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

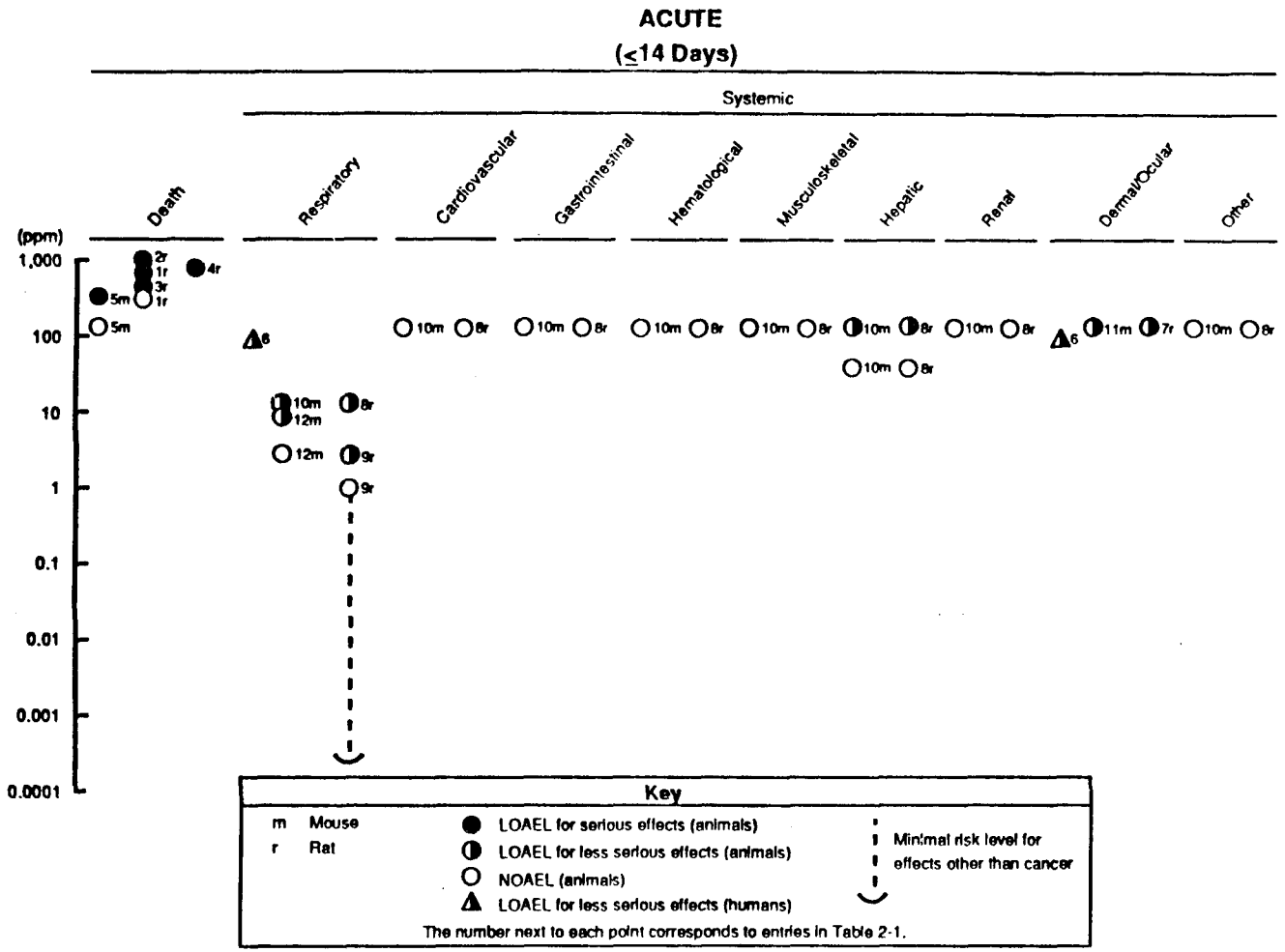
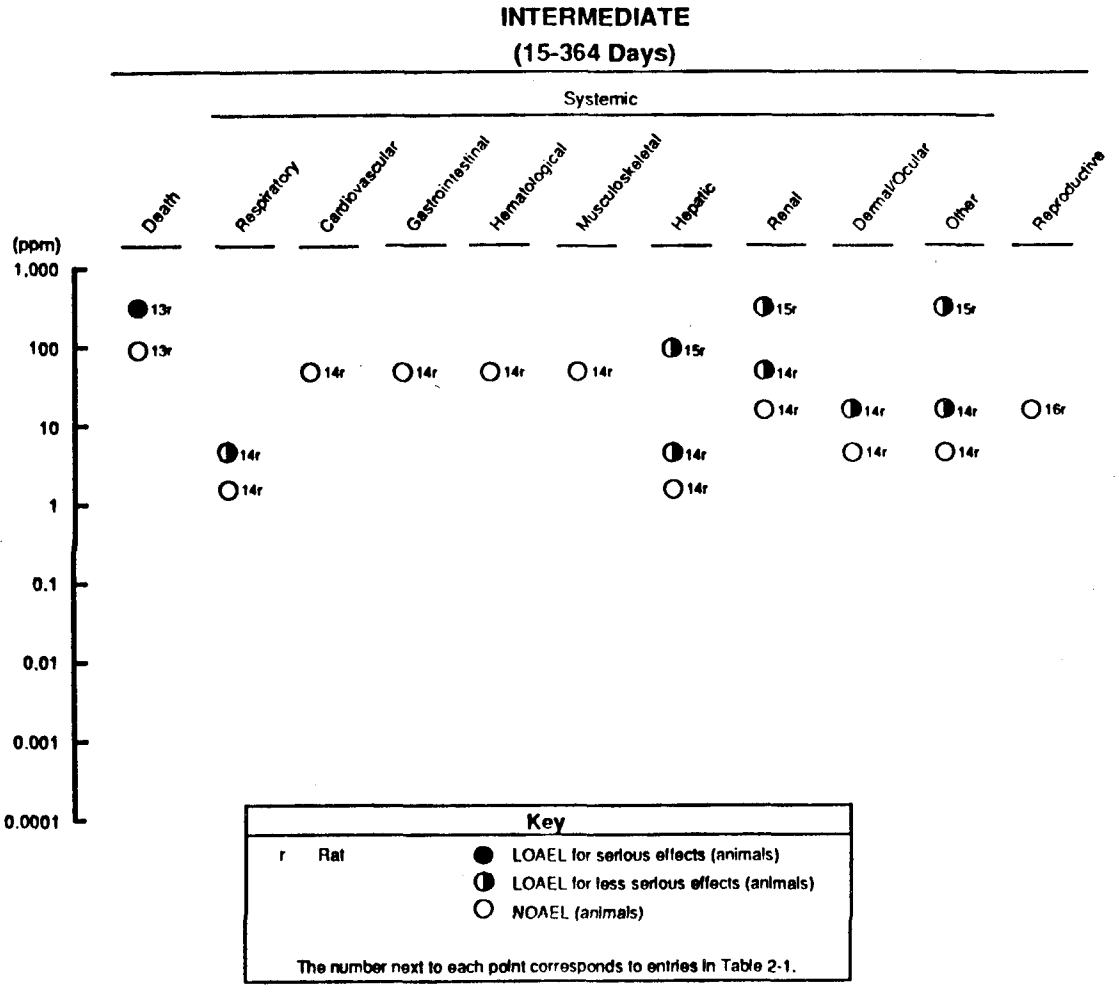


FIGURE 2-1 (Continued)



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

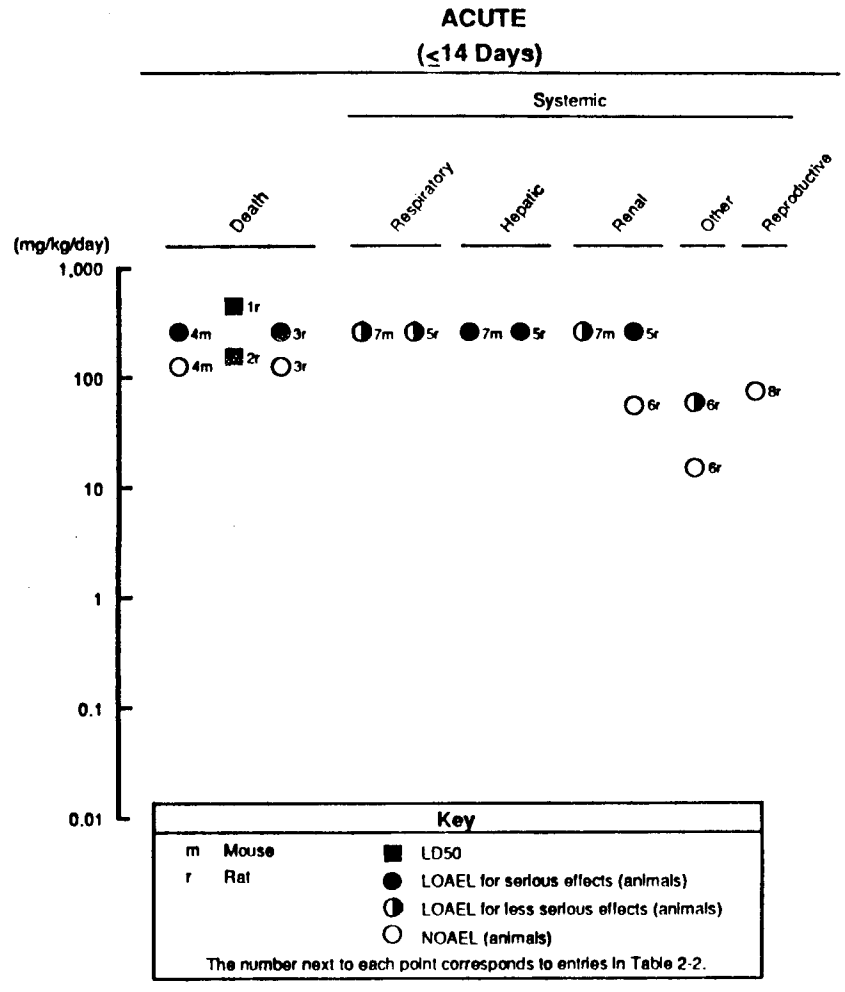


FIGURE 2-2 (Continued)

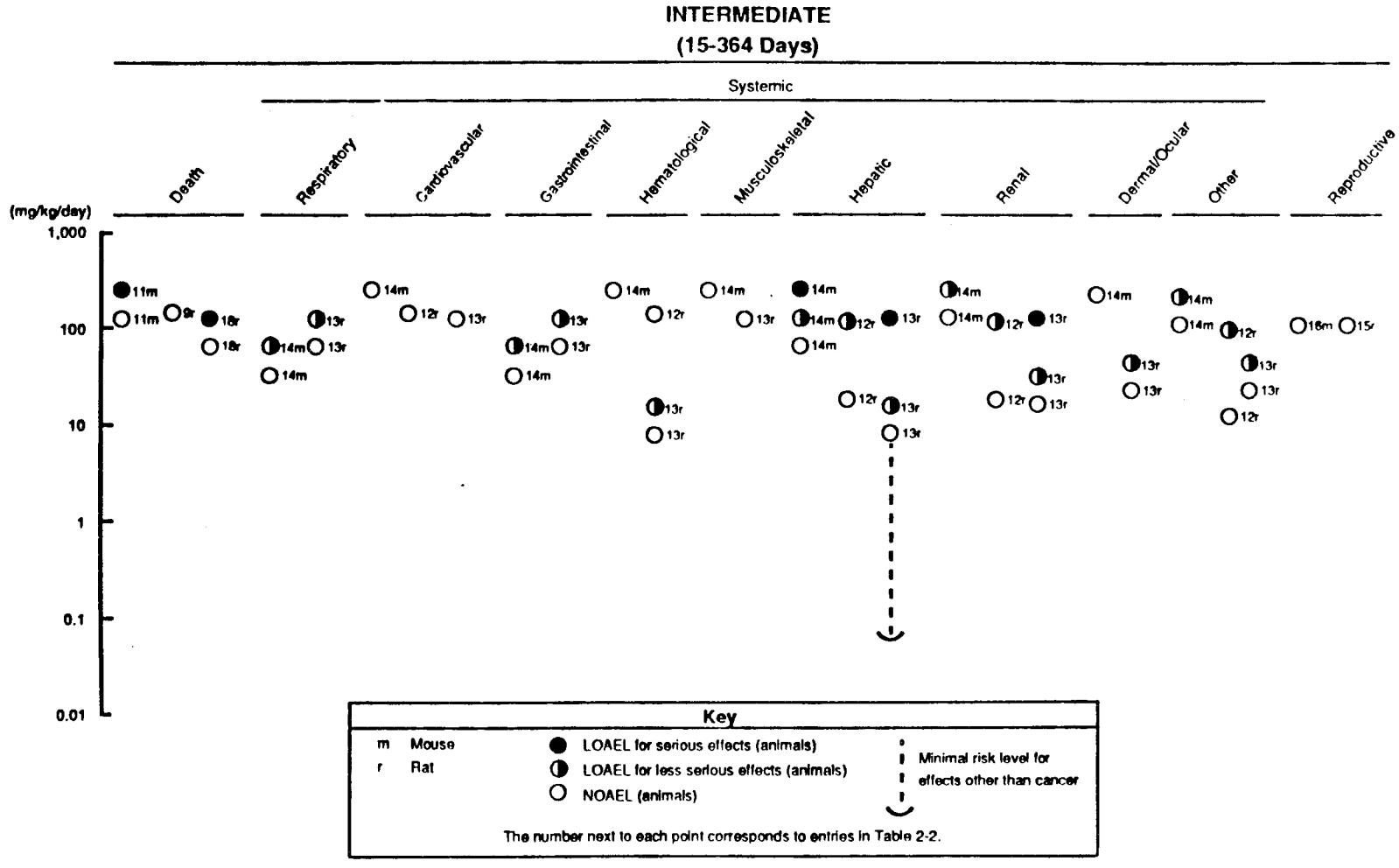
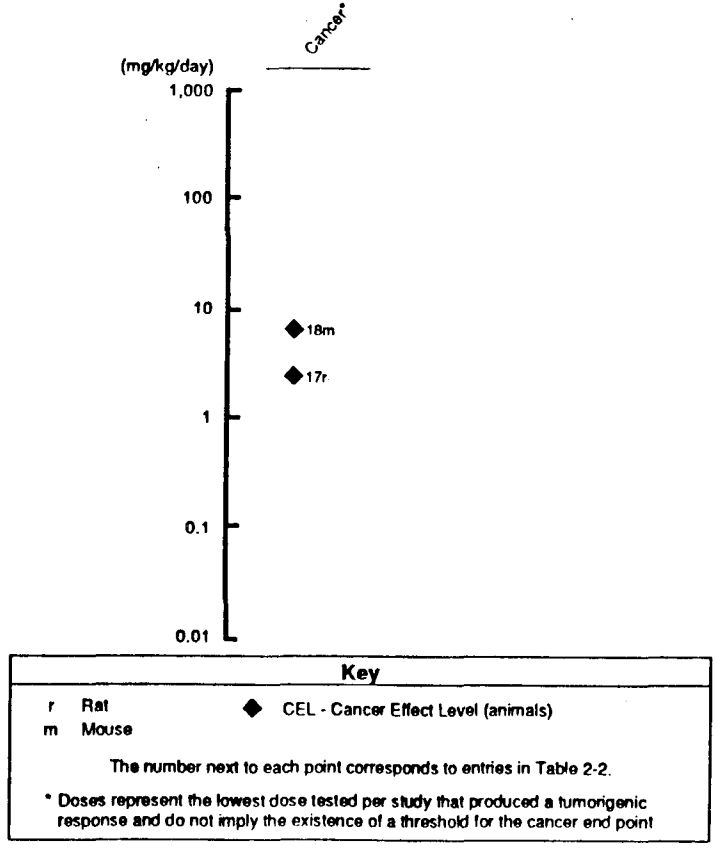


FIGURE 2-2 (Continued)

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

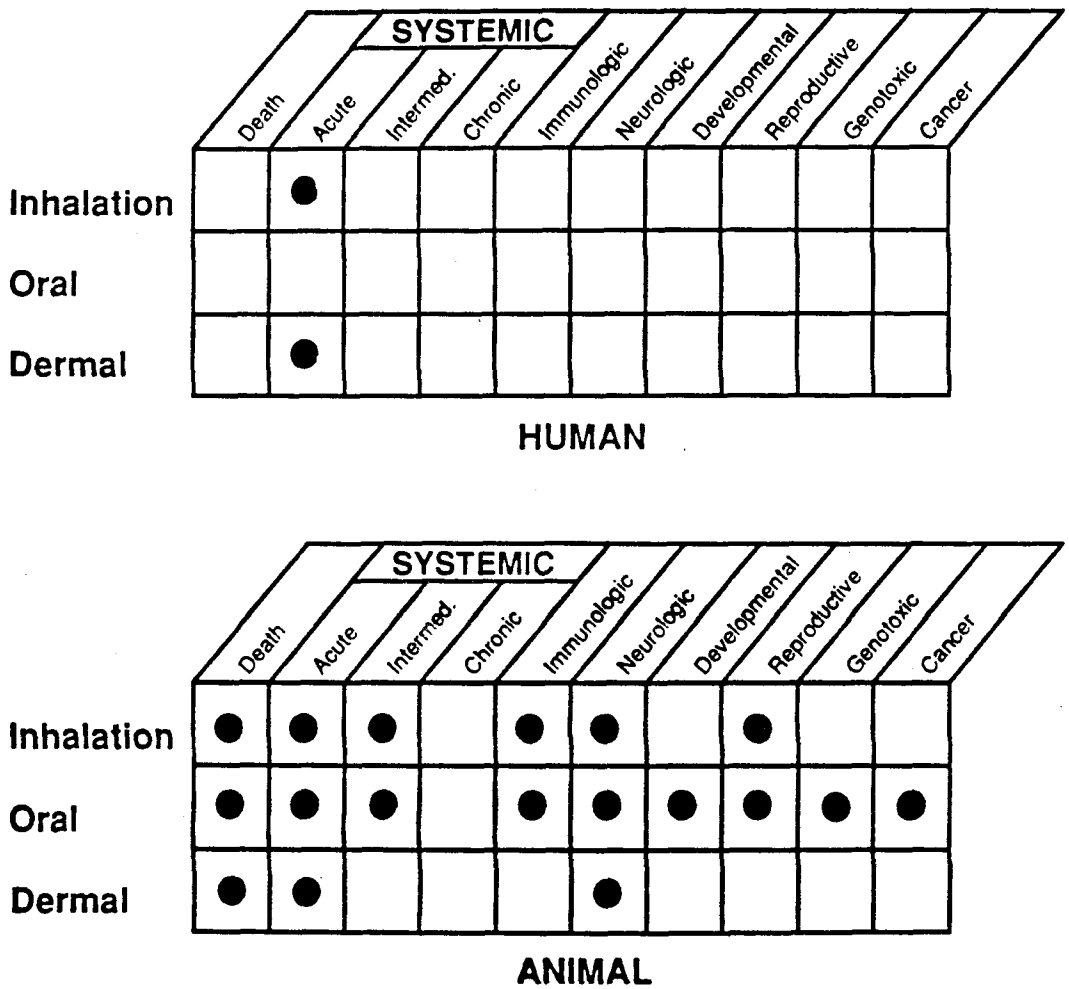
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2,3-trichloropropane are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,2,3-trichloropropane. Each dot in the figure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