0, 6, 20, and 60 mg/kg in mice (Burka 1990a). Preliminary results indicate that treatment resulted in increased incidences of tumors in both species (Mahmood et al. 1988; Weber and Sipes 1988).

The final report of an NTP continuous-breeding study is in preparation (Burka 1990b).

The results of a metabolism and mutagenicity study of 1,2,3-trichloropropanehave been reported as an abstract (Mahmood et al. 1988). Rats that were administered 30 mg/kg of ^{14}C-1,2,3-trichloropropane by gavage excreted approximately 50%, 20%, and 20% of the radioactivity in the urine, feces, and as carbon dioxide, respectively, in the following 60 hours. Two urinary metabolites were identified as N-acetyl-S-(3-chloro-2-hydroxypropyl) cysteine and 3-chloro-2-hydroxypropyl cysteine. Radioactivity was most concentrated in the liver, kidney, and forestomach. 1,2,3-Trichloropropane was mutagenic in Salmonella typhimurium TA100 in the Ames assay only in the presence of S9 or microsomes, and mutagenicity decreased upon addition of glutathione. The urine from the treated rats or synthetic N-acetyl-S-(3-chloro-2-hydroxypropyl) cysteine were not mutagenic in this assay.

Rats were administered a 30 mg/kg dose of ^{14}C-1,2,3-trichloropropane by intraperitoneal injection in a preliminary investigation into the role of biotransformation in 1,2,3-trichloropropane-induced tumor formation (Weber and Sipes 1988). Covalent binding to hepatic protein and DNA was demonstrated, suggesting that 1,2,3-trichloropropane is genotoxic. In vitro studies,

however, showed that glutathione decreased protein binding and increased the formation of water-soluble ^{14}C-1,2,3-trichloropropane equivalents, and that there was no significant covalent binding of 1,2,3-trichloropropane to DNA. The in vitro data indicated that the role of biotransformation in 1,2,3-trichloropropane-induced genotoxicity is still unclear.

The results of an investigation of the cardiotoxic and hepatic effects of 1,2,3-trichloropropane were reported in an abstract (Robinson et al. 1989). Rats were administered various doses of 1,2,3-trichloropropane by gavage for durations ranging from 1 to 10 days. Doses of 0.2, 0.4, 0.6, and 0.8 mmol/kg (29.5-117.9 mg/kg) produced myocardial necrosis in 0%, 0%, 10%, and 80% of the rats, respectively. This effect was observed after 6 days of treatment at 0.8 mmol/kg (117.9 mg/kg). Doses of 1.6-2.8 mmol/kg (235.9-412.8 mg/kg) caused increasing hepatotoxicity and eventual death but no myocardial necrosis. Tissue levels of 1,2,3-trichloropropane were markedly increased after 10 days compared to l-day exposure, suggesting bioaccumulation. Peripheral catecholamine depletion with 6-hydroxydopamine reduced myocardial necrosis from moderate to minimum severity. The results of this study suggested that dose and time of 1,2,3-trichloropropane exposure determine the appearance of heart or liver toxicity, and that cardiotoxic effects of 1,2,3-trichloropropane may involve bioaccumulation and sympathoadrenergic factors.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

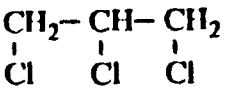
Data pertaining to the chemical identity of 1,2,3-trichloropropane are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

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

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of 1,2,3-Trichloropropane

Characteristic	Information	Reference
Chemical name	1,2,3-Trichloropropane	CAS 1989
Synonyms	Allyl trichloride; glycerol trichlorohydrin; trichlorohydrin	CAS 1989
Trade names	No data	
Chemical formula	$C_3H_5Cl_3$	CAS 1989
Chemical structure		
Identification numbers:		
CAS registry	96-18-4	CAS 1989
NIOSH RTECS	TZ9275000	RTECS 1989
EPA hazardous waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	No data	
HSDB	1340	CHEMLINE 1989
NCI	C60220	HSDB 1989
USDA	AI3-26040	CHEMLINE 1989

CAS = Chemical Abstracts Service
DOT/UN/NA/IMCO = Department of Transportation/ United Nations/ North America/ International Maritime Dangerous Goods Code
HSDB = Hazardous Substances Data Bank
NCI = National Cancer Institute
NIOSH = National Institute for Occupational Safety and Health
OHM/TADS = Oil and Hazardous Materials/ Technical Assistance Data System
RTECS = Registry of Toxic Effects of Chemical Substances
USDA = United States Department of Agriculture

TABLE 3-2. Physical and Chemical Properties of 1,2,3-Trichloropropane

Property	Information	Reference
Molecular weight	147.43	Weast 1985
Color	Colorless	Hawley 1981
Physical state	Liquid	Hawley 1981
Melting point	-14.7°C	Williams 1949
Boiling point	156.8°C	Riddick et al. 1986
Density at 20°C	1.3888 g/cm^3	Riddick et al. 1986
Dissociation constant at 25°C (pKa)	No data	
Odor	Strong, acrid; trichloroethylene-like: "sweet smelling"	Ruth 1986; HSDB 1989; McNeill 1979
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20°C	1750 mg/L	Riddick et al. 1986
Organic solvents	Soluble in ethyl alcohol and higher alcohols, chloroform and other chlorinated hydrocarbons, ethyl ether, benzene	Weast 1985; Williams 1949
Partition coefficients:		
Log octanol/water	1.98	EPA 1988b
Log K_oc[a]	1.99 (estimated)	Lyman et al. 1982
Bioconcentration factor[b]	9.2 (estimated)	Lyman et al. 1982
Vapor pressure at 25°C	3.1 mmHg	Mackay et al. 1982
Henry's law constant: at 25°C[c]	3.17×10^{-4} atm-m3/mol (calculated)	Lyman et al. 1982
Autoignition temperature	304°C (580°F)	Hawley 1981
Flashpoint		
open cup	82.2°C (180°F)	Hawley 1981
open cup	78.9°C (174°F)	Williams 1949
closed cup	73.3°C (164°F)	Williams 1949

TABLE 3-2 (Continued)

Property	Information	Reference
Flammability limits	No data	
Conversion factors		
ppm (v/v) to mg/m^3 in air (20°C)	1 ppm (v/v)x6.03 = mg/m^3	
mg/m^3 to ppm (v/v) in air (20°C)	1 mg/m^3x0.166 = ppm (v/v)	
Explosive limits	No data	

[a]Calculated from water solubility using equation 4-7 (Lyman et al. 1982).
[b]Calculated $_f$rom from log K_ow using equation 5-2 (Lyman et al. 1982).
[c]Calculated from vapor pressure and water solubility using equation 15-8 (Lyman et al. 1982).

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Recent data regarding production volumes for 1,2,3-trichloropropane are not available. The estimated 1977 production volume for the chemical ranged from 21 to 110 million pounds (EPA 1989b). Current manufacturers of 1,2,3-trichloropropane include Dow Chemical U.S.A., Freeport, Texas, and Shell Oil Company, Deer Park, Texas (SRI 1989). In 1977, two additional manufacturing locations were Dow Chemical U.S.A., a major producer in Midland, Michigan, and Columbia Organic Chemicals Co., a minor producer in Columbia, South Carolina (EPA 1989b). 1,2,3-Trichloropropane can be produced via the chlorination of propylene (Hawley 1981). Other reported methods for producing 1,2,3-trichloropropane include the addition of chlorine to ally1 chloride, reaction of thionyl chloride with glycerol, and the reaction of phosphorus pentachloride with either 1,3- or 2,3-dichloropropanol (NIOSH 1981; Williams 1949). 1,2,3-Trichloropropane also may be produced in potentially significant amounts as a byproduct of processes primarily used to produce other chemicals, including dichloropropene (a soil fumigant and nematocide), propylene chlorohydrin, propylene oxide, dichlorohydrin, and glycerol (Baier et al. 1987; NIOSH 1981). Technical-grade 1,2,3-trichloropropane reportedly varies between 97.5% and 99.4% purity (Alberti 1982; NTP 1983a). The material tested by the NTP (1983a) contains the following impurities: 0.066% water, 0.14% unspecified chlorohexene, two unspecified chlorohexadienes (0.24% and 0.13%), and total acidity of 48 ppm (as HCl).

4.2 IMPORT/EXPORT

No data concerning the import or export of 1,2,3-trichloropropane were located.

4.3 USE

1,2,3-Trichloropropane has, in the past, been used mainly as a solvent and extractive agent. No current information is available that indicates that the compound is still used for these purposes today. It dissolves a variety of resins, oils, waxes, and other materials while having a low solubility in water (Williams 1949). Common uses have included use as a paint- and varnish-remover, a cleaning and degreasing agent, and a cleaning and maintenance reagent (Hawley 1981; NIOSH 1981). Currently, it is used as a chemical intermediate, for example, in the production of polysulfone liquid polymers and dichloropropene, synthesis of hexafluoropropylene, and as a crosslinking agent in the synthesis of polysulfides (Baier et al. 1987; Ellerstein and Bertozzi 1982; Gangal 1980; HSDB 1989). No data were found concerning the approximate amounts currently used for particular purposes.

4.4 DISPOSAL

1,2,3-Trichloropropane has been identified as a hazardous waste by the EPA, and the disposal of this compound is regulated under the Resource

Conservation and Recovery Act (RCRA). Specific information regarding the federal regulations of land disposal of 1,2,3-trichloropropane is available (EPA 1988a). 1,2,3-Trichloropropane can be disposed of via atomization in a suitable incinerator equipped with appropriate effluent gas scrubbers (HSDB 1989). In case of accidental spills, the chemical may be disposed of by absorption onto vermiculite, dry sand, earth, or similar material followed by disposal in a secured landfill (HSDB 1989); however, land disposal may no longer be allowed by the disposal regulations discussed above. Significant removal of 1,2,3-trichloropropane from waste water and sewage may be accomplished through the use of activated sludge treatment processes (Matsui et al. 1975). No data were found concerning the approximate amounts disposed by the various methods.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

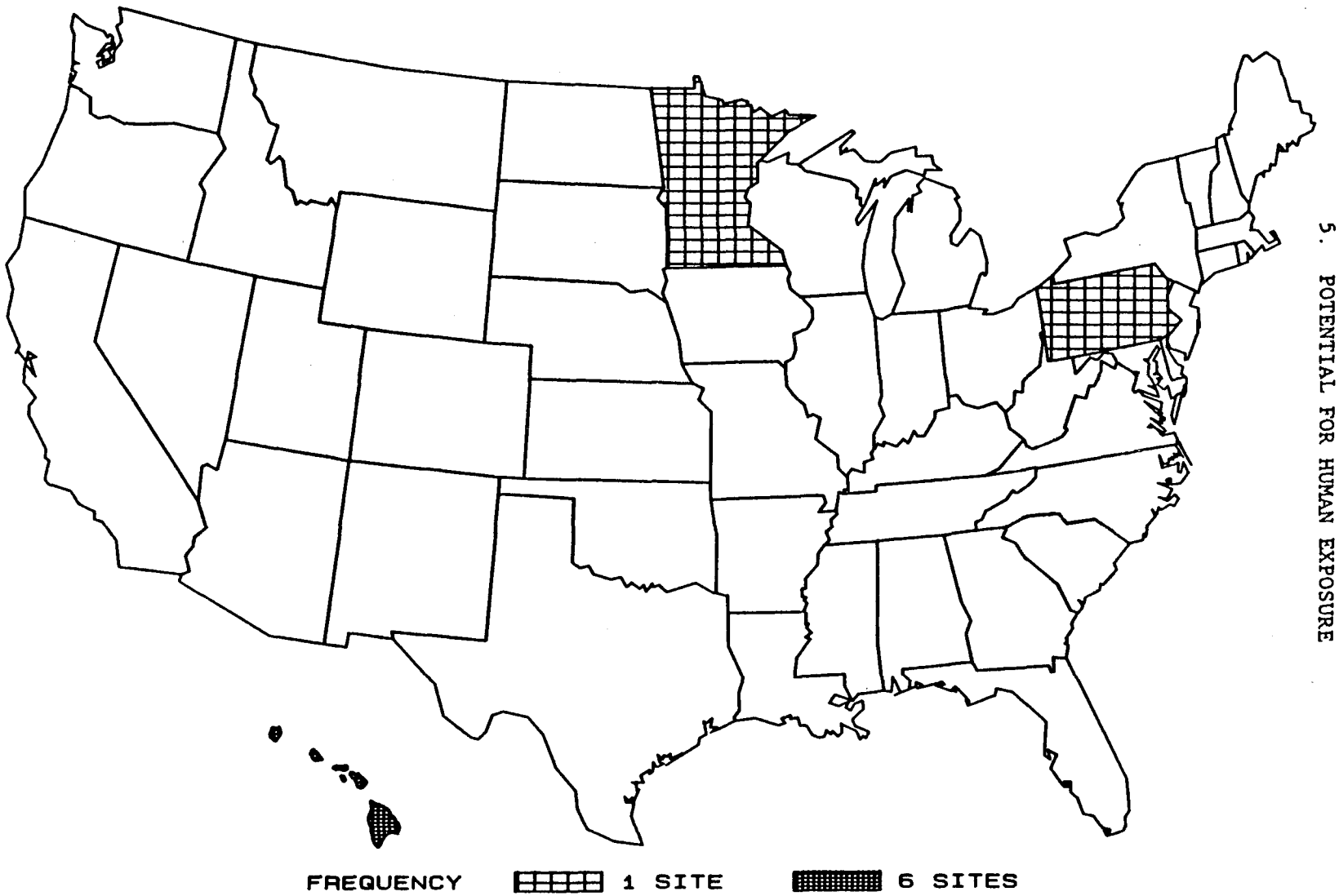
1,2,3-Trichloropropane is a man-made chemical that is present in the environment as a result of anthropogenic activity. Releases to the environment are likely to occur as a result of its manufacture, formulation, and use as a solvent and extractive agent, paint- and varnish-remover, cleaning and degreasing agent, cleaning and maintenance reagent, and chemical intermediate (HSDB 1989). Releases may occur as a result of the disposal of wastes from production of 1,2,3-trichloropropane and disposal of products that contain the chemical, especially at hazardous waste sites that received 1,2,3-trichloropropane-containing wastes. Release to soil can occur through the use of certain soil fumigants and nematocides that are known to contain 1,2,3-trichloropropane as an impurity and through the disposal of 1,2,3-trichloropropane-containing sewage sludge from municipal sewage treatment plants.

In ambient air, the primary removal process is expected to be the vaporphase reaction with photochemically generated hydroxyl radicals. In surface waters, the primary removal process is likely to be volatilization. In soil, the primary removal processes are volatilization from near-surface soil and leaching to groundwater. Aerobic biodegradation is probably a slow process in natural waters and soil. It may persist in groundwater for a relatively long time.

Data regarding the concentrations of 1,2,3-trichloropropane in the environment are limited, but concentrations should not be large except in case of an accidental spill. It has been found at low levels in the United States in a few rivers and bays, drinking water, groundwater, and hazardous waste sites. The EPA has identified 1,177 NPL sites. 1,2,3-Trichloropropane has been found at eight of the sites evaluated for the presence of this chemical. 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 EPA, the number may change. The frequency of these sites within the United States can be seen in Figure 5.1.

The general population can be exposed to low levels of 1,2,3-trichloropropane mainly by ingesting contaminated water. Members of the general population living near waste sites that contain 1,2,3-trichloropropane may be exposed to low levels of 1,2,3-trichloropropane in their drinking water if they obtain their household water from a well. Additional exposure may occur through the inhalation of contaminated air, especially for those who live near facilities that manufacture or use 1,2,3-trichloropropane or at treatment or disposal facilities. Inhalation and dermal exposure may occur during the use of consumer products containing 1,2,3-trichloropropane, such as certain paint removers. It is difficult to assess the extent of general population and occupational exposure because data are lacking. However, significant exposure to 1,2,3-trichloropropane may be unlikely because the compound may no longer be used for purposes other than a chemical intermediate, and current

FIGURE 5-1. FREQUENCY OF NPL SITES WITH 1,2,3-TRICHLOROPROPANE CONTAMINATION *



* Derived from View 1989

manufacturing processes generally occur in closed and tightly sealed systems (NIOSH 1981). The National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 statistically estimated that 492 workers are potentially exposed to 1,2,3-trichloropropane in the United States. The NOES database does not contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. This summary provides only estimates of the number of workers potentially exposed to chemicals in the workplace. Occupational exposure probably results from inhalation and dermal contact.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Data on releases of 1,2,3-trichloropropane to the atmosphere are lacking. Based on the few data available, current releases to the air are expected to be relatively small. Minor releases may have occurred as exhaust, stack, and fugitive emissions from its manufacture, formulation, and use as a solvent (HSDB 1989). 1,2,3-Trichloropropane may have been released in the past into the air as a result of its use as a paint- and varnish-remover, a degreasing agent, and a cleaning and maintenance reagent (Hawley 1981; NIOSH 1981). No information was found that indicates that 1,2,3-trichloropropane is still used for these purposes today. Very small amounts may be released during its use as a chemical intermediate and as a result of its formation during the synthesis of other organic chemicals (see Section 4.1). Volatilization from contaminated surface waters, effluent waters, and near-surface soils may also be minor atmospheric sources of this compound. This includes volatilization from identified and unidentified hazardous waste dumps that contain 1,2,3-trichloropropane and from farmland treated with 1,2,3-trichloropropane-contaminated fumigants and nematocides (no information is available to determine whether or not the soil fumigants and nematocides currently manufactured contain 1,2,3-trichloropropane). Small amounts may be released *to* the air during treatment of water containing 1,2,3-trichloropropane, because some of the chemical may be removed via evaporative stripping from the water.

5.2.2 Water

Data on the release of 1,2,3-trichloropropane to environmental waters are lacking. Based on the few data available, current releases to environmental waters are expected to be relatively small. Releases to surface water may have occurred through runoff of waste water from hazardous waste sites containing 1,2,3-trichloropropane and runoff from farmland treated with certain soil fumigants and nematocides that contain 1,2,3-trichloropropane. Releases to surface and groundwater may have occurred as a result of the improper disposal of 1,2,3-trichloropropane-containing industrial wastes or wastes from its use in paint- and varnish-removers, cleaning and degreasing agents, and maintenance reagents. Releases to groundwater may have occurred

as a result of the chemical leaching through soil at waste sites and agricultural soil treated with fumigants that contain the chemical. Small amounts of the chemical may have entered surface waters as a result of washout from 1,2,3-trichloropropane-contaminated air; however, some of the 1,2,3-trichloropropane removed from the atmosphere by washout is likely to have re-entered the atmosphere by volatilization. The chemical was found in groundwater at 0.71% of the sites in the Contract Laboratory Program Statistical Database (CLPSD) at a geometric mean concentration of 57.3 µg/L (CLPSD 1989). Note that the CLPSD includes data from both NPL and non-NPL sites.

5.2.3 Soil

Data on releases of 1,2,3-trichloropropane to soils are sparse, which makes a quantitative estimation of the magnitude of such releases impossible. However, releases to soils are expected to be relatively small based upon the available data. Releases to farmland soil have occurred as a result of the use of certain soil fumigants and nematocides known to contain 1,2,3-trichloropropane as an impurity. No current information is available, however, that indicates that these soil fumigants and nematocides still contain 1,2,3-trichloropropane. Releases of the chemical to soil may have occurred as a result of disposal of 1,2,3-trichloropropane-containing sewage sludge from municipal sewage treatment plants (Jacobs and Zabik 1983). Very small amounts of the chemical may be brought to the surface of the earth as a result of washout from 1,2,3-trichloropropane-containing air; however, much of the 1,2,3-trichloropropane removed from the atmosphere by washout may re-enter the atmosphere by volatilization from near-surface soil. Land disposal of wastes from its use in paint- and varnish-removers, cleaning and degreasing agents, and cleaning and maintenance reagents may have released 1,2,3-trichloropropane to soil. The chemical was found in soil at 0.71% of the sites in the CLPSD at a geometric mean concentration of 204 µg/kg (CLPSD 1989). Note that the CLPSD includes data from both NPL and non-NPL sites.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

No experimental or predictive data were located in the literature regarding the transport of 1,2,3-trichloropropane in the atmosphere. 1,2,3-Trichloropropane is expected to exist in the atmosphere predominantly in the vapor phase, based on its vapor pressure (Table 3-2) (Eisenreich et al. 1981; MacKay et al. 1982). The speculation that substantial amounts of 1,2,3-trichloropropane are not likely to be present in the particulate phase indicates that dry deposition to the earth's surface will not be an important removal process. Based upon its low water solubility and moderate vapor pressure (Table 3-2), very small amounts of 1,2,3-trichloropropane present in

air may be removed by wet deposition; however, much of the 1,2,3-trichloropropane removed from the atmosphere by washout is likely to re-enter the atmosphere by volatilization.

Based upon an estimated soil organic carbon partition coefficient (K_{oc}) of 98 (calculated from water solubility) (Lyman et al. 1982; Riddick et al. 1986), 1,2,3-trichloropropane is expected to display high mobility in soil (Swann et al. 1983); therefore, it has the potential to leach into groundwater. This predicted mobility is confirmed by the detection of 1,2,3-trichloropropane in groundwater from various locations (see Section 5.4.2). The vapor pressure of 1,2,3-trichloropropane (3.1 mmHg at 25°C) (MacKay et al. 1982), and the calculated Henry's law constant (3.17×10^{-4} atm-m^3/mol at 25°C) (Lyman et al. 1982) suggest that volatilization from either dry or moist soil to the atmosphere will be a significant environmental process.

1,2,3-Trichloropropane in surface water is expected to volatilize rapidly to the atmosphere. An experimental half-life of 56.1 minutes has been measured for evaporation of 1,2,3-trichloropropane from a 1 ppm solution, with a depth of 6.5 cm, stirred with a shallow pitch propeller at 200 rpm at 25°C under still air (less than 0.2 mph air currents) (Dilling 1977). Using the Henry's law constant, a half-life of 6.9 hours was calculated for evaporation from a model river 1 m deep, flowing at 1 m/set, with a wind velocity of 3 m/set, and neglecting adsorption to sediment (Lyman et al. 1982). A volatilization half-life of 3.5 days from a model pond can be estimated (EPA 1985). 1,2,3-Trichloropropane is not expected to significantly adsorb to sediment and suspended organic matter based upon the estimated K_{oc} of 98 (calculated from water solubility) (Lyman et al. 1982; Riddick et al. 1986). It is also not expected to significantly bioconcentrate in fish and aquatic organisms based upon an estimated bioconcentration factor (BCF) of 9.2 (calculated from log octanol-water partition coefficient (K_{ow}) (EPA 1988b; Lyman et al. 1982). No data were located to indicate a potential for 1,2,3-trichloropropane to biomagnify from lower to higher trophic states of the food chain, but based upon the estimated BCF, this is not likely.

5.3.2 Transformation and Degradation

5.3.2.1 Air

The primary degradation process for 1,2,3-trichloropropane in the atmosphere is expected to occur via gas-phase reaction with photochemically produced hydroxyl radicals. The rate constant for this process is an estimated 1.0475×10^{-12} cm^3/molecule-sec (Atkinson 1987). This corresponds to a half-life of 15.3 days at an estimated atmospheric concentration of 5×10^5 hydroxyl radicals/cm^3. Direct photolysis of 1,2,3-trichloropropane is not

expected to occur in the atmosphere because the chemical lacks a chromophore that absorbs light at environmentally significant wavelengths (greater than 290 nm) (Silverstein et al. 1974).

5.3.2.2 Water

Degradation of 1,2,3-trichloropropane in natural waters is expected to be a slow process. The chemical should volatilize from surface waters before significant degradation can occur. Hydrolysis of 1,2,3-trichloropropane in natural waters is not expected to be a significant removal process. The measured neutral and base hydrolysis rate constants at 25°C are 1.8×10^{-6} $hour^{-1}$ and 9.9×10^{-4} M^{-1} $hour^{-1}$, respectively (EPA 1988c). These rate constants correspond to a hydrolysis half-life of 44 years over a pH range of 5-9. Direct photolysis of 1,2,3-trichloropropane is not expected to occur in environmental waters because the chemical lacks a chromophore that absorbs light at environmentally significant wavelengths (greater than 290 nm) (Silverstein et al. 1974).

No studies were located regarding the biodegradation of 1,2,3-trichloropropane in natural waters. An aqueous screening study with activated sewage sludge has indicated that 1,2,3-trichloropropane can be removed by biological treatment processes and that at least part of the removal was due to volatilization. However, this study cannot be used to predict the biodegradability of this compound under natural conditions. Other authors have observed that halogenated hydrocarbons, in general, and especially those with multiple chlorine substitution, such as 1,1,2-trichloroethane and 1,1,2,2-tetrachloroethane, are recalcitrant towards biodegradation (Kawasaki 1980; Tabak et al. 1981). No data concerning the potential for anaerobic aqueous biodegradation of 1,2,3-trichloropropane were found.

5.3.2.3 Soil

No data specifically regarding the degradation of 1,2,3-trichloropropane in soil were found. However, it has been observed that 1,2-dichloropropane will not significantly biodegrade in soil (Roberts and Stoydin 1976). Therefore, 1,2,3-trichloropropane is expected to be even less biodegradable because it contains an additional chlorine. The rate of 1,2,3-trichloropropane loss from soil due to biodegradation may not be significant when compared with its loss by volatilization and leaching from soil. 1,2,3-Trichloropropane will be lost from the soil by evaporation (from both moist and dry near-surface soil) and by leaching to groundwater before 1,2,3-trichloropropane will hydrolyze in soil. Direct photolysis on the surface of soil will not occur.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

No data were located regarding the detection of 1,2,3-trichloropropane in ambient air in the United States. Therefore, no estimate of U.S. atmospheric levels of the chemical, including background levels, is possible.

5.4.2 Water

Limited data are available regarding the detection of 1,2,3-trichloropropane in environmental waters. It has been detected by one of the sampling techniques at less than 0.2 µg/L in drinking water from the Carrollton Water Plant in New Orleans, Louisiana, sampled during August, 1974; however, since two of the three sampling techniques failed to detect the compound, the significance of this detection is in question (Keith et al. 1976). 1,2,3-Trichloropropane has been qualitatively detected in the drinking water of Cincinnati, Ohio, sampled during 1978 (EPA 1984), and Ames, Iowa, on an unspecified date (EPA 1987). Data from the EPA STORET Data Base indicate that 1,2,3-trichloropropane was found in 39% of 941 samples of groundwater at a median concentration of 0.69 µg/L, at an average concentration of 1.0 µg/L, and a range of trace (below unspecified detection limit) to 2.5 µg/L (STORET 1989). It has been found at concentrations ranging from 0.1 to 5.0 µg/L in groundwater samples from California and Hawaii during small- and large-scale retrospective studies of farmlands possibly treated with fumigants and nematocides that contained 1,2,3-trichloropropane as an impurity (Cohen et al. 1986, 1987). The locations that had 1,2,3-trichloropropane-contaminated wells included the island of Oahu, Hawaii, and the Central Valley of California. Typical concentrations ranged from 0.2 to 2 µg/L. 1,2,3-Trichloropropane was found in water from nine of nine wells in Oahu, Hawaii, sampled in 1983 and 1984 at maximum concentrations ranging from 0.30 to 2.8 µg/L (Oki and Giambelluca 1987). The wells had been closed previously to drinking water use due to contamination with other halogenated hydrocarbons.1,2,3-Trichloropropane has been detected in groundwater from 2 of 10 sites in an agricultural community in Suffolk County, New York, at concentrations of 6 and 10 µg /L (Lykins and Baier 1985).

1,2,3-Trichloropropane was qualitatively found in 1 of 30 water samples from the Delaware, Schuylkill, and Lehigh Rivers, taken February 17-20, 1976 (DeWalle and Chian 1978). 1,2,3-Trichloropropane was qualitatively found in water from Narragansett Bay, Rhode Island, sampled during the summers of 1979 and 1980, and the winters of 1980 and 1981 (Wakeham et al. 1983). Some samples reportedly contained significant levels of the chemical. The chemical was qualitatively detected in effluent from an advanced waste treatment plant in Lake Tahoe, California, in 1974 (EPA 1984). The chemical was found in groundwater at 0.71% of the sites in the CLPSD, which includes data from both NPL and non-NPL sites, at a geometric mean concentration of 57.3 µg/L (CLPSD 1989). 1,2,3-Trichloropropane was found in 69 of 141 samples of sewage

sludges from municipal sewage treatment plants in Michigan in 1980 (Jacobs and Zabik 1983). The median and average concentrations of 1,2,3-trichloropropane in the sludges were 0.352 and 1.07 mg/kg, respectively, and the range was 0.00459-19.5 mg/kg on a dry-weight basis.

5.4.3 Soil

Limited data are available regarding the detection of 1,2,3-trichloropropane in soil samples. It has been found in soil samples from California and Hawaii during small- and large-scale retrospective studies at levels typically ranging from 0.2 to 2 ppb (Cohen et al. 1987). It was found at least 10 feet down in the soil profiles in Hawaii. 1,2,3-Trichloropropane may be present in these soils as a result of the use of dichloropropene (a soil fumigant and nematocide). 1,2,3-Trichloropropane is used in the preparation of this nematocide and is an impurity in the formulation of it (Baier et al. 1987). 1,2,3-Trichloropropane was not found in any of the soil samples from the sites in the CLPSD (1988). The detection of the chemical in the groundwater of hazardous waste sites, however, suggests that it is released to soil at these sites. The chemical was found in soil at 0.71% of the sites of the CLPSD at a geometric mean concentration of 204 pg/L (CLPSD 1989); the CLPSD includes data from both NPL and non-NPL sites.

5.4.4 Other Environmental Media

1,2,3-Trichloropropane has been qualitatively identified as a component of ethylene dichloride-tar, a tarlike, oily waste byproduct of vinyl chloride production that had been disposed of by dumping into the sea (Jensen et al. 1975). The chemical has been found in the volatile products from the thermal oxidative degradation of the flame-retardant plasticizer, tris(dichloropropy1) phosphate (Christos et al. 1977). No information was found that indicated that 1,2,3-trichloropropane has been found in food. Because of the lack of recent comprehensive monitoring data, the average daily intake of i,2,3-trichloropropane and the relative significance of each source of exposure cannot be determined.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

There are not enough measured data to assess the general population's exposure to this compound. The paucity of data may be the result of either a lack of 1,2,3-trichloropropane contamination in the environment or a lack of studies that attempt to identify and quantify the compound in the environment using sufficiently sensitive techniques. Based upon the few data available, the estimated transport and partitioning properties of the compound, and information on production and use, the following estimations concerning exposure can be made. A small part of the population may be exposed to very low levels of 1,2,3-trichloropropane through the ingestion of contaminated drinking water. Exposure to very low levels of 1,2,3-trichloropropane also may occur through the inhalation of contaminated air; however, no monitoring

data regarding the presence of 1,2,3-trichloropropane in the atmosphere in the United States were located. General exposure to air containing low levels may occur near chemical manufacturing facilities that produce 1,2,3-trichloropropane and certain other chemicals, near 1,2,3-trichloropropane-containing hazardous waste dumps, and farmlands treated with fumigants and nematocides that contain 1,2,3-trichloropropane. No current information is available, however, that indicates that 1,2,3-trichloropropane is still present in soil fumigant formulations, and commercial manufacturing processes generally occur in closed and tightly sealed systems (NIOSH 1981). Inhalation and dermal exposure may occur during the use of 1,2,3-trichloropropane as a solvent and extractive agent, in paint- and varnish-removers, in cleaning and degreasing agents, and in cleaning and maintenance reagents, although there is no current information that indicates that the compound is still used for these purposes (Hawley 1981; NIOSH 1981). No data regarding the detection of 1,2,3-trichloropropane in humans in the United States were located.

According to the NOES conducted by NIOSH from 1981 to 1983, 492 workers (of which 9 were women) were potentially exposed to 1,2,3-trichloropropane in the workplace in 1980 (NIOSH 1989); however, no report of actual measured exposure levels in any occupational situation in the United States was located. The NOES database does not contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals therein. This survey provides only an estimate of the number of workers potentially exposed to chemicals in the workplace. Occupational exposure to 1,2,3-trichloropropane is expected to be higher in facilities where the chemical or products containing the chemical are used than in facilities that produce 1,2,3-trichloropropane either directly or as a byproduct, since the commercial manufacturing processes generally occur in closed and tightly sealed systems (NIOSH 1981). Furthermore, exposure may result from procedures that require direct handling of the material; these include purification, formulation of products, sampling and quality control, packaging and storage, leakage of equipment, startup and shutdown procedures, maintenance, cleanup, spills, and other plant emergencies (NIOSH 1981).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Data regarding the presence of 1,2,3-trichloropropane in the environment are lacking, which prevents the thorough assessment of the potential for high exposure in various populations. Populations with potentially high exposure to 1,2,3-trichloropropane will generally include those that may be exposed to environmental contamination over long periods of time. These may include populations exposed to low levels of 1,2,3-trichloropropane via inhalation of contaminated air at or near both identified and unidentified 1,2,3-trichloropropane-containing waste disposal sites and landfills. Children playing in and around these sites may also be dermally exposed to soil containing 1,2,3-trichloropropane, although any 1,2,3-trichloropropane il surface soil would be expected to volatilize or leach through the soil.

Persons whose drinking water is derived from 1,2,3-trichloropropanecontaminated groundwater or surface water for a long period of time may be exposed to relatively high levels of 1,2,3-trichloropropane. Workers involved in the manufacture or use of 1,2,3-trichloropropane or 1,2,3-trichloropropanecontaining products may have the highest potential for exposure to 1,2,3-trichloropropane. Potentially high general population exposure may occur during the use of 1,2,3-trichloropropane-containing products, such as paint- and varnish-removers and cleaners, especially when they are used in poorly ventilated areas such as in the cleaning of reactors. Exposure through the manufacture or use of 1,2,3-trichloropropane-containing products may not be significant, however, since current manufacturing processes generally occur in closed and tightly sealed systems (NIOSH 1981) and no current information indicates that 1,2,3-trichloropropane is still used for those purposes listed.

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 1,2,3-trichloropropane 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 1,2,3-trichloropropane. 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. Physical and chemical property data are essential for estimating the transport and partitioning of a chemical in the environment. Many of the physical and chemical properties of 1,2,3-trichloropropane are available (Table 3-2) (Hawley 1981; HSDB 1989; Mackay et al. 1982; McNeil1 1979; Riddick et al. 1986; Ruth 1986; Weast 1985; Williams 1949). However, only estimated values are listed for the log K_{ow}, K_{oc}, and BCF (Lyman et al. 1982). Since the log K_{ow} was used to estimate the K_{oc} and BCF, an experimentally determined log K_{ow} would lead to less uncertainty in those estimated properties. Experimentally determined values would remove any doubt regarding the reliability of these data, although the techniques used for the estimations appear to be accurate.

Production, Import/Export, Use, and Disposal. Data regarding the production methods for 1,2,3-trichloropropane are available (Bauer et al.

1987; Hawley 1981; NIOSH 1981; SRI 1989; Williams 1949); however, data regarding current production, import, and export volumes, and use patterns are lacking. We do know that the chemical is currently produced (SRI 1989), but not in what quantities or whether future production levels will increase, We do not know if the chemical is widely used in the home, the environment, or in the workplace, but it does not appear that such widespread use is likely. It has not been found in food although foods may not have been tested for its presence. Use, release, and disposal information is useful for determining where environmental exposure to 1,2,3-trichloropropane may be high, and may help in estimating whether exposure is likely, and therefore may help to determine whether further toxicological studies are warranted. General data are available regarding the methods of disposal of 1,2,3-trichloropropane (HSDB 1989; Matsui et al. 1975), but information concerning the efficiencies of these methods, as well as the amount disposed of by each method is lacking. Specific disposal information, obtainable by polling industries or industry organizations, may be useful for determining environmental burden and potential concentrations where environmental exposures may be high. Rules and regulations governing land disposal of 1,2,3-trichloropropane are known (EPA 1988a).

Environmental Fate. The environmental fate of 1,2,3-trichloropropane remains unclear due to a lack of experimental data. We do not know where the chemical partitions in the environment. However, based upon estimated physical properties (Lyman et al. 1982), the chemical is expected to partition into the atmosphere and groundwater (Swann et al. 1983). It has been shown that the chemical leaches through soil (Cohen et al. 1986, 1987; Lykins and Baier 1985; Oki and Giamelluca 1987; STORET 1989). It is estimated that it can volatilize ,through near-surface soil and water to the atmosphere (EPA 1985; Lyman et al. 1982). Nothing definitive is known about the biodegradability of the compound. The rate constant for reaction with hydroxyl radicals in the atmosphere is an estimated value (Atkinson 1987), as are significant partition coefficient values used in predicting the environmental fate of the compound (EPA 1988b). Experimental data in these areas would aid in assessing the ultimate environmental fate of 1,2,3-trichloropropane, which would, in turn aid in assessing its background levels in the environment and levels of human exposure.

Bioavailability from Environmental Media. Studies have shown that 1,2,3-trichloropropane is absorbed through the lungs, gastrointestinal tract, and skin of animals (see Section 2.3.1) (Alpert 1982; Clark 1977; Johannsen et al. 1988; Sipes et al. 1982; Union Carbide 1958; Volp et al. 1984). This indicates that it may be absorbed through the inhalation of contaminated air, ingestion of contaminated water, food, and soil, and through dermal contact. The amount of 1,2,3-trichloropropane that is bioavailable from each route is not well documented, and no data were found for humans. Data on the bioavailability of 1,2,3-trichloropropane would be helpful in assessing the importance of environmental exposure levels.

Food Chain Bioaccumulation. The estimated BCF for 1,2,3-trichloropropane (EPA 1988b; Lyman et al. 1982) indicates that this compound would not significantly bioconcentrate in plants, aquatic organisms, or animals. No experimental data were found to support this conclusion. Information was unavailable on the biomagnification of 1,2,3-trichloropropane in food chains. Additional information on bioconcentration by plants, aquatic organisms, and animals and biomagnification in terrestrial and aquatic food chains could be helpful because it might help to indicate whether the chemical biomagnifies in food chains and thereby poses a potential for significant exposure. Biomagnification is not likely, however, based upon the estimated BCF.

Exposure Levels in Environmental Media. Limited data were available regarding the levels of 1,2,3-trichloropropane in the environment (Baier et al. 1987; CLPSD 1989; Cohen et al. 1986, 1987; Dewalle and Chian 1978; EPA 1984, 1987; Jacobs and Zabik 1983; Keith et al. 1976; Lykins and Baier 1985; Oki and Giambelluca 1987; STORET 1989; Wakeham et al. 1983). Information on exposure to 1,2,3-trichloropropane from environmental media would be useful, especially from drinking water derived from groundwater downgradient from 1,2,3-trichloropropane-containing hazardous waste disposal sites and other contaminated surface waters, air near facilities that make or use products containing the compound, and soil at waste disposal sites. Data concerning the presence of 1,2,3-trichloropropane in foods would also be useful in assessing potential exposure.

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

Exposure Registries. No exposure registries for 1,2,3-trichloropropane 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 this compound.

5.7.2 On-going Studies

Remedial investigations and feasibility studies conducted at the eight NPL sites known to be contaminated with 1,2,3-trichloropropane will add to the available database on exposure levels in environmental media, exposure levels in humans, and exposure registries and will increase the current knowledge regarding transport and transformation of 1,2,3-trichloropropane 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 1,2,3-trichloropropane and other volatile organic compounds. These data will indicate the frequency of occurrence and background levels of these compounds in the general population.

No other on-going studies were located.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring 1,2,3-trichloropropane 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 1,2,3-trichloropropane. 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 1,2,3-trichloropropane 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

No completed studies were located in the literature that reported the analysis of 1,2,3-trichloropropane in human biological matrices. Methods were located, however, for the analysis of the compound in rat biological matrices. These methods are listed in Table 6-l. With suitable modifications, the methods used to detect this chemical in animal samples may apply generally to its determination in human biological samples. Section 6.2 includes a discussion of the methods that may be most sensitive for the determination of 1,2,3-trichloropropane concentrations in environmental samples, including advantages and disadvantages of the commonly used methods. Initial testing to determine minimum detection limits, recovery, accuracy, and precision of the particular, suitably modified methods is necessary to gauge the applicability of the methods used to detect 1,2,3-trichloropropane in animal biological samples for the chemical's determination in human biological samples.

6.2 ENVIRONMENTAL SAMPLES

Methods for analyzing 1,2,3-trichloropropane in environmental samples are presented in Table 6-2. All of the methods listed use either adsorption on a sorption column (air samples) or purge-and-trap methods (solid and liquid samples), followed by thermal desorption and some form of gas chromatography (GC) with an appropriate detector as the analytical quantification technique. Purge-and-trap methods involve the purging of the vapor from the sample or its suspension in water with an inert gas and the trapping of the desorbed vapors in a sorbent trap. Particular care must be taken in sampling and storage of samples in view of the compound's high volatility. Although 1,2,3-trichloropropane was listed as a chemical that could be determined using the listed techniques, significant factors such as the detection limit and percent recovery were not reported for this chemical. Both halogen-specific detection (e.g., Hall electrolytic conductivity detectors) and mass spectrometry (MS) provide excellent detection limits (EPA 1986a; Ho 1989;

TABLE 6-1. Analytical Methods for Determining 1,2,3-Trichloropropane in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Exhaled air in rats	Dry air drawn through cage and trap filled with ethyl alcohol at -15°C	GC-ECD	No data	No data	Sipes et al. 1982
Urine, feces, bile, major tissues, blood	Sample homogenized and centrifuged, extracted with n-hexane; blood added to water and bile added to ethyl alcohol prior to extraction	GC-ECD	No data	No data	Sipes et al. 1982

ECD = electron capture detection
GC = gas chromatography

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Occupational air	Sample sorbed on charcoal; desorbed by CS_2	GC-FID (NIOSH method 1003)	0.3 mg/sample	95%	NIOSH 1987
Finished drinking/ raw source water	Purge and trap in Tenax/ silica/charcoal; thermally desorb	GC-HECD (EPA method 502.1)	No data	100% at 0.4 µg/L	EPA 1986a
Finished drinking/ raw source water	Purge and trap in Tenax/ silica/charcoal; thermally desorb	Subambient programmable HRGC-MS (EPA method 524.1)	No data	No data	EPA 1986a
Finished drinking/ raw source water	Purge and trap in Tenax/ silica/charcoal; thermally desorb	Cryofocusing (wide or narrow bore) HRGC-MS (EPA method 524.2)	0.03 µg/L (wide bore) 0.14 µg/L (narrow bore)	108% at 0.5-10 µg/L (wide bore) 96% at 0.5 µg/L (narrow bore)	EPA 1986a
Drinking water	Purge and trap in Tenax/ silica/charcoal; thermally desorb	GC-HECD and PID in series	0.03 µg/L	97%	Ho 1989
Liquid and solid waste, groundwater, soil, and sludge	Soil and viscous samples dispersed in water or methanol/water; purge and trap in Tenax/silica/charcoal and thermally desorb	GC-HECD (EPA method 5030 and 8010)	No data	No data	EPA 1986b
Solid and liquid waste, soil	Sample dispersed in a glycol; purged and trapped in Tenax/ silica/charcoal; thermally desorbed	GC-ECD and PID in series	No data	No data	Lopez-Avila et al. 1987
Citrus fruit (lemon, orange, grapefruit)	Sample blended with water; distilled into cyclohexane in essential oil apparatus; cleanup on Flourisil column; injected into GC	GC-ECD	No data	98%-99% at 0.01 ppm	Tonogai et al. 1986

ECD = electron capture detector
FID = flame ionization detector
GC = gas chromotagraphy
HECD = Hall electron capture detector
HRGC = high-resolution gas chromatography
MS = mass spectrometry
NIOSH = National Institute for Occupational Safety and Health
PID = photoionization detector

Lopez-Avila et al. 1987; Ramus et al. 1984). An advantage of halogenspecific detectors is that they are very sensitive and specific to halogen compounds. MS, on the other hand, provides additional confirmation of the identity of a compound through its ion fragment patterns. High-resolution gas chromatography (HRGC) with capillary columns coupled with MS provides better resolution and increased sensitivity for volatile compounds than packed columns. In this method, desorbed compounds are cryogenically trapped onto the head of the capillary column. This HRGC-MS method overcomes some common problems involved in analyses of excessively complex samples, samples with large ranges of concentrations, and samples that also contain nonvolatile compounds (Dreisch and Munson 1983; EPA 1986a).

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

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. No biomarker, other than possibly 1,2,3-trichloropropane itself, that can be associated quantitatively with exposure to 1,2,3-trichloropropane has been identified (see Section 2.5). Even the compound itself may not be a quantitative biomarker of exposure because the levels found have not been proven to qualitatively reflect exposure levels. Nevertheless, there are methods for analyzing 1,2,3-trichloropropane in most of the biological matrices for the rat, although important information such as detection limits and recoveries was not reported (Sipes et al. 1982). These methods may be sufficient for the analysis of human biological matrices.

No biomarkers have been identified that can be associated quantitatively with effects caused by exposure to 1,2,3-trichloropropane. Therefore, methods for biomarkers of effects are not currently available.

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

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 analyzing 1,2,3-trichloropropane and other volatile organic compounds in blood. These methods use high resolution gas chromatography and magnetic sector mass spectrometry, which gives detection limits in the low ppt (parts per trillion) range.

7. REGULATIONS AND ADVISORIES

National regulations and guidelines pertinent to human exposure to 1,2,3-trichloropropane are summarized in Table 7-l. Guidance from the World Health Organization and the International Agency for Research on Cancer is not available.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to 1,2,3-Trichloropropane

Agency	Description	Information	References
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL	50 ppm (300 mg/m^3)	OSHA 1989 (29 CFR 1910)
	TWA	10 ppm (60 mg/m^3)	OSHA 1989 (29 CFR 1910)
Guidelines:			
a. Air:			
ACGIH	TLV-TWA (skin)	10 ppm (60 mg/m^3)	ACGIH 1989
b. Water:			
EPA ODW	Health advisories		IRIS 1991
	Longer-term, child	0.6 mg/L	
	Longer-term, adult	2 mg/L	
	DWEL (lifetime)	0.2 mg/L	
c. Other:			
EPA	RfD (oral)	6x10^{-3} mg/kg/day	IRIS 1991
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		NATICH 1988
Connecticut		6 mg/m^3 (8-hr avg)	
North Dakota		3 mg/m^3 (8-hr avg) 4.5 mg/m^3 (1-hr avg)	
Nevada		7.143 mg/m^3 (8-hr avg)	
Virginia		5 mg/m^3 (24-hr avg)	

ACGIH = American Conference of Governmental Industrial Hygienists
avg = average
DWEL = Drinking Water Equivalent Level
EPA = Environmental Protection Agency
hr = hour
OSHA = Occupational Safety and Health Administration
PEL = Permissible Exposure Limit
RfD = Reference dose
TLV = Threshold Limit Value
TWA = Time-Weighted Average

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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 (Kd) -- 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$_{(50)}$ (LC_{50}) -- 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$_{(Lo)}$ (LD_{Lo}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

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

Lethal Time$_{(50)}$ (LT_{50}) -- 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.

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.

9. GLOSSARY

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

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-l 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-l

(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,

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-l) 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-l).

(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 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. CELs 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.

(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 in10,000,000. 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 (q1*).

(19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

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) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
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					11		
38	Rat	18 mo 5d/wk 7hr/d				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 x 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)

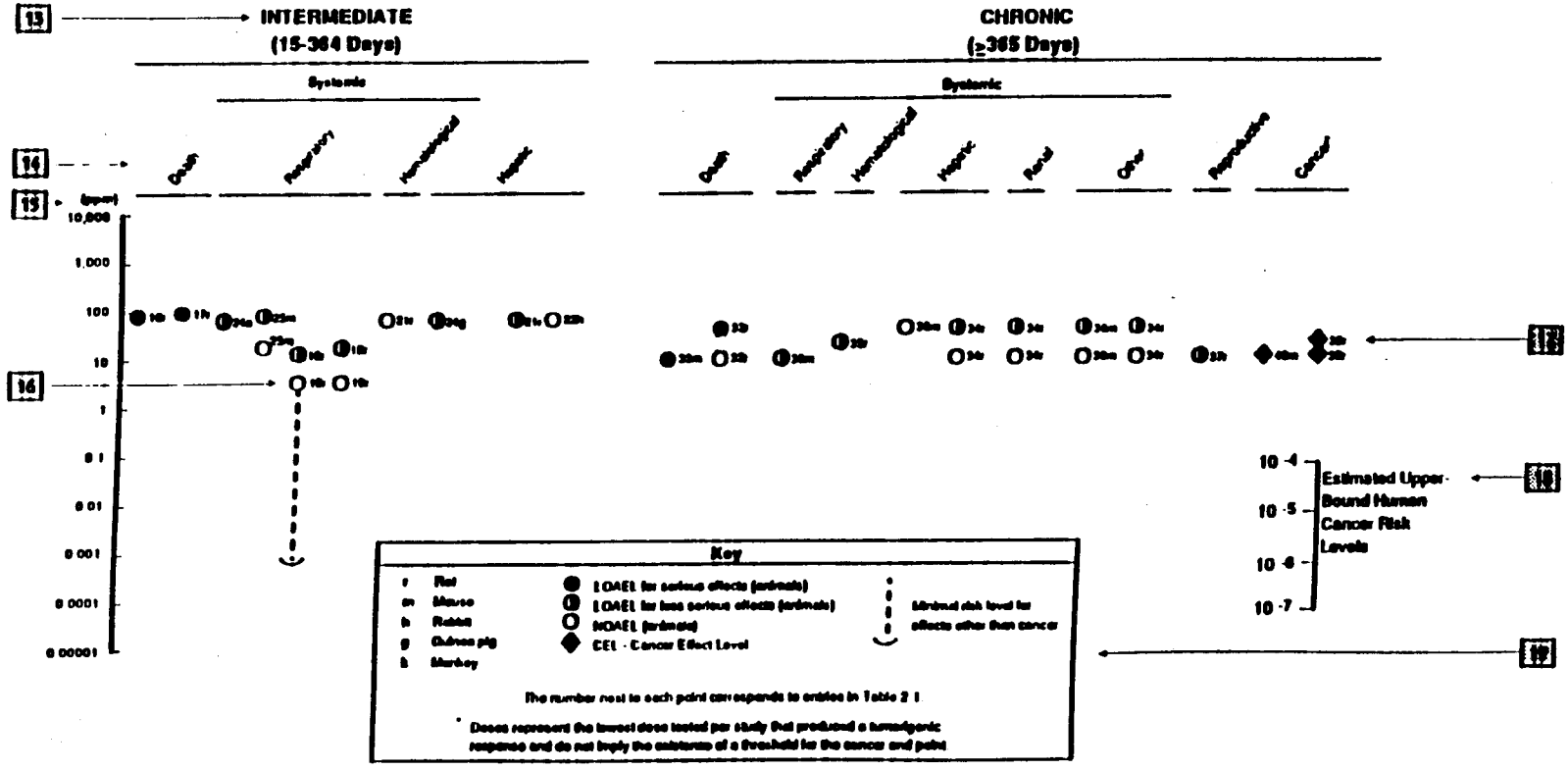

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

APPENDIX A

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 aquaint 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 continous 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.

APPENDIX B

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
Kd	adsorption ratio
kg	kilogram
Koc	octanol-soil partition coefficient
Kow	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
LOAEL	lowest-observed-adverse-effect level

APPENDIX B

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
NIOSHTIC	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	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor

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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

APPENDIX C

PEER REVIEW

A peer review panel was assembled for 1,2,3-trichloropropane. The panel consisted of the following members: Dr. Hugh Farber, Private Consultant, Midland, MI; Dr. I.G. Sipes, Professor and Head, Department of Toxicology, University of Arizona, Tucson, AZ; and Dr. Shane Que Hee, Associate Professor, School of Public Health, University of California, Los Angeles, CA. These experts collectively have knowledge of 1,2,3-trichloropropane'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.

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