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-dichloroethene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

There are two geometric isomers of 1,2-dichloroethene, the cis form and the trans form. Isomers of an organic substance are different structures with the same molecular formula. In this case, the cis and trans forms have the chlorine atoms in different positions around the double bond. Each of these geometric isomeric forms has slightly different physical, chemical, and biological properties, because of their different molecular structures. These properties determine how the compound may affect the health of exposed individuals and how 1,2 dichloroethene behaves in air, water, and soil. The trans isomer is the more common industrial product.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others 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, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing 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. “Serious” effects are

those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining 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 LSE tables and figures may differ depending on the user’s perspective. Public health officials and others 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 (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for 1,2-dichloroethene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects, MRLs can be derived for acute, intermediate, and chronic durationexposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), 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.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

2.2.1.1 Death

A single fatality was reported to have occurred after inhalation of 1,2dichloroethene vapor in a small enclosure (Hamilton 1934). Neither the level and duration of exposure associated with the fatality nor the symptoms of toxicity were reported. The isomeric composition of the vapor was not reported. No further information regarding lethal effects in humans following inhalation of 1,2-dichloroethene could be located in the literature.

The lethality of a single exposure by inhalation of trans-1,2-dichloroethene has been determined in mice (Gradiski et al. 1978). The lethal concentration resulting in 50% fatalities (LC_{50}) was 21,723 ppm trans-1,2-dichloroethene, presented in Table 2-l and in Figure 2-1, and was for a single 6-hour exposure. The cause of death was not reported.

No other studies were located regarding lethality following inhalation exposure to cis- or trans- 1 ,2dichloroethene in any animal species.

2.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, endocrine, dermal, or ocular effects in humans or animals after inhalation exposure to cis- or trans-1,2-dichloroethene. The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-l.

Table 2-1. Levels of Significant Exposure to 1,2-Dichloroethene - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	ACUTE EXPOSURE						
	Death						
1	Mouse (OF1,SPF)	6 hr				21723 F (LC_{50})	Gradiski et al. 1978 trans
	Systemic						
2	Rat (Wistar SPF)	8 hr	Resp		200 F (slight hyperemia of lung with alveolar septum distention in 6/6)		Freundt et al. 1977 trans
			Cardio	1000 F		3000 F (severe fibrous swelling and hyperemia, barely maintained striation in 2/6)	
			Hemato	200 F	1000 F (decreased erythrocyte count)		
			Musc/skel	3000 F			
			Hepatic		200 b F (slight fatty degeneration)	1000 F (slight to severe fatty degeneration of lobules in 2/6)	
			Renal	3000 F			
3	Rat (Wistar SPF)	1-2 wk 5 d/wk 8 hr/d	Resp		200 F (slight capillary hyperemia and alveolar septum distention in all rats)		Freundt et al. 1977 trans
			Cardio	200 F			
			Musc/skel	200 F			
			Hepatic		200 F (slight fatty accumulation in liver lobule)		
			Renal	200 F			

Table 2-1. Levels of Significant Exposure to 1,2-Dichloroethene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
4	Rat (CD,BR)	10 d Gd 7-16 6 hr/d	Bd Wt	2000 F	6000 F (reduced body weight gain of dams of 13%)	12000 F (reduced body weight gain of 33%)	Hurtt et al. 1993 trans
			Other		2000 F (reduced food consumption of dams on gestational days 13-15)		
Immunological/Lymphoreticular							
5	Rat (Wistar SPF)	8 hr		200 F	1000 F (slight degeneration of Kuppfer cells in 2/6)		Freundt et al. 1977 trans
6	Rat (Wistar SPF)	1-2 wk 5 d/wk 8 hr/d			200 F (slight fatty accumulation in Kupffer cells)		Freundt et al. 1977 trans
7	Rat (Wistar SPF)	8 hr			200 F (decreased leukocyte count)		Freundt et al. 1977 trans
Neurological							
8	Rat (CD,BR)	10 d Gd 7-16 6 hr/d		6000 F	12000 F (lethargy and salivation)		Hurtt et al. 1993 trans
9	Mouse (Swiss OF1)	4 hr		1582 M	1720M (45% decreased duration of immobility in behavioral despair swimming test)		De Ceaurriz et al. 1983 NS
Developmental							
10	Rat (Crl: CDBR)	10 d Gd 7-16 6 hr/d		6000		12000 (significant decrease in mean fetal weight)	Hurtt et al. 1993 trans

Table 2-1. Levels of Significant Exposure to 1,2-Dichloroethene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
11	Rat (Wistar SPF)	8 or 16 wk 5 d/wk 8 hr/d	Resp		200 F (slight capillary hyperemia and alveolar system distention)		Freundt et al. 1977 trans
			Cardio	200 F			
			Musc/skel	200 F			
			Hepatic		200 c F (slight fatty accumulation in liver lobules)		
			Renal	200 F			
Immunological/Lymphoreticular							
12	Rat (Wistar SPF)	8 or 16 wk 5 d/wk 8 hr/d			200 F (slight fatty accumulation in Kupffer cells)		Freundt et al. 1977 trans

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

[b]Used to derive an acute inhalation minimal risk level (MRL) of 0.2 ppm. Concentration is adjusted by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

[c]Used to derive an intermediate inhalation MRL of 0.2 ppm. Concentration is adjusted by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = female; Gd = gestational day; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s).

Figure 2-1. Levels of Significant Exposure to 1,2-Dichloroethene - Inhalation

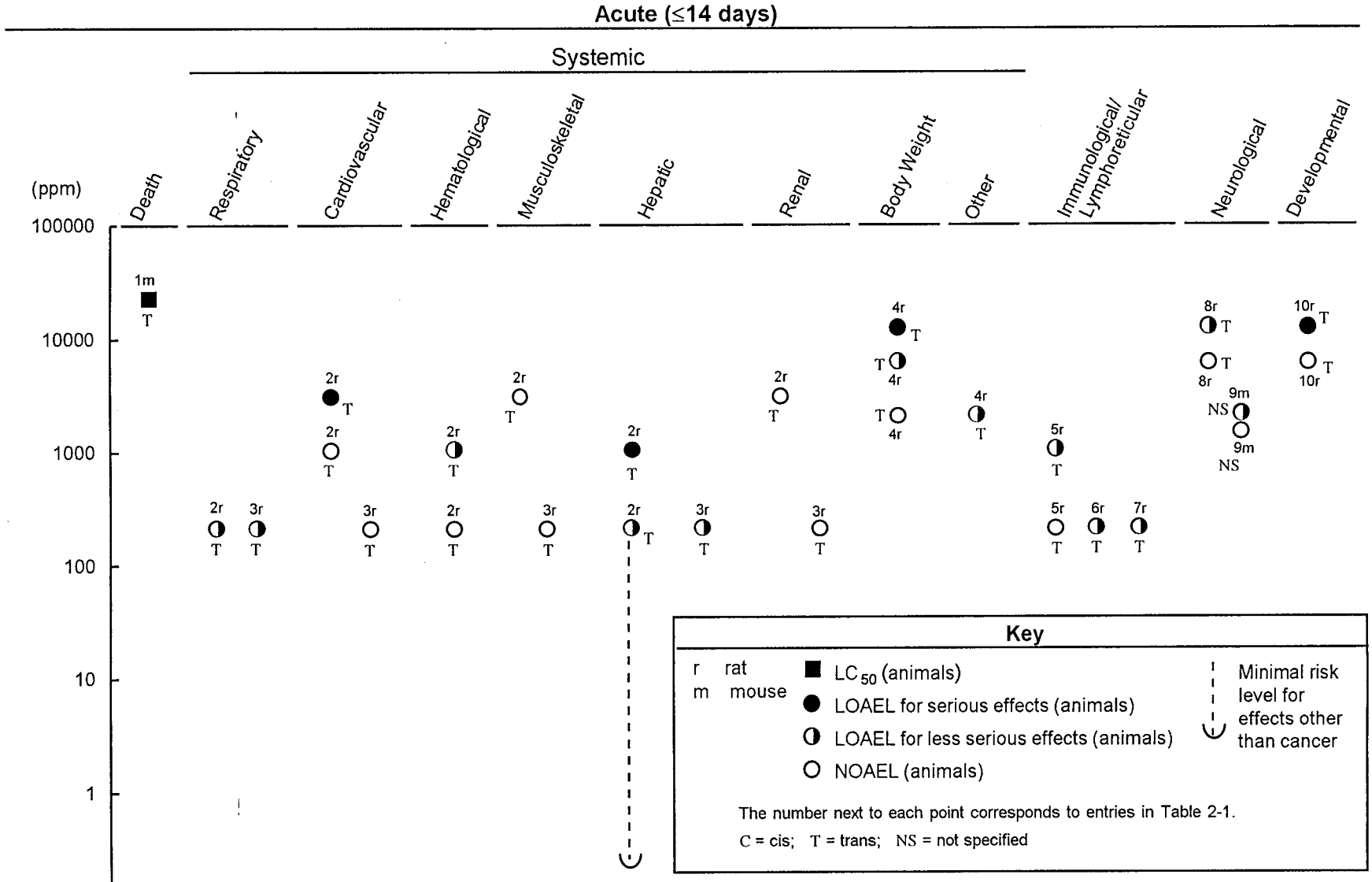
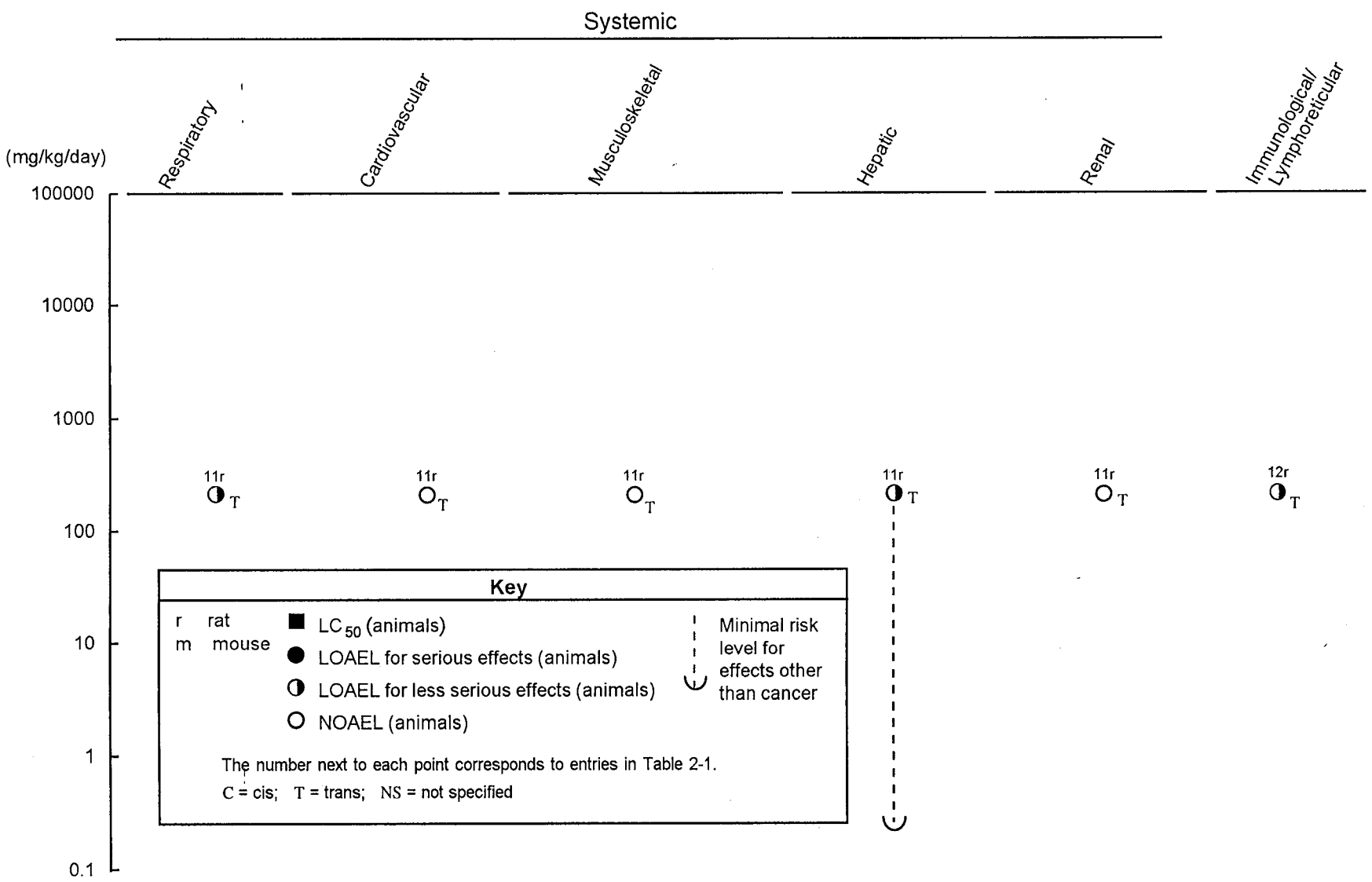


Figure 2-1. Levels of Significant Exposure to 1,2-Dichloroethene - Inhalation (continued)

Intermediate (15-364 days)



2. HEALTH EFFECTS

Respiratory Effects. No studies were located regarding respiratory effects in humans following inhalation exposure to cis- or trans-1,2-dichloroethene.

Pathologic changes in the lung have been described in rats exposed to trans-1,2-dichloroethene (Freundt et al. 1977). The pathology consisted of pulmonary capillary hyperemia, and alveolar septal distention. As shown in Table 2-l and Figure 2-1, after repeated exposure to 200 ppm effects in the lung were more severe than effects that occurred after a single exposure. This is the only reported study of lung pathology in animals exposed to trans-1,2-dichloroethene. This study had several weaknesses: several of the control rats also developed pulmonary capillary hyperemia and alveolar septal distention, a small number of animals were examined, and the upper respiratory tract was not examined for pathology. Also, a statistical evaluation of the histological data was not presented. Corroborative evidence for toxicity of trans-1,2-dichloroethene to the lung has not been reported.

No studies were located regarding the effects of cis-1,2-dichloroethene on the respiratory tract of any animal species.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following inhalation exposure to cis- or trans-1,2-dichloroethene.

Pathological changes in the heart have been observed in rats exposed to trans-1,2-dichloroethene (Freundt et al. 1977). The changes were described as severe fibrous swelling of the myocardium and hyperemia. As shown in Table 2-l and Figure 2- 1, the effects were evident after an 8-hour exposure to 3,000 ppm but not after exposures to lower levels. Corroborative evidence for heart toxicity of trans-1,2-dichloroethene has not been reported.

No studies were located regarding the effects of cis-1,2-dichloroethene on the cardiovascular system of any animal species.

Hematological Effects. No studies were located regarding hematological effects in humans following inhalation of cis- or trans-1 ,2dichloroethene.

Effects on composition of the blood and plasma have been observed in rats exposed to trans-1,2-dichloroethene (Freundt et al. 1977). A reduction in the number of erythrocytes was

observed after an 8-hour exposure to 1,000 ppm trans-1,2-dichloroethene. No studies were located regarding hematological effects in animals after inhalation exposure to cis- 1,2dichloroethene.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following inhalation exposure to cis- or trans-1,2-dichloroethene.

Histological examination of muscle tissue revealed no compound-related effects in rats exposed to 200, 1,000 or 3,000 ppm trans-1,2dichloroethene for up to 16 weeks (Freundt et al. 1977).

Hepatic Effects. No studies were located regarding hepatic effects in humans following inhalation of cis- or trans-1,2-dichloroethene.

Pathological changes in the liver, consisting of fatty accumulation of liver lobules and Kupffer cells, have been observed in a small group of rats exposed to trans-1,2-dichloroethene (Freundt et al. 1977). Five of six rats exposed to 200 ppm for 8 hours had livers that appeared normal when stained for fat accumulation, but one rat showed evidence of fat deposition. Although fat accumulation was not observed in the control rats for the 200 ppm exposure group, control rats for other exposure groups also showed histopathological evidence of fat accumulation in Kupffer cells. However, the incidence and severity of fat accumulation did increase with increasing exposure levels and duration. This study is the basis of an acute-duration inhalation MRL of 0.2 ppm for trans-1,2-dichloroethene, as explained in the footnote to Table 2-l and in Appendix A. In the same study, rats were exposed to 200 ppm trans-1,2-dichloroethene for 8 hours per day, 5 days per week for either 8 or 16 weeks. Fatty accumulation was found in hepatocytes (liver lobules). This LOAEL of 200 is the basis for the intermediate-duration inhalation MRL of 0.2 ppm for trans-1,2-dichloroethene, as explained in the footnote to Table 2-l and in Appendix A.

A single 8-hour exposure to cis- or trans-1,2-dichloroethene at 200 ppm has been shown to increase hexobarbital sleeping time and zoxazolamine paralysis time in rats (Freundt and Macholz-1978). These effects were more pronounced at higher 1,2-dichloroethene concentrations; the effects due to the cis isomer are stronger than those of the trans isomer. These effects suggest inhibition of the mixed function oxidase system.

2. HEALTH EFFECTS

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to cis- or trans- 1,2-dichloroethene.

Histological examination of the kidney revealed no compound-related effects in rats exposed to 200, 1,000 or 3,000 ppm trans-1,2-dichloroethene for up to 16 weeks (Freundt et al. 1977). No studies were located regarding renal effects in animals after inhalation exposure to cis-1,2-dichloroethene.

Body Weight Effects. No studies were located regarding body weight effects in humans following inhalation of cis- or trans-1,2-dichloroethene.

Weight gain in pregnant rats was inversely related to dose from 2,000 to 12,000 ppm trans-1,2-dichloroethene, and was concomitant with the reduced food consumption of dams at 2,000 ppm on gestational days 13-15 in the developmental study of Hurtt et al. (1993). No studies were located regarding body weight effects in animals after inhalation exposure to cis-1,2-dichloroethene.

Other Systemic Effects. No studies were located regarding other systemic effects in humans following inhalation of cis- or trans-1,2-dichloroethene.

Several other systemic effects were found in the study of Hurtt et al. (1993). Brown-stained periocular hair was observed in all rats exposed to trans-1,2-dichloroethene at concentrations of 2,000-12,000 ppm. This effect was also observed in 1 of 24 control rats. Reduced food consumption of dams was observed on gestational days 13-15 at a concentration of 2,000 ppm. No studies were located regarding other systemic effects in animals after inhalation exposure to cis-1 ,2dichloroethene.

2.2.1.3 Immunological and Lymphoreticular Effects

Detailed studies were not located regarding the immunological or lymphoreticular effects-in humans or animals after inhalation exposure to cis- or trans-1 ,2dichloroethene.

Freundt et al. (1977), however, reported that inhalation exposure of rats to trans-1,2-dichloroethene at a concentration of 200 ppm or greater caused slight to severe fatty degeneration of Kupffer cells. Kupffer cells are highly phagocytic macrophages involved in protecting the systemic circulation from

gastrointestinal bacteria. In addition, decreased leukocyte (white blood cell) counts were observed in rats after an 8-hour exposure to 200 and 1,000 ppm trans-1 ,2dichloroethene, and pneumonic infiltration was observed after 8 and 16 weeks exposure to 200 ppm, suggesting that inhalation of trans- 1,2-dichloroethene may have adverse immunological effects.

2.2.1.4 Neurological Effects

Inhalation of high concentrations of vaporized trans-1,2-dichloroethene depresses the central nervous system in humans. Low levels of trans-1,2dichloroethene have been reported to cause neurological effects (Lehmann and Schmidt-Kehl 1936). Inhalation of 6.8-8.8 mg/L (1,700-2,220 ppm) of trans-1,2-dichloroethene for 5 minutes, or of 4.8 mg/L (1,200 ppm) for 10 minutes, reportedly caused nausea, drowsiness, fatigue, vertigo, and intracranial pressure in two human subjects. It is uncertain whether the human subjects were exposed to a vapor or an aerosol; however, based on information on the volatility of trans-1,2-dichloroethene, it was likely a vapor (see Chapter 3). Also, the degree of purity of the trans isomer and the precise concentrations are unclear.

The effects of inhaled cis- or trans-1,2-dichloroethene on the nervous system have not been extensively examined in animals. Hurtt et al. (1993) reported increased incidences of lethargy and salivation in pregnant rats exposed to 12,000 ppm trans-1,2-dichloroethene. Behavioral changes have been observed in mice exposed acutely (4 hours) to 1,2dichloroethene (form not specified) (De Ceaurriz et al. 1983). The reported changes consisted of a dose-related decrease in the duration of immobility in the “behavioral despair” swimming test. A 45% decrease in the total duration of immobility occurred at a concentration of 1,720 ppm. The neurological significance of changes in the duration of swimming immobility is not known. Frantik et al. (1994) studied inhibition of propagation and maintenance of the electrically evoked seizure discharge in rats and mice. The air concentration evoking a 30% depression in the duration of hindlimb tonic extension in rats was 1,810 ppm and the air concentration evoking a 30% increase in the latency for hindlimb tonic extension in mice was
3,400 pp.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to cis- or trans- 1,2-dichloroethene.

Significant increases in the mean number of resorptions per litter were seen in rats exposed to 6,000 and 12,000 ppm of trans-1,2-dichloroethene for 6 hours per day on days 7-16 of gestation (Hurtt et al. 1993). The authors interpreted this increase as not being treatment related because resorption values were within the range of historical controls. No studies were located regarding reproductive effects in animals after inhalation exposure to cis-1,2-dichloroethene.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to cis- or trans- 1,2-dichloroethene.

Inhalation exposure to trans-1,2-dichloroethene has been shown to affect fetal weight in animals. Hurtt et al. (1993) administered trans-1,2-dichloroethene to pregnant rats 6 hours daily, on days 7-16 of gestation, at 0, 2,000, 6,000, or 12,000 ppm. Mean fetal weights were significantly reduced in the litters of the dams exposed to 12,000 ppm. However, the reduced mean fetal weights probably resulted from reduced food consumption and reduced weight gain, which were seen in the pregnant rats in this study. No studies were located regarding developmental effects in animals after inhalation exposure to cis-1,2-dichloroethene.

2.2.1.7 Genotoxic Effects

No studies were located regarding in vivo genotoxic effects in humans or animals after inhalation exposure to cis- or trans- 1,2-dichloroethene.

Genotoxicity studies (*in vitro*) are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to cis- or trans-1,2-dichloroethene.

2. HEALTH EFFECTS

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding lethality in humans from ingestion of cis- or trans-1,2-dichloroethene. Lethal effects of orally-administered trans-1,2-dichloroethene in rats and mice have been investigated. Acute-duration dose levels exceeding 1,000 mg/kg are lethal in both species: 7 of 10 rats died following exposure to 1,130 mg/kg/day trans-1,2-dichloroethene (Freundt et al. 1977), and 2 of 6 rats died following exposure to 4,900 mg/kg/day cis-1,2-dichloroethene (McMillan 1986). In mice, LD_{50} values ranging from 2,200 mg/kg/day (males) to 2,400 mg/kg/day (females) were reported from trans-1,2-dichloroethene exposure (Munson et al. 1982). The difference in these values among and between rats and mice could be attributable to a number of different factors, including species differences, strain differences, age of animals, physiological status (e.g., fasting), experimental conditions, and vehicle used to dissolve the chemical. Symptoms associated with lethal oral doses included decreased activity, ataxia, suppressed or total loss of righting reflex, and depressed respiration (Barnes et al. 1985; Hayes et al. 1987). Necropsy revealed severe pulmonary capillary hyperemia and alveolar septal distension, along with fibrous swelling and hyperemia of cardiac muscle in several rats (Hayes et al. 1987), and hyperemia of the mucosal surface of the stomach and small intestine in mice (Barnes et al. 1985). In a 16day study, increased mortality was observed in rats exposed to 970 mg/kg/day cis-1,2-dichloroethene; 2 of 20 rats died within the first week of dosing (McCauley et al. 1990). Although the cause of death was not reported, the rats displayed central nervous system depression and secretions around the nose and mouth. In a 90-day study of cis-1,2-dichloroethene, 3 of 10 male rats treated with 290 mg/kg/day, 4 of 10 male rats treated with 870 mg/kg/day, and 1 of 10 female rats treated with both 32 and 97 mg/kg/day died within the first week of dosing. The incidence of these deaths was not statistically significant when compared with controls (l/20); no other rats died during the 90-day treatment, and the authors could not specifically relate the death to the chemical exposure (McCauley et al. 1990). The LD_{5O} values, the highest NOAEL values, and all reliable LOAEL values for death in each species in the acute-duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Table 2-2. Levels of Significant Exposure to 1,2-Dichloroethene - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	ACUTE EXPOSURE						
	Death						
1	Rat (Wistar SPF)	once (GO)				1130 F (7/10 died)	Freundt et al. 1977 trans
2	Rat (Sprague-Dawley)	once (GO)				7900 M (LD_{50})	Hayes et al. 1987 trans
						10000 F (LD_{50})	
3	Rat (Sprague-Dawley)	7 d 1x/d (GO)				970 (2/20 died)	McCauley et al. 1990 cis
4	Rat (Sprague-Dawley)	once (GO)				4900 M (2/6 died)	McMillan 1986 cis
5	Mouse (CD-1)	once (G)				2100 M (LD_{50})	Barnes et al. 1985 trans
						2400 F (LD_{50})	
6	Mouse (CD-1)	once (G)				2200 M (LD_{50})	Munson et al. 1982 trans
						2400 F (LD_{50})	

Table 2-2. Levels of Significant Exposure to 1,2-Dichloroethene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Systemic						
7	Rat (Wistar SPF)	once (GO)	Resp	940 F		1130 F (pulmonary capillary hyperemia and alveolar septal distention in 2/10)	Freundt et al. 1977 trans
			Cardio	940 F		1130 F (fibrous swelling and hyperemia, disorganization of striated pattern of cardiac muscle in 2/10)	
			Musc/skel	1600 F			
			Hepatic	1600 F			
			Renal	1600 F			
8	Rat (Sprague-Dawley)	14 d 1x/d (GO)	Resp	1900			McCauley et al. 1990 cis
			Cardio	1900			
			Gastro	1900			
			Hemato	1900 M 97[b] F		290 F (significant decreases in hematocrit and in erythrocyte count)	
			Musc/skel	1900			
			Hepatic	1900 M 97 F		290 F (significant decrease in blood urea nitrogen)	
			Renal	970 M 290 F	1900 M 970 F (increase absolute & relative kidney weights)		
			Endocr	1900			
			Dermal	1900			
			Bd Wt	1900			
			Metabolic	290M	970M (significant increase in serum calcium)		

Table 2-2. Levels of Significant Exposure to 1,2-Dichloroethene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
9	Rat (Sprague-Dawley)	once (GO)	Hepatic		2500M (56% increase in plasma sorbitol dehydrogenase activity)		McMillan 1986 cis
10	Mouse (CD-1)	14 d 1x/d (G)	Resp	210M			Barnes et al. 1985 trans
			Hemato		210M (12% decrease in fibrinogen levels and 7% decrease in prothrombin time)		
			Hepatic	210M			
			Renal	210M			
			Bd Wt	210M			
	Neurological						
11	Rat (Sprague-Dawley)	14 d 1x/d (GO)		970		1900 (CNS depression)	McCauley et al. 1990 cis
12	Mouse (CD-1)	once (G)		1200	1600 (decreased activity)	2800 (ataxia and loss of righting reflex)	Barnes et al. 1985 trans
13	Mouse (CD-1)	7 d 1x/d (G)		100M	300M (taste aversion)		Kallman et al. 1983 cis and trans

Table 2-2. Levels of Significant Exposure to 1,2-Dichloroethene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	INTERMEDIATE EXPOSURE						
	Systemic						
14	Rat (Sprague-Dawley)	90 d ad lib (W)	Resp	3114 M 2809 F			Hayes et al. 1987 trans
			Hemato	3114 M 2809 F			
			Hepatic	3114 M 2809 F			
			Renal	3114 M 353 F	1257 F (12% increase in kidney weight)		
			Bd Wt	3114 M 2809 F			

Table 2-2. Levels of Significant Exposure to 1,2-Dichloroethene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
15	Rat (Sprague-Dawley)	90 d 1x/d (GO)	Resp	870			McCauley et al. 1990 cis
			Cardio	870			
			Gastro	870			
			Hemato	32[c] M 97 F	97 M (decreased hematocrit) 290 F (decreased hematocrit)		
			Musc/skel	870			
			Hepatic	32	97 (significant increase relative liver weight)		
			Renal	290 M 870 F	870 M (significant increase relative kidney weight & decrease blood urea nitrogen and creatinine)		
			Endocr	870 F			
			Dermal	870			
			Bd Wt	32 M 870 F	97 M (10% decreased body weight)	290 M (27% decreased body weight)	
16	Rat (Sprague-Dawley)	30 d 1x/d (GO)	Resp		480 (significantly depressed relative lung weight)		McMillan 1986 cis and trans
			Cardio	480			
			Gastro	480			
			Hemato			480 M (significantly depressed CBC, RBC, hemoglobin, and hematocrit)	
			Hepatic		480 (significantly increased relative liver weight)		
			Renal	480			
			Bd Wt	480			
			Other	480			

Table 2-2. Levels of Significant Exposure to 1,2-Dichloroethene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
17	Mouse (CD-1)	90 d ad lib (W)	Resp	387 M 224 F	452 F (11% decrease relative lung weight)		Barnes et. al. 1985 trans
			Hepatic	17[d] M 452 F	175M (increased serum alkaline phosphatase & 8% increase relative liver weight)		
			Renal	452			
			Bd Wt	452			
	Immunological/Lymphoreticular						
18	Mouse (CD-1)	90 d ad lib (W)		23 F	224 F (23% increase leukocyte count & 18% decrease relative thymus weight)		Barnes et. al. 1985 trans
19	Mouse (CD-1)	90 d ad lib (W)		387 M 452 F			Shopp et al. 1985 trans

[a]The number corresponds to entries in Figure 2-2.

[b]Used to derive an acute oral minimal risk level (MRL) of 1 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive an intermediate oral MRL of 0.3 mg/kg/day for cis-1,2-dichloroethene; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[d]Used to derive an intermediate oral MRL of 0.2 mg/kg/day for trans-1,2-dichloroethene; dose is adjusted by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; CBC = complete blood cell (count); CNS = central nervous system; d = day(s); Endocr = endocrine; F = female (G) = gavage; Gastro = gastrointestinal; (GO) = gavage in oil; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; RBC = red blood cell (count); Resp = respiratory; wk = week(s); (W) = water

Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethene - Oral

Acute (≤14 days)

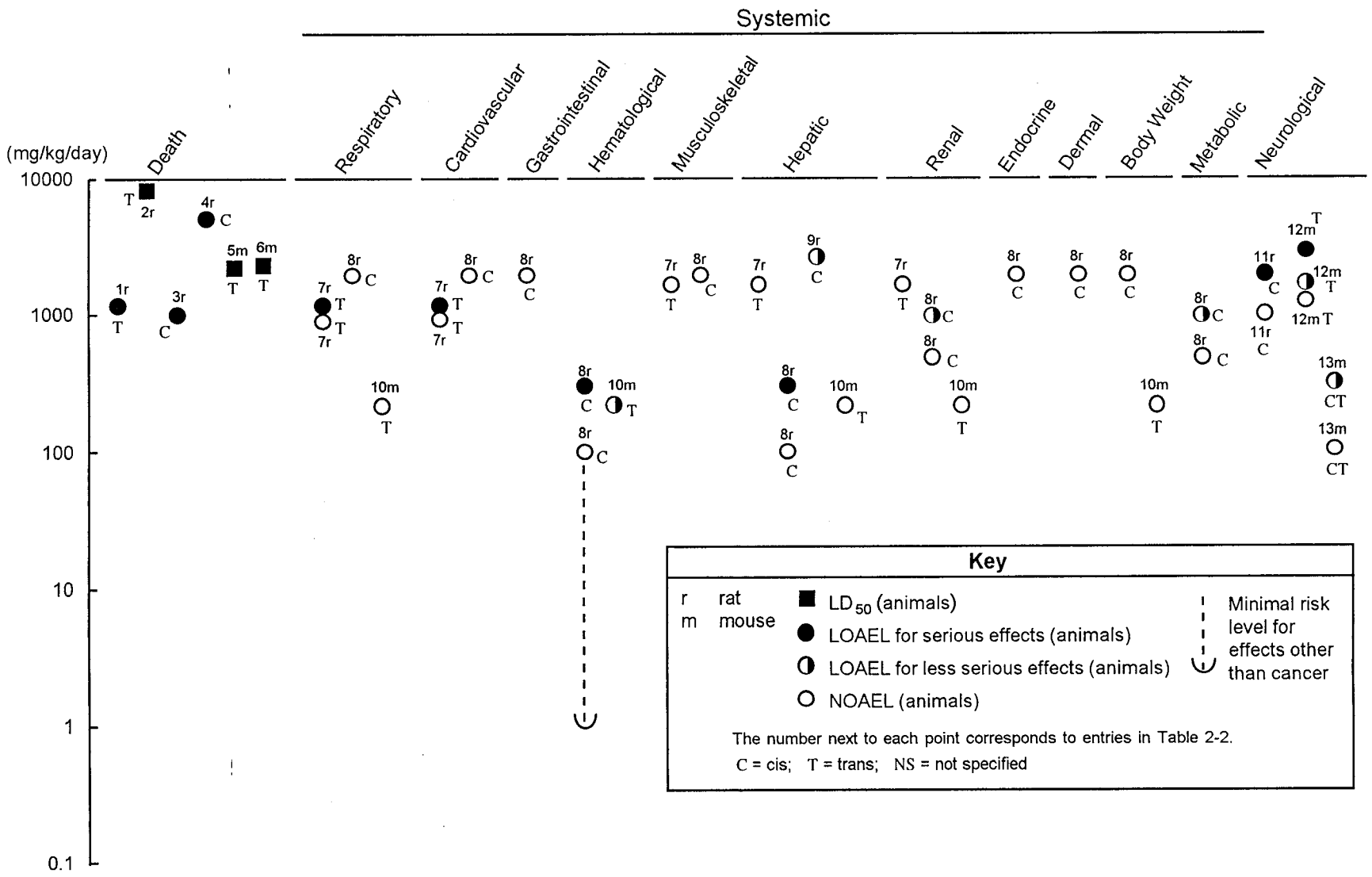
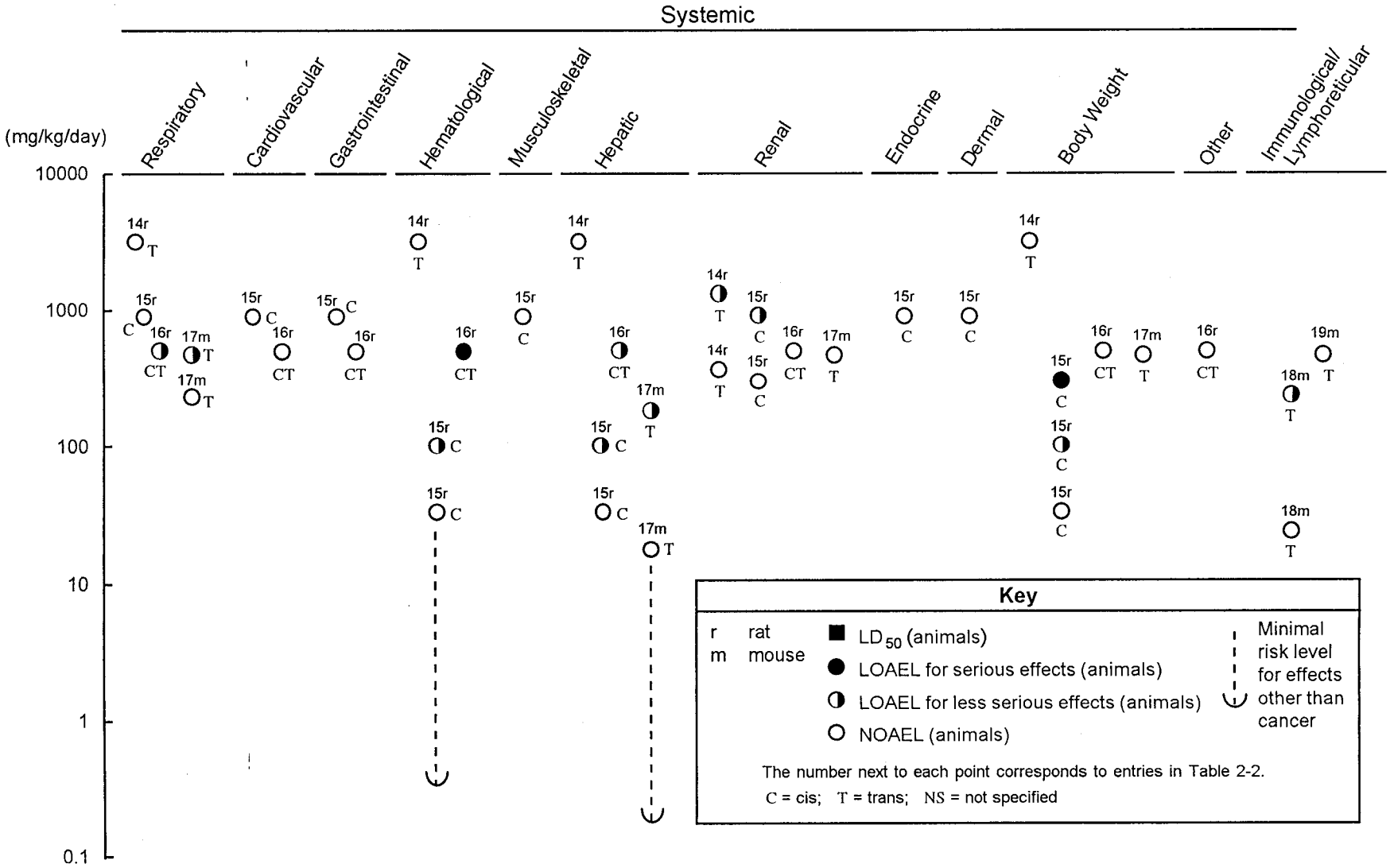


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethene - Oral (continued)

Intermediate (15-364 days)



2.2.2.2 Systemic Effects

No studies were located regarding ocular effects in humans or animals after oral exposure to cis- or trans-1,2-dichloroethene. The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect 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 following oral exposure to cis- or trans- 1,2-dichloroethene.

The effects of orally administered 1,2-dichloroethene on the respiratory tract of animals have not been examined extensively. As shown in Table 2-2 and Figure 2-2, male mice have been shown to tolerate exposure to 387 mg/kg body weight per day of trans-1,2-dichloroethene administered in drinking water for up to 90 days without developing histopathological changes in the lung (Barnes et al. 1985). The only change reported in this study was a slight decrease (11%) in lung weight in female mice at 452 mg/kg/day. No change in lung weight occurred in male rats exposed to 3,114 mg/kg/day trans-1,2dichloroethene for 90 days (Hayes et al. 1987). Pulmonary capillary hyperemia and alveolar septal distention have been observed in rats given lethal doses of trans-1,2-dichloroethene (Freundt et al. 1977). It is not clear whether this pathology represents a primary effect of the chemical on the lung or is secondary to disruption of cardiovascular function prior to death. It is notable that similar changes have been observed in rats exposed by inhalation to trans-1,2-dichloroethene (see Section 2.2.1.2).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following oral exposure to cis- or trans-1,2-dichloroethene.

Female rats exposed to 1,130-l ,400 mg/kg trans-1 ,2dichloroethene through oral gavage (single exposure) showed changes in cardiac muscle structure along with swelling and hyperemia (Freundt et al. 1977). No cardiovascular effects were noted in rats exposed to 1,900 mg/kg/day cis-1,2-dichloroethene for 14 days or 870 mg/kg/day cis-1,2-dichloroethene for 90 days (McCauley et al. 1990).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following oral exposure to cis- or trans- 1,2-dichloroethene.

2. HEALTH EFFECTS

Mice that received lethal doses of trans- 1,2-dichloroethene had hyperemia of the stomach and small intestines (Barnes et al. 1985). No gastrointestinal effects were noted in rats exposed to 1,900 mg/kg/day cis-1,2-dichloroethene for 14 days or 870 mg/kg/day cis- 1 ,2dichloroethene for 90 days (McCauley et al. 1990).

Hematological Effects. No studies were located regarding hematological effects in humans following oral exposure to cis- or trans- 1 ,2-dichloroethene.

McMillan (1986) reported unchanged values of electrolytes, total blood cell counts, and total leukocyte counts, as compared to controls, from 14-day administration of a 50% mixture of the l,2dichloroethene cis and trans isomers (480 mg/kg/day) in rats. In contrast, the same dose, administered over 30 days, resulted in a significant depression of the total blood cell count, the red blood cell count, peripheral blood hemoglobin, and hematocrit levels.

No significant changes in hematological parameters occurred in rats (Hayes et al. 1987) or mice (Barnes et al. 1985) following oral exposure to trans-1,2-dichloroethene. As shown in Table 2-2 and Figure 2-2, rats tolerated repeated doses of 3,114 mg/kg/day (males) and 2,809 mg/kg/day (females) of trans-1 ,2dichloroethene in drinking water (emulsified with emulphor, a polyethoxylated vegetable oil) for 90 days without exhibiting significant hematological abnormalities (Barnes et al. 1985; Hayes et al. 1987). In contrast, dose-related hematotoxicity was the most evident effect in rats exposed orally by gavage to cis-1,2-dichloroethene in corn oil (McCauley et al. 1990). Decreased red blood cell count and hematocrit levels were observed in female rats exposed to 290 mg/kg/day for 14 days. No such changes were detected in female rats after exposure to 97 mg/kg/day or in male rats at all dose levels. Based on this value, an acute-duration oral MRL of 1 mg/kg/day was calculated for cis-1,2-dichloroethene as described in the footnote to Table 2-2 and in Appendix A. Similarly, decreased hematocrit levels were found in male rats exposed to 97 mg/kg/day cis-1,2-dichloroethene for 90 days and decreased hemoglobin levels were reported in both sexes at 290 mg/kg/day. The NOAEL level was 32 mg/kg/day. This. value was used for derivation of an intermediate-duration oral MRL –for cis-1,2-dichloroethene of 0.3 mg/kg/day as described in the footnote to Table 2-2 and in Appendix A.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following oral exposure to cis- or trans- 1,2-dichloroethene.

2. HEALTH EFFECTS

Histological examination of muscle tissue revealed no compound-related effects in rats exposed to 1,900 or 870 mg/kg/day of cis-1,2-dichloroethene for 14 or 90 days, respectively (McCauley et al. 1990), or in rats exposed by gavage to 1,600 mg/kg/day of trans-1,2-dichloroethene (Freundt et al. 1977).

Hepatic Effects. No studies were located regarding hepatic effects in humans following oral exposure to cis- or trans- 1,2-dichloroethene.

Liver pathology has been demonstrated in rats exposed orally to lethal or near lethal doses (e.g., 70% lethal dose) of trans- 1,2-dichloroethene. At 1,130 mg/kg/day of trans- 1,2-dichloroethene, 2 of 10 rats had severe fatty infiltration of the liver lobules and Kupffer cells; however, these effects were not seen in the rats given higher doses (Freundt et al. 1977). The pathology is similar to that observed in rats exposed by the inhalation route (i.e., fatty degeneration of the Kupffer cells and liver lobules) (Freundt et al. 1977). However, for oral exposure, the effects occurred only after exposure to lethal dose levels. As shown in Table 2-2 and Figure 2-2, repeated exposure to lower levels of trans-1,2-dichloroethene in drinking water for 90 days was tolerated by mice and did not result in liver pathology. However, at 175 mg/kg/day increased serum alkaline phosphatase was seen, indicating some degree of hepatic damage (Barnes et al. 1985).

McMillan (1986) examined the hepatic toxicity of cis- and trans-1,2-dichloroethene in rats after oral and intraperitoneal administration, respectively. At an exposure level of 4,400 mg/kg (single dose) of trans-1,2-dichloroethene, a significant increase in plasma alanine aminotransferase was noted, and at 2,500 mg/kg (single dose) of cis-1,2-dichloroethene, a significant increase in plasma sorbitol dehydrogenase activity was noted. Intermediate exposure (30 days) did not result in any treatmentrelated lesions in the liver. However, significantly elevated liver weights were noted at 480 mg/kg/day of a mixture of the cis and trans isomers for 30 days.

Biochemical changes in the liver have been reported in mice and rats exposed to cis- and trans-1,2-dichloroethene (Barnes et al. 1985; Jenkins et al. 1972). However, a connection between these biochemical changes and the pathology or impaired liver function has not been established. As such, the effects can not be classified as adverse or as being indicative of liver toxicity. Changes in hepatic alkaline phosphatase, tyrosine transaminase, glucose-6-phosphatase, and plasma alanine transaminase activities have been observed in rats exposed to single oral doses of 400 or 1,500 mg/kg

of cis- or trans-1,2dichloroethene (Jenkins et al. 1972). Although the changes observed in these enzyme activities were significant, the validity of the study is limited by the lack of dose-related patterns of the changes, the use of only three or four rats per treatment group, and the lack of reporting of animal responses to dosing. A dose-related decrease in the levels of serum glutamicoxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) was observed in female mice exposed to 23-452 mg/kg/day of trans-1,2-dichloroethene in the drinking water for 90 days (Barnes et al. 1985). Increased serum levels of these hepatic enzymes are usually indicative of liver damage; the toxicological significance of decreased levels is unknown. Increased serum alkaline phosphatase and increased relative liver weights were seen in male mice exposed to 175 mg/kg/day of trans-1,2-dichloroethene for 90 days. No such effects were noted in female mice. Based on a NOAEL of 17 mg/kg/day, an intermediate-duration oral MRL for trans-1,2-dichloroethene of 0.2 mg/kg/day was calculated as described in the footnote to Table 2-2 and in Appendix A.

The effect of 90-day exposure to trans-1,2-dichloroethene (17-452 mg/kg/day in drinking water) on hepatic microsomal drug metabolism was assessed by Barnes et al. (1985). In contrast to findings with inhalation exposure studies, oral exposure to trans-1,2-dichloroethene had no effect on the duration of hexobarbital-induced narcosis. In addition, no significant changes were found in hepatic microsomal cytochrome P-450 or cytochrome bg specific content. However, a decrease in microsomal aniline hydroxylase activity was reported in all exposed groups. A significant decrease in hepatic glutathione levels occurred in males after 90 days of exposure to 387 mg/kg/day.

A dose-related increase in relative liver weight was observed in rats exposed for 14 and 90 days to cis-1,2-dichloroethene (McCauley et al. 1990). In the 90-day study, effects were significant at 97 mg/kg/day and above. Slight increases in serum cholesterol were observed in the female rats in the 14-day study, and slight decreases in SGOT were observed in the 90-day study. The increased liver weight and biochemical changes cannot be considered adverse because they were not associated with histopathological liver lesions.

Renal Effects. No studies were located regarding renal effects in humans following oral exposure to cis- or trans- 1,2-dichloroethene.

The effects of 1,2-dichloroethene on the kidney have not been examined extensively in laboratory animals. The few studies that have been reported provide evidence to suggest that the kidney is

probably not a primary target for toxicity of trans-1,2-dichloroethene. As presented in Table 2-2 and Figure 2-2, animals tolerated repeated exposure to trans-1 ,2dichloroethene in drinking water without adverse effects on the kidney. A dose-related increase in absolute and relative kidney weight occurred in female rats treated with trans-1,2-dichloroethene for 90 days, but no histopathological lesions were identified (Hayes et al. 1987). No detectable chemically-induced changes in blood urea nitrogen or serum creatinine levels were found in animals exposed to trans-1,2-dichloroethene in either the 14-day or 90-day exposure study (Barnes et al. 1985; Hayes et al. 1987).

A significant increase in rat kidney weight was reported from a 16-day oral exposure to a 50% mixture of the 1,2-dichloroethene isomers (480 mg/kg/day) (McMillan 1986). An increase in absolute and relative kidney weight, along with a decrease in blood urea nitrogen, was also found in female rats exposed for 14 days to 970 mg/kg/day of cis-1,2-dichloroethene, and in male rats orally exposed to 1,900 mg/kg/day of cis-1,2-dichloroethene (McCauley et al. 1990). However, these changes did not occur in female rats exposed to 870 mg/kg/day of the cis isomer or less for 90 days. In male rats exposed to 870 mg/kg/day of cis-1,2-dichloroethene for 90 days, a significant increase in relative kidney weight and decreases in blood urea nitrogen and creatinine levels occurred. No changes occurred in males exposed to 1,900 mg/kg/day or less for 14 days. The toxicological significance of decreased blood urea nitrogen and creatinine levels is not clear since increases in these parameters are usually associated with renal toxicity. Furthermore, no histological evidence of kidney pathology was observed. In the absence of histological and clinical evidence of renal toxicity, the toxicological significance of the increased kidney weight is not known.

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to cis-or trans-1,2-dichloroethene.

Histological examination revealed no compound-related effects in the thyroid in rats exposed to cis-1,2-dichloroethene at doses up to 1,900 or 870 mg/kg/day for 14 or 90 days, respectively (McCauley et all 1990).

Dermal Effects. No studies were located regarding dermal effects in humans following oral exposure to cis- or trans- 1,2-dichloroethene.

2. HEALTH EFFECTS

Histological examination revealed no compound-related effects on the skin of rats exposed to cis-1,2-dichloroethene at doses up to 1,900 or 870 mg/kg/day for 14 or 90 days, respectively (McCauley et al. 1990).

Body Weight Effects. No studies were located regarding body weight effects in humans following oral exposure to cis- or trans-1 ,2dichloroethene.

Body weight was not altered either by 21 or 210 mg/kg/day of trans-1,2-dichloroethene administered for 14 days to mice by gavage (Barnes et al. 1985). In rats, body weight was not altered by a 16day exposure to a 50% mixture of the 1,2-dichloroethene isomers (480 mg/kg/day) (McMillan 1986), nor by exposure to trans-1,2-dichloroethene (353-3,114 mg/kg/day) in drinking water for 90 days (Hayes et al. 1987). Significant changes in body weight gain were observed in both male and female rats treated with cis-1,2-dichloroethene for 14 days (McCauley et al. 1990). The changes were not dose-related; increased body weight gain occurred at 97 and 290 mg/kg/day and decreased body weight gain occurred at 970 and 1,900 mg/kg/day. The toxicological significance of these binodal body weight changes over a 14-day treatment period is not clear, although it could be due to decreased food intake at higher doses. In the 90-day study, only the male rats receiving the highest dose of cis-1,2-dichloroethene (870 mg/kg/day) had significantly decreased body weight gain when compared with control males.

Other Systemic Effects. No studies were located regarding other systemic effects in humans following oral exposure to cis-or trans-1,2-dichloroethene.

In female rats, a significant increase in water consumption was seen at 97 mg/kg/day. The authors stated that since cis-1,2-dichloroethene was administered by gavage, this effect must be considered to be compound-related and not associated with water palatability. They additionally noted that determining whether this effect is related to the compound's influence on the renal, central nervous system, or other-organ system will require more data (McCauley et al. 1990).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans following oral exposure to cis- or trans- 1,2-dichloroethene.

The effect of orally-administered trans-1,2-dichloroethene on the immune system has been investigated in rats and mice. No effects were seen on the spleen (Freundt et al. 1977; McCauley et al. 1990) or on leukocyte counts (Barnes et al. 1985; McMillan 1986; Munson et al. 1982) in rats or mice. Barnes et al. (1985) reported increased leukocyte count and decreased relative thymus weight in female mice exposed to 224 mg/kg/day of trans-1,2-dichloroethene for 90 days. Mice exposed to trans-1,2-dichloroethene (up to 220 mg/kg/day by gavage) for 14 days showed no significant changes in cell-mediated or humoral immunity (Munson et al. 1982; Shopp et al. 1985). Repeated exposure of mice to trans-1,2dichloroethene in drinking water for 90 days had no effect on the cell-mediated immune status of either sex or on the humoral immune status of females (Shopp et al. 1985). A suppression in humoral immune status, as measured by spleen cell antibody production directed against sheep erythrocytes, was observed in male mice treated with each of three doses (17, 175, and 387 mg/kg/day) of trans- 1,2-dichloroethene. Although the suppression was significant, it was not severe enough to depress the functional ability of the humoral immune system, as indicated by a normal spleen cell response to B cell mitogen lipopolysaccharide and normal hemagglutination titers. The highest NOAEL values for immunological effects in mice in each duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Immunological effects were noted from exposure to 1,900 mg/kg/day of cis-1,2-dichloroethene in rats for 14 days, while an increase in absolute and relative thymus weights was noted in female rats exposed to 870 mg/kg/day for 90 days (McCauley et al. 1990).

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to cis- or trans- 1,2-dichloroethene.

The neurological effects of cis- and trans-1,2-dichloroethene in animals have not been extensively examined, though acute exposure and stimuli/response research do provide insight. Signs of central nervous system depression have been observed in rats and mice at the terminal stages after receiving lethal doses of cis- and trans-1,2-dichloroethene (Barnes et al. 1985; Hayes et al. 1987; McCauley et al. 1990). Central nervous system depression (not further specified) was reported in rats treated with cis-1,2-dichloroethene at 1,900 mg/kg/day for 14 days (McCauley et al. 1990). The highest NOAEL

value and the LOAEL values from each reliable study with neurological end points are presented in Table 2-2 and plotted in Figure 2-2.

Dose-related conditioned taste aversion to saccharin was produced in mice exposed to a mixture of cis and trans-1,2-dichloroethene (Kallman et al. 1983). This neurobehavioral test will detect both neurological and non-neurological effects that are perceived by the test animal to be adverse. The nature of the adverse stimuli that results in taste aversion has not been identified.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to cis- or trans- 1,2-dichloroethene.

Neither acute nor intermediate exposures (14 and 90 days) have caused histological changes in reproductive organs of rats exposed to levels of cis-1,2-dichloroethene up to 1,900 mg/kg/day (McCauley et al. 1990). Rats exposed by gavage showed no treatment-related lesions in mammary glands, clitoral glands, ovaries, uterus, seminal vesicles, prostate, testes or preputial glands. No treatment-related histopathological lesions in the reproductive organs were seen in rats exposed to trans-1,2-dichloroethene for up to 90 days (Barnes et al. 1985; Hayes et al. 1987).

No studies were located regarding the following effects in humans or animals following oral exposure to cis- or trans-1,2-dichloroethene:

2.2.2.6 Developmental Effects

2.2.2.7 Genotoxic Effects

Genotoxicity studies- are discussed in Section 2.5.

2.2.2.8 Cancer

2. HEALTH EFFECTS

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding lethal effects in humans following dermal exposure to cis- or trans- 1.2-dichloroethene.

No deaths were reported from application of trans-1,2-dichloroethene at 5,000 mg/kg body weight on clipped, intact skin of 2 male and 3 female rabbits (Brock 1990). Table 2-3 summarizes the significant dermal exposure studies, presenting the highest NOAEL values and all LOAEL values from each important study. No studies were located regarding lethal effects in animals following dermal exposure to cis- 1,2-dichloroethene.

2.2.3.2 Systemic Effects

No dermal exposure studies of cis- or trans-1,2 dichloroethene were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or endocrine effects in humans or animals.

Dermal Effects. No studies were located regarding dermal effects in humans following dermal exposure to cis- or trans- 1,2-dichloroethene.

Dermal effects have been shown in laboratory animals exposed dermally to trans-1,2-dichloroethene. Application of 170 mg/kg (0.5 mL) of trans-1,2dichloroethene for 24 hours to clipped, intact skin of 1 female and 5 male rabbits under an occlusive wrapping produced mild or moderate erythema at all observation times (24, 48 and 72 hours) (Brock 1990). In a separate experiment (Brock 1990), 5,000 mg/kg of trans-1,2-dichloroethene was applied to the clipped, intact skin of 2 male and 3 female rabbits. Severe dermal irritation was observed, but no clinical signs of toxicity other than body weight loss were found. No studies were located regarding dermal effects in animals following dermal exposure to cis- 1,2-dichloroethene.

Table 2-3. Levels of Significant Exposure to 1,2-Dichloroethene - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL				Reference Chemical Form
				Less Serious		Serious		
ACUTE EXPOSURE								
Systemic								
Human	5-30 min (airborne)	Ocular	280 M ppm	830 M ppm	(slight burning of eyes)			Lehmann and Schmidt-Kehl 1936 trans
Rat (Crl: CDBR)	10 d Gd 7-16 6 hr/d (airborne)	Dermal	12000 F ppm					Hurtt et al. 1993 trans
		Ocular		2000 F ppm	(lacrimation)			
Rabbit (New Zealand White)	20 sec (eyes)	Ocular				3.3 F mg/kg	(transient severe corneal opacity, moderate iritis, and conjunctivitis)	Brock 1990 trans
Rabbit (NS)	24 hr	Dermal		170 mg/kg	(mild or moderate erythema)			Brock 1990 Abstract trans
Rabbit (NS)	24 hr	Dermal				5000 mg/kg	(severe dermal irritation)	Brock 1990 Abstract trans
		Bd Wt		5000 mg/kg	(body weight loss not otherwise specified)			

Bd Wt = body weight; d = day(s); F = female; Gd = gestational day; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); NOAEL = no-observable-adverse-effect level; NS = not specified; sec = second(s)

2. HEALTH EFFECTS

Ocular Effects. An early study by Lehmann and Schmidt-Kehl (1936) reported a slight burning of the eyes in two human subjects exposed for 30 minutes to concentrations between 830 and 2,220 ppm of trans-1,2-dichloroethene in air. The subjects were exposed under controlled conditions, not as an occupational accident. It is not certain whether the subjects were exposed to a vapor or to an aerosol of this chemical. The accuracy of the reported exposure levels is questionable because of the insensitivity of the methods used in 1936 to measure the concentration of 1,2dichloroethene in air. Also, the degree of purity of the trans isomer used is uncertain. No studies were located regarding ocular effects in humans following dermal exposure to cis-1,2-dichloroethene.

Severe corneal opacity, moderate iritis, conjunctivitis and lacrimation have been shown in rats after direct eye exposure to trans-1,2-dichloroethene. Trans-1,2-dichloroethene (0.01 mL) was placed in the lower conjunctival sac of two female rabbits and 20 seconds later, the eyes of one rabbit were washed with tap water while the eyes of the other rabbit remained unwashed. Severe cornea1 opacity was observed in the washed eye and moderate iritis and conjunctivitis were observed in both treated eyes; however, all irritation was resolved by day 3 (Brock 1990). Airborne exposure to trans-1,2-dichloroethene caused lacrimation in rats at 2,000 ppm (Hurtt et al. 1993). No studies were located regarding ocular effects in animals following dermal exposure to cis-1,2-dichloroethene.

Body Weight Effects. No studies were located regarding body weight effects in humans following dermal exposure to cis- or trans- 1,2-dichloroethene.

Brock (1990) applied 5,000 mg/kg trans-1,2-dichloroethene to the clipped, intact skin of 2 male and 3 female rabbits. Loss of body weight (amount unspecified) was observed. No studies were located regarding body weight effects in animals following dermal exposure to cis-1,2-dichloroethene.

2. HEALTH EFFECTS

No studies were located regarding the following effects in humans or animals following dermal exposure to cis- or trans- 1,2-dichloroethene:

2.2.3.3 Immunological and Lymphoreticular Effects

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

2.3 TOXICOKINETICS

1,2-Dichloroethene appears to be absorbed quickly by the lungs. One study reported that approximately 75% of the inhaled chemical was absorbed through the lungs in humans. 1,2-Dichloroethene is metabolized in the liver, by hepatic microsomal cytochrome P-450, to form dichloroethanol and dichloroacetic acid. Animal studies have shown that metabolism of the cis isomer occurs faster than metabolism of the trans isomer, and the cis isomer frequently inhibits activity or destroys cytochrome P-450 levels, while the trans isomer frequently increases the enzyme levels. No information is available on the excretion of 1.2-dichloroethene in humans or animals.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

In tests for partitioning between human blood and air (Gargas et al. 1989), the results show a relatively high affinity of 1,2-dichloroethene for blood (cis- 1,2-dichloroethene - blood:air partition coefficient =

9.58 [±0.70] and trans-1,2-dichloroethene = 6.04 [±0.38]). Several other studies appear to support the conclusion that 1,2dichloroethene is absorbed relatively quickly by the lungs. Sato and Nakajima (1979) reported blood:air partition coefficients (ratio concentrations in blood and air at 37 °C) of 9.2 and 5.8 for cis and trans isomers of 1,2-dichloroethene, respectively. Both isomers of 1,2-dichloroethene in inspired air achieve an equilibrium with the whole animal within 1.5-2 hours (Filser and Bolt 1979). Gargas et al. (1988, 1989) determined 1iquid:air and tissue:air partition coefficients for cis- and trans-1,2-dichloroethene. Partition coefficients were determined with 0.9% saline; olive oil; and blood, liver, muscle, and fat tissues from rats. The partition coefficients for cis-1,2-dichloroethene are: blood = 21.6 (±2.0), 0.9% saline = 3.25 (±0.12), olive oil = 278 (±6), fat = 227 (±11), liver = 15.3 (±11), and muscle = 6.09 (±1.02). The coefficients for trans-1,2-dichloroethene are: blood = 9.58 (±0.94), 0.9% saline = 1.41 (±0.04), olive oil = 178 (±6), fat = 148 (±11), liver = 8.96 (±0.61), and muscle = 3.52 (±0.54). Lehmann and Schmidt-Kehl (1936) reported that 72-75% of inhaled trans-1,2-dichloroethene is absorbed through the lungs in humans. Further insight is provided by Anderson et al. (1980), who reported that trans-1,2-dichloroethene follows mixed-form uptake kinetics, with a composite of a slow first-order and a saturable uptake process.

No studies were located regarding the rate and extent of cis- or trans-1,2dichloroethene absorption for the following:

2.3.1.2 Oral Exposure

2.3.1.3 Dermal Exposure

2.3.2 Distribution

No studies were located regarding the distribution of cis- and trans-1,2-dichloroethene following exposure by any routes.

2.3.3 Metabolism

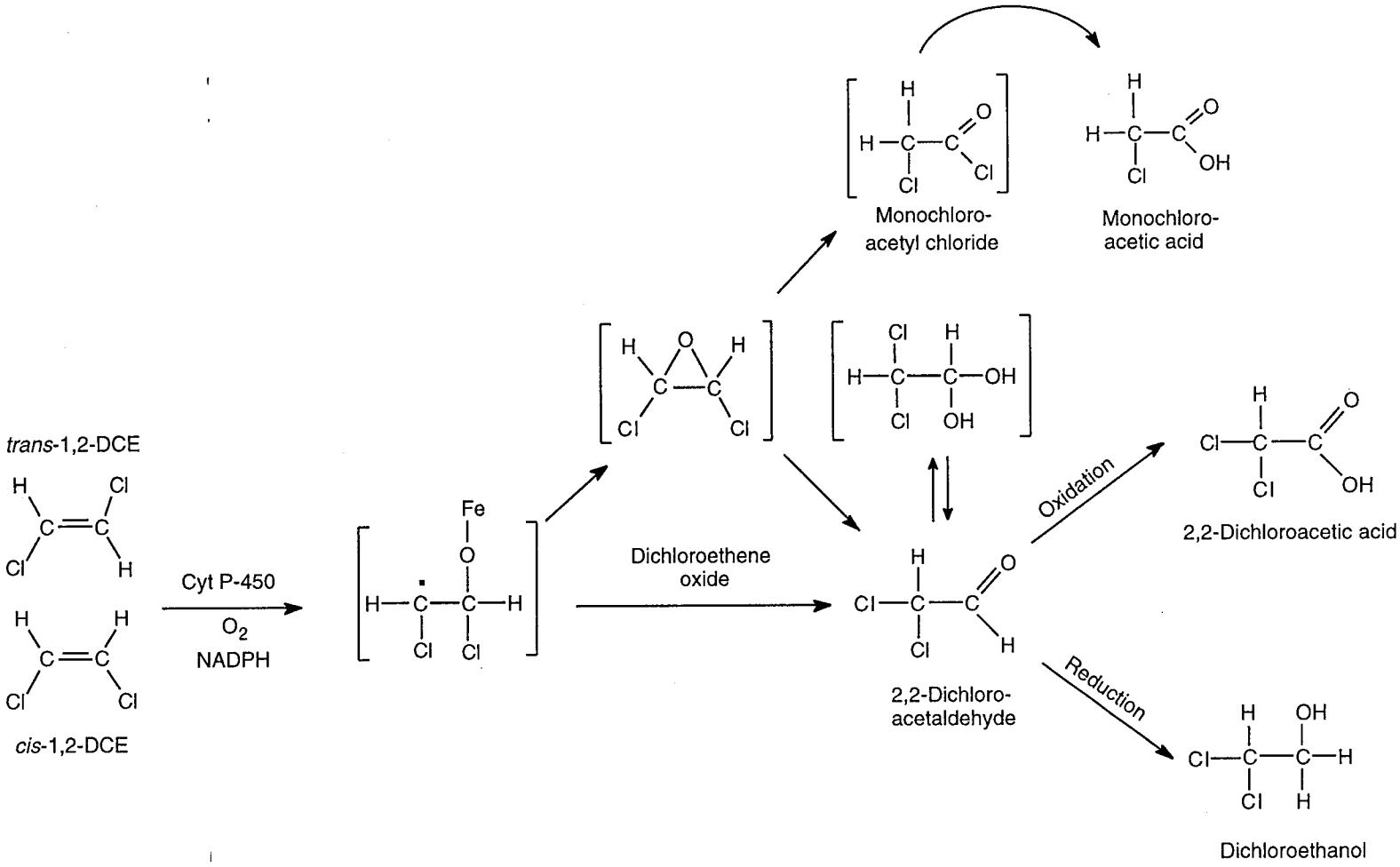
Metabolism of 1,2-dichloroethene is initially catalyzed by hepatic microsomal cytochrome P-450 (Costa and Ivanetich 1982, 1984). Although there is no direct evidence, studies on the synthesis of the epoxides suggest that this metabolism involves epoxidation of the ethylene double bond, forming

dichlorinated epoxides (Figure 2-3). Dichlorinated epoxides, in turn, can undergo a non-enzymatic rearrangement. Studies on the metabolism of 1,2-dichloroethene by hepatic microsomes and hepatocytes provide evidence to suggest that dichloroacetaldehyde is the predominant metabolite of microsomal cytochrome P-450 and that it, in turn, is extensively converted to dichloroethanol and dichloroacetate by cytosolic and/or mitochondrial aldehyde and alcohol dehydrogenases present in hepatocytes (Costa and Ivanetich 1982, 1984; Leibman and Ortiz 1977). This is consistent with the report that both the cis and trans isomers of 1,2-dichloroethene were converted to dichloroethanol and dichloroacetic acid by perfused rat liver (Bonse et al. 1975).

Similarities and differences have been observed in the metabolism of cis- and trans-1,2-dichloroethene. Both isomers have been shown to bind to the active site of hepatic cytochrome P-450 (Costa and Ivanetich 1982). In addition, classic inhibitors of cytochrome P-450 have been shown to inhibit the production of dichloroacetaldehyde from both isomers. The binding and metabolism of 1,2-dichloroethene do not appear to be specific for any one form of cytochrome P-450. The cis isomer had a 4-fold greater rate of turnover in hepatic microsomes in vitro than the trans isomer. This is consistent with studies on isolated perfused rat livers, where metabolism of the cis isomer occurred at a greater rate than metabolism of the trans isomer (Bonse et al. 1975). In addition, differences between cis- and trans-1,2-dichloroethene in the rates of formation of dichloroethanol and dichloroacetic acid have been reported in rat hepatocytes (Costa and Ivanetich 1984).

Several reports suggest that 1,2dichloroethene can alter cytochrome P-450 and mixed-function oxidase activities. McMillan (1986) reported depression of cytochrome P-450 dependent microsomal metabolism by both isomers of 1,2-dichloroethene, while Paolini et al. (1992) reported the induction of cytochrome P-450 enzymes by trans-1,2-dichloroethene. Freundt and Macholz (1978) demonstrated that each of the isomers of 1,2dichloroethene competitively inhibited the metabolism of hexobarbital in vivo following a single 8-hour inhalation exposure of rats to 200 ppm of these isomers. The effects of the cis isomer were more potent than those of the trans isomer. In addition, trans-1,2-dichloroethene competitively inhibited the oxidative *N*-demethylation of aminopyrine and the *O*-demethylation of p-nitroanisole by hepatic microsomes. Bronzetti et al. (1984) demonstrated that an intraperitoneal injection of the trans isomer can increase cytochrome P-450 levels (consistent with the work of Paolini 1992) and aminopyrine *N*-demethylase activity in mice, while injection of the cis isomer more frequently tended to inhibit activity or destroy the enzyme.

Figure 2-3. Postulated Metabolic Scheme for 1,2-Dichloroethene



Adapted from Costa and Ivanetich 1982

2. HEALTH EFFECTS

The metabolic elimination of 1,2-dichloroethene has been described as a saturable, dose-dependent process (Filser and Bolt 1979). In rats exposed to atmospheric concentrations of 1,2-dichloroethene that exceed a "point of saturation," elimination proceeds by zero-order kinetics (rate independent of the concentration of the compound); below saturation, first-order kinetics apply (Filser and Bolt 1979). Pharmacokinetic studies on 1,2dichloroethene elimination in the gas phase of a closed inhalation exposure system show that cis-1,2-dichloroethene has a higher rate of first-order clearance than the trans isomer. The cis isomer also exhibits a higher rate of metabolic elimination under saturation conditions, in comparison to the trans isomer. This observation is consistent with the higher rate of metabolism of the cis isomer relative to the trans isomer by rat liver microsomes (Costa and Ivanetich 1982) and by isolated perfused liver (Bonse et al. 1975).

2.3.4 Excretion

No studies were located regarding the excretion of 1,2-dichloroethene in humans or animals following exposure by any routes.

2.4 MECHANISMS OF ACTION

Both cis- and trans-1,2-dichloroethene are volatile, lipophilic molecules that easily move through the respiratory and gastrointestinal systems. Based on their molecular size and lipophilicity, they probably pass through membranes by simple (passive) diffusion. Toxicokinetic evidence shows they have a high affinity for lipids and blood, but little accumulation in tissues. Both the cis and trans isomers of 1,2-dichloroethene are converted to dichloroethanol and dichloroacetic acid by rat liver (Bonse et al. 1975, with the cis isomer exhibiting a higher rate of metabolism than the trans isomer (Costa and Ivanetich 1982).

1,2-Dichloroethene isomers inhibit liver enzymes involved in metabolism and may increase the "toxic" response to other chemicals (Bolt et al. 1980; McMillan 1986). Reactive metabolites of 1,2-dichloro ethene modify the heme moiety of hepatic microsomal cytochrome P-450, resulting in a loss of both cytochrome P-450 and heme (Costa and Ivanetich 1982). This modification could account for the observed *in vivo* and *in vitro* inhibition of other cytochrome P-450 substances by 1,2-dichloroethene. Compounds, such as carbon monoxide, that inactivate or inhibit the cytochrome P-450 system, should

also inhibit the metabolism of 1,2-dichloroethene. 1,2Dichloroethene is oxidized to its epoxide, which is relatively stable (Bolt et al. 1980). Its lack of genotoxicity is related to this stability.

The differences in metabolism, and possibly toxicity, between the cis and tram isomers have been partially explained by differences in the stereochemistry of the epoxides formed. The asymmetrical metabolites appear to be more electrophilic and also more mutagenic (Greim et al. 1975; Henschler 1977). The cis isomer is more actively metabolized than the tram isomer, because the trans isomer is a more stable form and the proximity of the two chlorine atoms in the cis isomer increases the binding to other molecules with which it reacts (Henschler 1977).

Physiologically based pharmacokinetic modeling (PBPK) has been used to explain metabolic rates for 1,2-dichloroethene. A model that included suicide enzyme inhibition-resynthesis has been used to describe the metabolism of 1,2-dichloroethene in the rat (Gargas et al. 1990). In this model, metabolism results in the inactivation of cytochrome P-450, which could result in an increase or decrease in the toxicity of 1,2dichloroethene.

2.5 RELEVANCE TO PUBLIC HEALTH

Inhalation, oral, and dermal routes of exposure to 1,2dichloroethene are of concern to humans because 1,2-dichloroethene has been found in air, drinking water, and soil (Shah and Singh 1988; Westrick et al. 1984; VIAR 1987). Toxicokinetic data are very limited for both human and animal exposures. Partition coefficients suggest that 1,2-dichloroethene has a much stronger affinity for blood and fats than for air. Although the compound is relatively lipophilic, there is no good evidence for accumulation in important organs such as liver, brain, kidney, and adipose tissue. Tissue saturation should not be found at anticipated exposure levels. 1,2Dichloroethene is likely to be metabolized to more hydrophilic by-products, and, therefore, eliminated quickly by the kidneys as metabolites.

The most significant effects of 1,2-dichloroethene exposure are hematological and hepatic. At high levels of exposure, clinical symptoms that have been reported in humans exposed to 1,2dichloroethene in air include nausea, drowsiness, fatigue, intracranial pressure and ocular irritation. One fatality has been reported. No information is available on oral toxicity for 1,2dichloroethene in humans. No information is available on the relative toxicities of the cis and trans isomers of 1,2dichloroethene in humans.

2. HEALTH EFFECTS

Pathological lesions of the heart, liver, and lungs have been reported in rats exposed to trans-1,2-dichloroethene in air. Ataxia and respiratory depression occur in the terminal stages prior to death in animals. Since these conditions have not been observed in humans, their relevance to public health is not known.

A variety of genotoxicity tests have been performed for 1,2-dichloroethene. The predominant results are negative, and no carcinogenicity studies were found in the literature. Federal and international agencies have given 1,2dichloroethene a non-cancer rating or a “not classifiable” rating.

Minimal Risk Levels for 1,2-Dichloroethene.

MRLs have been derived for acute and intermediate exposure to the cis and trans isomers of 1,2-dichloroethene; no chronic studies are available from which to derive MRLs for chronic exposure. The derivation of each MRL is discussed fully in Appendix A.

Inhalation MRLs.

- An MRL of 0.2 ppm has been derived for acute-duration exposure (14 days or less) and for intermediate-duration inhalation exposure (15-364 days) to trans- 1,2-dichloroethene.

The acute MRL is based on a LOAEL of 200 ppm for trans-1,2-dichloroethene over an 8-hour period that caused fatty degeneration of the liver (Freundt et al. 1977). Longer periods of exposure at 200 ppm showed increased numbers and severity of response. The intermediate MRL is based on the same study and effects (Freundt et al. 1977) in which rats were exposed to 200 ppm trans-1,2-dichloroethene for 8 hours per day, 5 days per week for 8 or 16 weeks. An uncertainty factor of 1,000 is used: 10 for using a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability.

No chronic inhalation MRL has been derived for trans-1,2-dichloroethene because no study tested 1,2-dichloroethene for a sufficiently long period of time. No acute-, intermediate- or chronic-duration MRLs have been derived for cis-1,2-dichloroethene because of lack of data.

2. HEALTH EFFECTS

Oral MRLs.

Studies of oral exposure to 1,2-dichloroethene exist to develop oral MRLs for both the cis and trans isomers.

- An MRL of 1 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to cis- 1.2-dichloroethene.

This MRL for the cis isomer is based on a NOAEL of 97 mg/kg/day for decreased red blood cell counts and hematocrit levels in female rats exposed to 97 mg/kg/day cis-1,2-dichloroethene for 14 days (McCauley et al. 1990). An uncertainty factor of 100 is used: 10 for extrapolation from animals to humans, and 10 for human variability. Hematological effects have also been noted in other oral studies (Barnes et al. 1985).

No acute oral MRL has been derived for trans- 1,2-dichloroethene.

Separate intermediate-duration oral MRLs were derived for exposure to the cis and trans isomers.

- An MRL of 0.3 mg/kg/day has been derived for intermediate-duration oral exposure to

al. 1985). An uncertainty factor of 100 was developed for the MRL, using factors of 10 for animal-to-human extrapolation and 10 to protect sensitive individuals. In this study, serum alkaline phosphatase levels were significantly increased. Though the two highest doses caused increased serum alkaline phosphatase levels in a non-dose-related manner, the effects are consistent with the fatty accumulation in hepatocytes. This hepatic intermediate end point is slightly lower than a hematological NOAEL (decreased hematocrit). Other organs and end points were an order of magnitude less sensitive to cis- 1,2-dichloroethene than were hepatic and hematologic target organs.

Death. A fatality was reported to have occurred after inhalation of 1,2-dichloroethene in a small enclosure (Hamilton 1934). Details regarding the exposure levels (cis and trans) in this accident and the cause of death are not available. No reports of lethality related to oral exposure of humans to 1,2-dichloroethene were located.

Terminal symptoms in animals exposed orally to cis- or trans-1,2-dichloroethene involve central nervous system depression (e.g., ataxia and loss of righting reflex) and respiratory depression (Barnes et al. 1985; Hayes et al. 1987; McCauley et al. 1990; Munson et al. 1982). Results of studies in which animals have inhaled or ingested trans-1,2,-dichloroethene implicate the heart, liver, and lung as potential targets for toxicity (Barnes et al. 1985; Freundt et al. 1977; Hayes et al. 1987; McMillan 1986). The relative lethal potency of the cis and trans isomers to each other is not known.

Systemic Effects. Trans-1,2dichloroethene appears to be an ocular irritant in humans. Two human participants in a self-experimentation study reported mild burning of the eyes after acute exposure to either vapors or aerosols of trans-1,2-dichloroethene (Lehmann and Schmidt-Kehl 1936). No other specific systemic effects have been reported in humans. Cis- 1 ,2dichloroethene may induce a similar toxicological effect; however, no reports were located that specifically implicated cis- 1.2-dichloroethene as an ocular irritant.

Systemic effects-involving the heart, liver, and lungs have been observed in animals exposed to trans-1,2-dichloroethene. Evidence for serious adverse effects in these organs consists of only one study (Freundt et al. 1977). Effects reported in the rat include lung lesions (hyperemia and alveolar septal distension), fibrous swelling of the myocardium, and fatty degeneration of the liver. All three effects were observed after inhalation exposures to trans- 1,2-dichloroethene at concentrations of 200 ppm or greater for 8 hours. Liver and lung lesions were observed after gavage dosing, but only

after near lethal doses were administered. The treatment groups in this study were too small to establish a high degree of confidence in these findings. However, one additional serious systemic effect was found in rats-reduced weight gain for pregnant dams exposed to airborne 1,2-dichloroethene (Hurtt et al. 1993). Exposure of rats (Hayes et al. 1987) or mice (Barnes et al. 1985) to trans-1,2-dichloroethene at doses up to 3,114 mg/kg/day, in the drinking water for 90 days, did not result in adverse systemic effects.

Increased liver and kidney weights were observed in rats treated orally with cis-1,2-dichloroethene for 14 or 90 days, but these increased organ weights were not accompanied by any histopathological lesions in either organ (McCauley et al. 1990). Rats exposed to the cis isomer by gavage for 14 and 90 days showed a dose-related decrease in red blood cell count and hematocrit levels (McCauley et al. 1990). Hematotoxicity was not observed in mice or rats exposed to the trans isomer (Barnes et al. 1985; Hayes et al. 1987). The different results in the rat studies could be due to differential toxicity between the two isomers, as well as to other factors, including initial age of the rats, vehicle differences, and different exposure methods. Hayes et al. (1987) exposed rats with an initial age of 26 days to the trans isomer in a 1% emulphor drinking water suspension, while McCauley et al. (1990) treated rats with an initial age of 70 days with the cis isomer in corn oil by gavage. Data regarding toxic systemic effects of 1,2-dichloroethene in animals are too limited to draw any conclusions for human exposure.

Respiratory Effects. Pulmonary effects of inhalation and oral exposure to 1,2-dichloroethene have been shown over a range of exposure levels and for both inhalation and oral routes. No effect levels are reported from 485 to 2,000 mg/kg/day; however, several studies found pronounced respiratory effects around 1,000 mg/kg/day or 1,000 ppm (Freundt et al. 1977; McCauley et al. 1990; McMillan 1986). All these values are relatively high.

Cardiovascular Effects. The likelihood of acute exposure to 1,2-dichloroethene is quite small. Only at high levels (3,000 ppm or 1,100 mg/kg/day) is there animal evidence of swelling of heart muscle and congestion of blood in and near the heart (Freundt et al. 1977).

Hematological Effects. There are known blood effects of 1,2-dichloroethene, but these occur at exposure levels above those expected for the general population. Acute- and intermediate-exposure hematologic studies are the bases for oral MRLs for cis-1,2-dichloroethene (McCauley et al. 1990).

2. HEALTH EFFECTS

Musculoskeletal Effects. Animal studies have not reported effects on the musculoskeletal system (Freundt et al. 1977; McCauley et al. 1990). Thus, it does not appear that musculoskeletal effects are of concern for human exposure to 1,2-dichloroethene.

Hepatic Effects. Liver effects in animals include fatty degeneration of liver lobules; such effects are reasonable to anticipate among humans, though exposure levels of greater than 100 mg/kg/day are not anticipated. Higher exposure levels produced enzyme changes (decreased serum alkaline phosphatase, serum albumin and blood urea nitrogen or increased plasma enzyme activity) according to some of the available literature (Freundt et al. 1977; McMillan 1986). Acute- and intermediate-exposure hepatic studies are the bases for inhalation MRLs for trans-1,2-dichloroethene (Freundt et al. 1977) and for an oral MRL for tram-1,2dichloroethene (Barnes et al. 1985).

Renal Effects. Reduced kidney function and increased kidney weight are expected with acute high level exposure (McCauley et al. 1990; McMillan 1986); however, the public health concern is relatively small because such effects are not known to occur at chronic lower level exposure.

Dermal Effects. Acute exposure of the skin causes effects that are readily reversible. Irritation and mild effects on skin are the most frequent effects likely to be observed (Brock 1990).
Ocular Effects. Acute exposure causes readily reversible effects such as a slight burning of the eyes (Lehman and Schmidt-Kehl 1936).

Body Weight Effects. Acute- and intermediate-duration exposure has affected weight gain in pregnant and young rats (Hurtt et al. 1993; McCauley et al. 1990). In pregnant rats, reduced food consumption was observed along with reduced weight gain. Intermediate oral exposure caused smaller weight gains for growing rats.

Immunological and Lymphoreticular Effects. There are no reports of immunological effects in humans as a result of exposure to cis- or trans-1,2-dichloroethene by any route. Studies in rats and mice have not shown effects on the spleen, leukocytes, or liver Kupffer cells (Barnes et al. 1985; Freundt et al. 1977; McMillan 1986; Munson et al. 1982). Studies in mice have demonstrated perturbations of the humoral immune system (suppressed spleen cell antibody production against sheep erythrocytes) after exposure to trans-1,2-dichloroethene (Shopp et al. 1985). The observed changes in

the humoral immune system did not constitute a functional impairment of the humoral immune response and, therefore, are not considered to be adverse. The data regarding immunological effects of 1,2-dichloroethene in animals are too limited to draw any conclusion about potential immunological effects in humans.

Neurological Effects. The central nervous system depressant properties of 1 ,2dichloroethene represent an important effect in humans. Dizziness, drowsiness, vertigo, and intracranial pressure are some of the symptoms that have been reported in humans after inhalation of trans-1,2-dichloroethene (Lehmann and Schmidt-Kehl 1936). These symptoms disappeared quickly after exposure was terminated. The pharmacological basis for the 1,2-dichloroethene-mediated narcosis has not been studied.

Central nervous system depression (e.g., ataxia, loss of righting reflex) has been observed in some animal studies as well, but only at the terminal stages after the administration of lethal doses of both cis- and trans.-1,2-dichloroethene (Hayes et al. 1987; McCauley et al. 1990; Munson et al. 1982). A study in rats and mice reported on the air concentrations evoking a depression in the duration of hindlimb extension (Frantik et al. 1994). A marked species dependent effect was observed in this study. Therefore, it is difficult to draw any conclusions regarding the significance of this type of neurological effect in humans.

Reproductive Effects. There are no reports of reproductive effects in humans as a result of exposure to cis- or trans-1,2-dichloroethene by any route.

It is not known whether reproductive effects may be of concern to humans. One study showed an increase in resorption rates in rats; however, the authors interpreted this effect as not being treatment related (Hurtt et al. 1993).

Developmenta! Effects. There are no reports of developmental effects in humans as a result of exposure to cis- or trans-1,2dichloroethene by any route.

It is not known whether developmental effects may be of concern to humans. Fetal weights were reduced significantly in a developmental rat study; however, this was probably due to reduced food consumption in the pregnant rats (Hurtt et al. 1993).

2. HEALTH EFFECTS

Genotoxic Effects. Genotoxic effects of cis- and trans-1,2-dichloroethene in humans are unknown. Mutagenicity of 1,2dichloroethene has been examined in a variety of test systems. *In vivo* tests (Table 2-4) indicate that cis-1,2-dichloroethene, but not trans-1,2-dichloroethene, is genotoxic. The cis isomer was found to be mutagenic in the host-mediated assay using a series of Salmonella tester strains in mice (Cema and Kypenova 1977). Bronzetti et al. (1984) also found that the cis isomer was mutagenic in *Saccharomyces* cerevisiae D7 in a host-mediated assay in mice, with significant increases in convertants at the trp locus and revertants at the ilv locus. Cantelli-Forti and Bronzetti (1988) also reported that cis-1,2-dichloroethene was mutagenic in the *S. cerevisiae* D7 strain in mice. Dose-dependent toxicity increased in the presence of the mouse, S9 microsomal fraction. In addition, repeated intraperitoneal injection of cis- 1,2-dichloroethene produced chromosomal aberrations in mouse bone marrow cells (Cema and Kypenova 1977). Negative results were obtained with trans-1,2-dichloroethene in these assays.

In vitro tests of genotoxicity of the cis and trans isomers are summarized in Table 2-5. Neither isomer was genotoxic with or without metabolic activation in *Escherichia* coli K12 (Greim et al. 1973, in several strains of *S. typhimurium* in spot tests (Cema and Kypenova 1977; Mortelmans et al. 1986), or in gene mutation and gene conversion tests in S. cerevisiue D7 (Galli et al. 1982). However, Bronzetti et al. (1984) found positive results for gene mutation tests of the cis isomer in *S. cerevisiue* D7, with metabolic activation. Neither isomer produced chromosomal aberrations or sister chromatid exchanges in Chinese hamster cells (Sawada et al. 1987). The cis isomer, but not the trans isomer, induced unscheduled DNA synthesis in rat hepatocytes (Costa and Ivanetich 1984).

Cancer. To date, cancer effects of cis- and trans-1,2-dichloroethene have not been studied in humans or animals.

2.6 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).

Table 2-4. Genotoxicity of cis- and trans-1,2-Dichloroethene *In Vivo*

Species (test system)	End point	Results	Reference
cis-1,2-Dichloroethene			
Mammalian systems:			
Mouse bone	Chromosomal aberrations	+	Cerna and Kypenova 1977
Host-mediated assays:			
Salmonella typhimurium	Gene mutation	+	Cerna and Kypenova 1977
(mouse host-mediated assay)			
Saccharomyces cerevisiae D7	Gene mutation	+	Cantelli-Forti and Bronzetti 1988
		+	Bronzetti et al. 1984
(mouse host-mediated assay)			
S. cerevisiae D7	Gene conversion	+	Bronzetti et al. 1984
(mouse host-mediated assay)		–	Cantelli-Forti and Bronzetti 1988
trans-1,2-Dichloroethene			
Mammalian systems:			
Chromosomal aberrations	Mouse bone marrow	–	Cerna and Kypenova 1977
Host-mediated assays:			
S. typhimurium	Gene mutation	–	Cerna and Kypenova 1977
(mouse host-mediated assay)		–	Cantelli-Forti and Bronzetti 1988
S. cerevisiae D7	Gene mutation	–	Bronzetti et al. 1984
(mouse host-mediated assay)			
S. cerevisiae D7	Gene conversion	–	Bronzetti et al. 1984
(mouse host-mediated assay)		–	Cantelli-Forti and Bronzetti 1988

+ = positive result; – = negative result

Table 2-5. Genotoxicity of cis- and trans-1,2-Dichloroethene *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
cis-1,2-Dichloroethene				
Prokaryotic organisms:				
Escherichia coli K12	Gene mutation	–	–	Greim et al. 1975
Salmonella typhimurium	Gene mutation	ND	–	Cerna and Kypenova 1977
		–	–	Mortelmans et al. 1986
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae D7	Gene mutation	+	–	Bronzetti et al. 1984
		–	–	Galli et al. 1982
S. cerevisiae D7	Gene conversion	–	–	Galli et al. 1982
Mammalian cells:				
Chinese hamster CHL cells	Chromosomal aberrations	–	–	Sawada et al. 1987
Chinese hamster CHL cells	Sister chromatic exchange	–	–	Sawada et al. 1987
Rat hepatocytes	Unscheduled DNA synthesis	NA	–	Costa and Ivanetich 1984
trans-1,2-Dichloroethene				
Prokaryotic organisms:				
E. coli K12	Gene mutation	–	–	Greim et al. 1975
		–	–	Cantelli-Forti and Bronzetti 1988
S. typhimurium	Gene mutation	ND	–	Cerna and Kypenova 1977

Table 2-5. Genotoxicity of cis- and trans-1,2-Dichloroethene *In Vitro* (continued)

Species (test system)	End point	Result		Reference
		With activation	Without activation	
trans-1,2-Dichloroethene (continued)				
Eukaryotic organisms:				
Fungi:				
S. cerevisiae D7	Gene mutation	–	–	Bronzetti et al. 1984
		–	–	Galli et al. 1982
S. cerevisiae D7	Gene conversion	–	–	Bronzetti et al. 1984
		–	–	Galli et al. 1982
Mammalian cells:				
Chinese hamster CHL cells	Chromosomal aberrations		–	Sawada et al. 1987
Chinese hamster CHL cells	Sister chromatid exchange	–	–	Sawada et al. 1987
Rat hepatocytes	Unscheduled DNA synthesis	NA	–	Costa and Ivenetich 1984

NA = not applicable; ND = no data; – = negative results; + = positive results.

2. HEALTH EFFECTS

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. 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 (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 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-dichloroethene are discussed in Section 2.6.1.

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 (NAWNRC 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 as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often 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-dichloroethene are discussed in Section 2.6.2.

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 pr other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to 1,2-Dichloroethene

There currently are no biomarkers available to quantify exposure to 1,2-dichloroethene.

Methods exist for determining 1,2dichloroethene in blood and biological tissues (see Chapter 6), but specific levels of 1,2-dichloroethene have not been directly correlated with exposure via any route. Acetonemia and acetone exhalation were observed in rats after inhalation exposure to halogenated ethylenes, including cis- and trans-1,2-dichloroethene (Filser et al. 1978). (Acetone is not a metabolite of 1,2dichloroethene exposure, but rather may be caused by stimulation of cellular systems that lead to increased acetone production.) Acetone exhalation occurred during exposure of rats to a concentration of trans- 1,2-dichloroethene as low as 50 ppm. This finding cannot, however, be used as a biomarker of exposure because the amount of acetone exhaled was not correlated with different exposure concentrations. Furthermore, acetone exhalation is not specific for 1 ,2dichloroethene since acetone can be found in blood and exhaled air after exposure to other chemicals such as vinyl chloride, vinylidene fluoride, and perchloroethylene (Filser and Bolt 1980), as well as in patients with diabetes, hepatic insufficiency, and other metabolic disorders.

2.6.2 Biomarkers Used to Characterize Effects Caused by 1,2-Dichloroethene

There currently are no biomarkers available to characterize effects caused by 1,2-dichloroethene in humans.

As discussed in Section 2.6.1, acetonemia and acetone exhalation were observed in rats after inhalation exposure to halogenated ethylenes, including the two isomers of 1,2-dichloroethene (Filser et al. 1978). Based on results of experiments with vinylidene fluoride, Filser and Bolt (1980) concluded that metabolites, rather than the parent compounds, were involved in invoking this response. Based on results of studies with the monohaloacetate metabolites of vinylidene fluoride and vinylidene chloride, which are known to inhibit enzymes of the citric acid cycle, Filser et al. (1982) suggested that the production of acetone by the halogenated ethylenes might also result from the inhibition-of the enzymes of the citric acid cycle. This would lead to an increase in mitochondrial acetyl-coenzyme A and, consequently, to an alteration in lipid and fatty acid metabolism and ketosis. A similar mechanism was suggested for 1,2-dichloroethene because the primary metabolite, dichloroacetate, can also increase ketone levels in the body. If such a mechanism operated, acetone exhalation could conceivably serve as a biomarker for such effects as fatty degeneration of the liver, which has been

observed in rats exposed to 1,2-dichloroethene (Freundt et al. 1977). However, acetone exhalation is extremely common and is associated with some disorders that do not obviously produce any liver degeneration.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDRKDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.7 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding the health effects in humans or animals exposed to 1,2-dichloroethene in combination with other chemicals that are likely to be found with 1,2-dichloroethene in the environment, workplace, or at hazardous waste sites.

As mentioned in Section 2.3.3, both isomers of 1,2-dichloroethene can inhibit the cytochrome P-450-dependent metabolism of hexobarbital (Freundt and Macholz 1978). Such inhibition has also been shown to increase hexobarbital sleeping time. Costa and Ivanetich (1982) showed that multiple forms of hepatic microsomal cytochrome P-450, including the forms induced by P-naphthoflavone and phenobarbital, can bind and metabolize 1,2-dichloroethene. Thus, 1,2-dichloroethene may potentiate the toxic actions of any chemical that undergoes detoxication by cytochrome P-450-dependent metabolism by competing for binding to the active site of cytochrome P-450. Conversely, 1,2-dichloroethene may antagonize the toxic actions of any chemical that undergoes toxic activation by cytochrome-P-450-dependent metabolism.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,2-dichloroethene than will most persons exposed to the same level of 1,2-dichloroethene in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting

end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

While no populations with unusual susceptibility to the health effects of 1,2-dichloroethene could be identified, based on the available literature, certain diabetics may be unusually susceptible because of impairment of glucose metabolism and increased production of acetone. In addition, individuals with impaired livers, such as alcoholics, and those with exposure to other halogenated hydrocarbons may be unusually susceptible to 1,2-dichloroethene exposure.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

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

2.9.1 Reducing Peak Absorption Following Exposure

1,2-Dichloroethene is available commercially as the cis or trans isomer or as a mixture. Human exposure to 1,2dichloroethene may occur by inhalation, ingestion, or by dermal contact. There are conflicting data regarding the relative toxicity of the two isomers. Vapors are extremely irritating to the eyes and upper respiratory tract, and once absorbed can cause central nervous system and respiratory depression. 1,2-Dichloroethene was used as a general anesthetic in humans, and central nervous system depression is one of its toxic effects (ACGIH 1991). It is recommended that exposed individuals be moved to fresh air and administered 100% humidified supplemental oxygen. The potential risk of aspiration, especially for infants, leading to airway and pulmonary damage, usually outweighs the potential benefit of administering syrup of ipecac to induce emesis (TOMES 1994). Once in the care of a health professional, gastric lavage can be useful if administered within 1 hour of the exposure to reduce the amount of absorbed solvent.

Following ocular contamination, the eyes should be irrigated with copious amounts of room temperature water or normal (0.9%, w/v, isotonic) saline, for at least 15 minutes. Reversible, corneal opacification has been described after exposure to 1,2-dichloroethene vapor, and ophthalmologic consultation should generally be sought after ocular contamination to evaluate the potential ocular damage (Gosselin 1984).

Following acute exposure to many chlorinated solvents, hypotension and cardiac arrhythmias due to myocardial sensitization have led to ventricular fibrillation and death (TOMES 1994). Unfortunately there is no specific treatment for 1,2dichloroethene exposure except for supportive measures to combat the effects of central nervous system, respiratory depression, and cardiac irritability.

2.9.2 Reducing Body Burden

The body does not retain significant amounts of 1,2-dichloroethene. It is largely excreted through the lungs; thus, prompt and adequate ventilation is the only known way to reduce body burden (ACGIH 1991). There is no currently recognized treatment to enhance elimination, and orthodox treatment for ingestion is entirely supportive.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

Clinical effects caused by acute exposure to 1,2-dichloroethene include central nervous system and respiratory depression, eye and upper respiratory irritation, nausea, vomiting, weakness, tremors, and epigastric cramps, all of which may resolve rapidly after the exposure ceases. There is one reported industrial fatality caused by inhalation of vapor in a small enclosure, but the level of exposure, symptoms of toxicity, and isomeric composition are unknown (ACGIH 1991). Muscular cramping and vomiting have been relieved by intravenous administration of calcium gluconate (Gosselin 1984). The mechanism of action for the central nervous system effects of 1,2-dichloroethene has not been clearly established, but may be related to solvent effects on cellular membranes. Neurotransmitter effects have also been demonstrated for some solvents, and it is reasonable to speculate that these effects on neurotransmitters might be mitigated by pharmacologic intervention. However, no such interventions are currently available for clinical use.

Fatty degeneration of the liver has been reported in animal studies, but 1,2-dichloroethene appears to have less hepatic and renal toxicity than many other chlorinated hydrocarbons (ACGIH 1991).

However, ethanol in alcoholic beverages may compete with or enhance the metabolic activation of solvents and can increase the severity of health effects, particularly liver toxicity. Alcoholic beverages should be avoided following exposure to 1,2dichloroethene and other solvents.

2.10 ADEQUACY OF THE DATABASE

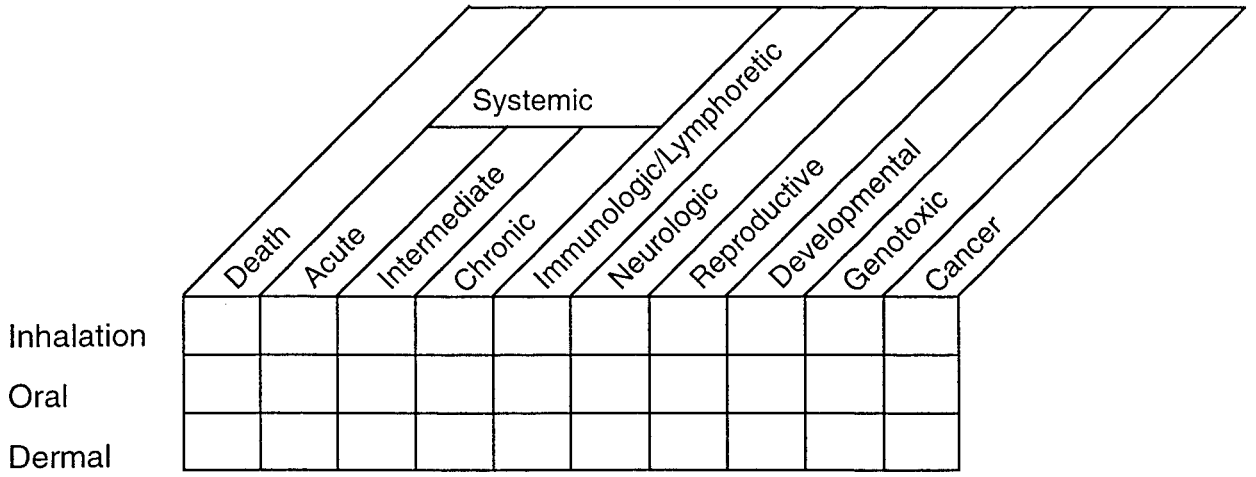
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,2-dichloroethene is available. Where adequate information 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-dichloroethene.

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 the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

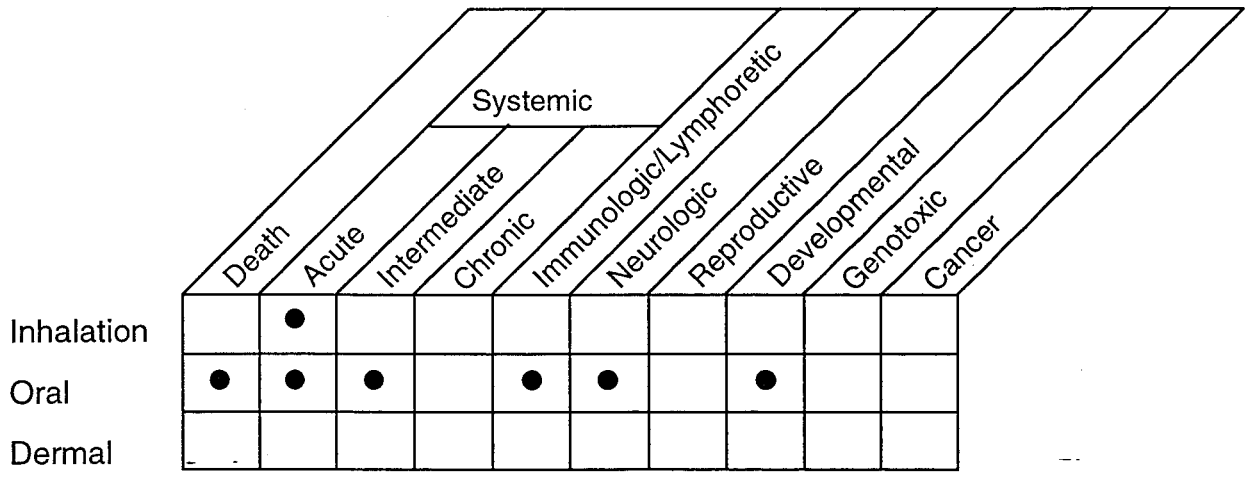
2.10.1 Existing Information on Health Effects of 1,2-Dichloroethene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2-dichloroethene are summarized in Figures 2-4 and 2-5. The purpose of these figures is to illustrate the existing information concerning the health effects of 1,2-dichloroethene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989),-is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 2-4. Existing Information on Health Effects of cis-1,2-Dichloroethene



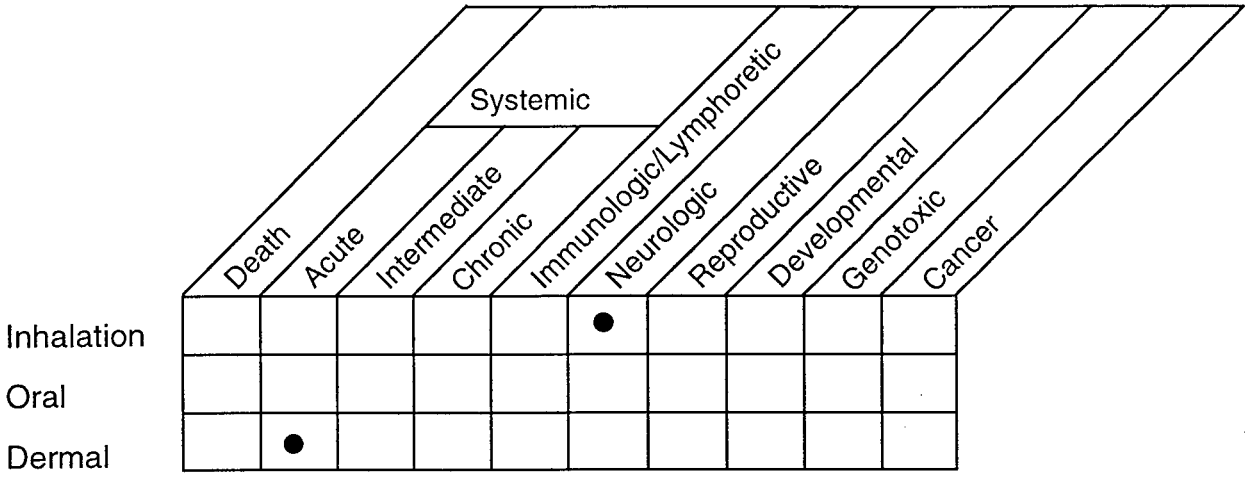
Human



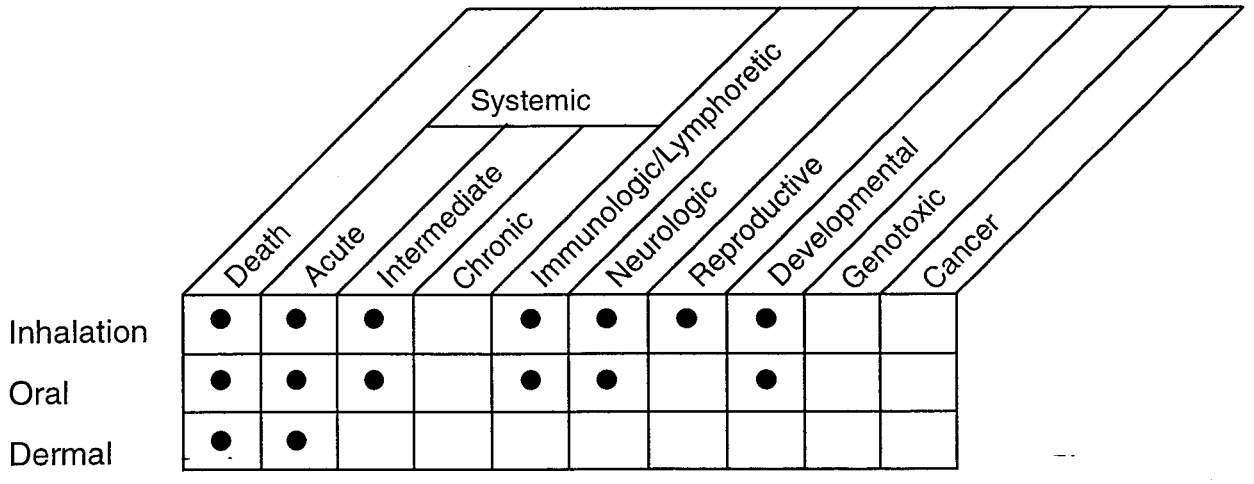
Animal

● Existing Studies

Figure 2-5. Existing Information on Health Effects of trans-1,2-Dichloroethene



Human



Animal

● Existing Studies

2. HEALTH EFFECTS

There are very few studies or case reports of human exposure to 1,2-dichloroethene by any route of exposure. One report describes neurologic symptoms in humans following acute inhalation of trans-1,2-dichloroethene. This property of depressing the central nervous system is an important effect of 1,2-dichloroethene exposure. Another study reported an industrial fatality related to accidental inhalation exposure to 1,2-dichloroethene (isomeric composition unknown).

Information has been reported regarding the lethality and toxic effects of trans-1,2-dichloroethene in animals exposed by the inhalation and oral routes for acute and intermediate durations. For inhalation and oral exposure routes, toxicity to the heart, liver, blood, and lung has been reported. Central nervous system depression has been reported in animals given lethal doses of trans-1,2-dichloroethene by the oral route. Several studies examined the effects of either cis- or trans-1,2-dichloroethene on the immune systems of mice exposed by inhalation or oral routes. A 14-day and a 90-day gavage study of cis-1,2-dichloroethene found hematological effects in rats. No information is available on the toxic effects of chronic exposure to either cis- or trans-1,2-dichloroethene by any route. In addition to central nervous system effects, inhalation exposure to trans- 1,2-dichloroethene appears to affect development of the fetus and development of the newborn and young. When inhaled, there also may be effects on reproduction because of reduced maternal weight gain and reduced litter size. As shown in Figures 2-4 and 2-5, no information on carcinogenic effects in animals by inhalation, oral, or dermal exposure is available for either cis- or trans-1,2-dichloroethene. No studies were located regarding genotoxic effects in humans or animals after inhalation, oral, or dermal exposure to 1,2-dichloroethene, but studies in mice injected intraperitoneally indicate that the cis isomer may be genotoxic; the trans isomer has shown no indication of being genotoxic.

2.10.2 Identification of Data Needs

Acute-Duration Exposure. Reliable health effects data for human exposure by any route to 1,2-dichloroethene were not located. One human fatality was reported, but the cause of death, the length of exposure, and the concentration and isomeric identity of 1,2-dichloroethene in the air were not described (Hamilton 1934). Two human volunteers reported mild burning of the eyes after acute dermal exposure to trans-1,2-dichloroethene (Lehmann and Schmidt-Kehl 1936). However, the methods used in 1936 to generate and test for exposure levels were relatively insensitive, and it is unclear whether the 1,2-dichloroethene was in an aerosol or gaseous state. No information was located for systemic toxicity in humans after oral exposure or for the relative toxicities of the cis and trans

isomers of 1,2-dichloroethene in humans. The acute lethal levels of trans-1,2-dichloroethene were established after inhalation exposure in mice and after oral exposure in mice and rats (Barnes et al. 1985; Freundt et al. 1977; Gradiski et al. 1978; Hayes et al. 1987; Kallman et al. 1983; McMillan 1986; Munson et al. 1982). An acute-duration inhalation MRL was derived from the Freundt et al. (1977) study, based on the hepatic effect of fatty degeneration of the liver seen at 200 ppm in rats. A wide range of LD_{50} values for the trans isomer, 1,300-10,000 mg/kg/day, exists in the present literature. Inhalation LC_{50} and oral LD_{50} values for cis-1,2-dichloroethene are not well defined. One study suggests an LD_{50} around 5,000 mg/kg/day for the cis isomer (McMillan 1986). Pathological lesions in the heart, liver, and lungs were reported in rats after acute inhalation exposure to trans-1,2-dichloroethene; however, the study was limited in size and scope (Freundt et al. 1977). Neurological problems, such as narcosis, lethargy, and behavioral changes, have been shown with acute inhalation of both cis and trans isomers (De Ceaurriz et al. 1983; Hurtt et al. 1993). Oral exposure to 1,2-dichloroethene is also associated with central nervous system depression and other neurological effects (Barnes et al. 1985; Hayes et al. 1987). The finding of acetone in the air exhaled by 1,2-dichloroethene-exposed rats indicates possible alterations in lipid and fatty acid metabolism at high exposure levels (Filser and Bolt 1980). This may support the observation of fatty infiltration of liver in the rat inhalation study. Evidence of target effects for oral acute exposure exists for both the cis and trans isomers. Hematotoxicity after acute oral exposure to cis- and trans-1,2-dichloroethene was reported in rats and mice and included adverse effects of decreases in fibrinogen levels, hematocrit, and erythrocyte counts (Barnes et al. 1985; McCauley et al. 1990). The NOAEL value for decreased hematocrit in female rats was used for the derivation of an acute oral MRL for cis-1,2-dichloroethene. Serious respiratory, cardiovascular, and hepatic effects were also noted in rats exposed orally. Along with the serious responses of pulmonary and fibrous hyperemia, alveolar distention, cardiac muscle changes, and decreases in blood urea nitrogen, milder hepatic changes were recorded (Barnes et al. 1985; Freundt et al. 1977; McCauley et al. 1990; McMillan 1986). Limited data were located for dermal exposure to trans-1,2-dichloroethene indicating mild to moderate, reversible, dermal and ocular effects (Brock 1990; Hurtt et al. 1993; Lehmann and Schmidt-Kehl 1936). The available toxicity data do not allow a definitive conclusion regarding the relative toxicity of the cis and tram isomers. However, *in vivo* and *in vitro* studies suggest differences in the metabolism of the two isomers (Filser et al. 1978, 1979, 1982; Gargas et al. 1988, 1989, 1990; Sato and Nakajima 1979). Furthermore, pharmacokinetic data are insufficient to identify target organs for either isomer across routes of exposure. Further studies to identify target organs of cis- and trans-1,2-dichloroethene toxicity and to assess dose-response relationships would be particularly useful

for inhalation and dermal exposure routes. Additional oral exposure studies would increase the possibilities of assessing dose-response relationships and target organs. The information is important for populations living near hazardous waste sites that might be exposed to 1,2-dichloroethene for brief periods of time.

Intermediate-Duration Exposure. No studies were located regarding intermediate-duration exposure to 1,2-dichloroethene in humans by any route of exposure. Liver and lung toxicity of trans-1,2-dichloroethene in rats, similar to that found with acute exposure, was observed after intermediate-duration inhalation exposure (Freundt et al. 1977). The exposure level that was associated with capillary hyperemia, alveolar distention and pneumonic infiltration, and fatty accumulation in liver lobules and Kupffer cells was the same as that tested with acute exposure; therefore, an intermediate inhalation MRL at the same level as the acute inhalation MRL was derived. Studies in rats and mice exposed orally to trans-1,2-dichloroethene at doses ranging from 17 to 3,100 mg/kg/day (Barnes et al. 1985; Hayes et al. 1987; McCauley et al. 1990; McMillan 1986; Shopp et al. 1985) have examined many target organs including the blood, liver, kidneys, lungs, heart and immune system. Respiratory (lung weight), hematological (blood cell counts), and body weight effects were reported at doses of 100 to 400 mg/kg/day (Barnes et al. 1985; McCauley et al. 1990; McMillan 1986). Hepatic effects in male mice at 175 mg/kg/day and a NOAEL at 17 mg/kg/day are the basis for an intermediate-duration oral MRL for trans-1,2-dichloroethene (Barnes et al. 1985). Hematologic effects at 97 mg/kg/day and a NOAEL at 32 mg/kg/day are the basis of an intermediate-duration oral MRL for cis-1,2-dichloroethene. A 60-day oral study of trans-1,2-dichloroethene in rats, available as an abstract, indicated that the lungs, spleen, and kidney are targets (see Section 2.10.3). The full published report may provide dose-response data when it becomes available. The differences in the observed effects of cis- and trans-1,2-dichloroethene that were seen in rats in the oral 90-day studies may be due to differences in toxicity of these isomers as discussed above (see acute-duration exposure) (Barnes et al. 1985; Hayes et al. 1987; McCauley et al. 1990; McMillan 1986; Shopp et al. 1985). No studies were located regarding 1,2-dichloroethene toxicity in animals after dermal exposure. Additional studies regarding 1,2-dichloroethene toxicity after inhalation exposure are necessary, with a specific need for inhalation studies using the cis isomer. Because people living near hazardous waste sites may be exposed for longer periods of time, more dose-response data for intermediate-duration exposures by all routes are important. The target organs-liver, blood, and lungs-should be emphasized.

2. HEALTH EFFECTS

Chronic-Duration Exposure and Cancer. No human or animal data were located regarding health effects of long-term (chronic) exposure to 1,2-dichloroethene by inhalation, oral, or dermal routes. Therefore, no chronic MRLs could be derived. There is a need to conduct chronic animal studies with the isomers of 1,2-dichloroethene by inhalation, oral and dermal routes. These studies could provide information on subtle toxicological changes in organs/systems and on dose-response relationships associated with 1,2-dichloroethene toxicity. Furthermore, there are communities around hazardous sites that may be exposed to low levels of 1,2-dichloroethene for long periods of time.

No studies were located regarding the carcinogenic potential of 1,2-dichloroethene in humans and animals following inhalation, oral, or dermal exposure. However, genotoxicity studies revealed mutagenic activity of the cis isomer in the host-mediated assay (Cantelli-Forti and Bronzetti 1988; Cema and Kypenova 1977; Galli et al. 1982; Greim et al. 1975; Sawada et al. 1987). Furthermore, a 60-day oral study of trans-1,2-dichloroethene in rats, which was available in abstract form, indicated a high incidence of lymphosarcoma in the lungs (see Section 2.10.3). Although this study has not yet been published, it raises a concern about the carcinogenicity of 1,2-dichloroethene, which should be further investigated in long-term oral and inhalation studies of both isomers. In humans, dermal exposure is less likely than oral or inhalation exposure; however, dermal studies could add valuable insights about 1 ,2dichloroethene toxicity.

Genotoxicity. No study was located regarding 1,2-dichloroethene genotoxicity in humans. Neither isomer of 1,2-dichloroethene was mutagenic in in vitro experiments with *E. coli, S. typhimurium*, and S. cerevisiae (Cantelli-Forti and Bronzetti 1988; Cema and Kypenova 1977; Galli et al. 1982; Greim et al. 1975). Neither isomer produced chromosomal aberrations or sister chromatid exchanges in Chinese hamster cells (Sawada et al. 1987). Reductions in numbers of convertants and revertants (positive results) were obtained with the cis isomer, but not the trans isomer, in host-mediated assays in mice (Cantelli-Forti and Bronzetti 1988). Furthermore, repeated intraperitoneal injections of the cis isomer induced chromosomal aberrations in mouse bone marrow cells (Cema and Kypenova 1977); thus, cis-1,2-dichloroethene may be a potential mutagen in animals. The weight of evidence ef genotoxicity is still small; additional studies would help to confirm the existing information or uncover unknown genetic effects. Chronic animal studies might elucidate the potential for, or isomeric differences in, cancer development. If an appropriate group of exposed workers could be identified, cytogenetic testing might help determine 1 ,2dichloroethene's genotoxic potential in humans.

2. HEALTH EFFECTS

Reproductive Toxicity. No studies were located regarding reproductive toxicity of 1,2-dichloroethene in humans by inhalation, oral, or dermal exposure. No studies were located regarding reproductive toxicity of 1,2-dichloroethene in animals following dermal exposure. An inhalation study published in 1993 (Hurtt et al. 1993) is the sole report to address the reproductive effects of 1,2-dichloroethene. In this study, maternal weight gain was reduced, proportional to dose, and possible increases in resorption were reported. In other studies, histopathological examination of the reproductive organs of animals exposed orally for 90 days to 1,2-dichloroethene has not shown effects on reproductive organs (Hayes et al. 1987; McCauley et al. 1990). Further investigation of reproductive effects, including results of dermal exposure, are necessary for understanding possible effects suggested by the existing evidence on the reproductive system.

Developmental Toxicity. No studies were located regarding developmental effects in humans after inhalation, oral, or dermal exposure to cis- or trans-1,2-dichloroethene. No data are available on developmental effects in animals after oral or dermal exposure to 1,2-dichloroethene. Fetal weights appear to be reduced after exposure to 1,2-dichloroethene, as shown in an inhalation study (Hurtt et al. 1993). During critical developmental stages (days 7-16 in rats), trans-1,2-dichloroethene exposure was associated with reduced weight gain in rat pups at a level of 12,000 ppm. Additional developmental toxicity studies in animals by inhalation, oral, and dermal exposure may provide relevant information for humans exposed near hazardous waste sites.

Immunotoxicity. No information about 1,2-dichloroethene toxicity to the human immune system was located. Findings of fatty degeneration of Kupffer cells, decreased numbers of white blood cells, and pneumonic infiltration in rats after inhalation exposure to trans-1,2-dichloroethene (Freundt et al. 1977), and of suppressed humoral immune status in male mice exposed to trans.-1,2-dichloroethene in drinking water for 90 days, as measured by mouse spleen cell antibody production (Shopp et al. 1985), suggest that 1,2-dichloroethene may be immunotoxic. Immunological studies of cis- 1 ,2dichloroethene and additional studies of trans-1,2-dichloroethene would help determine more definitely the immunotoxic potential and possible differences between the isomers. No immunotoxicity-data in animals were located for the dermal route of exposure. New dermal studies would be valuable, both because no such studies have been reported and because of the potential immuno-dermal effects of dermal exposure.

2. HEALTH EFFECTS

Neurotoxicity. Symptoms of central nervous system depression (vertigo, drowsiness, intracranial pressure, nausea) were observed in two human volunteers during a 30-minute inhalation exposure to 1,2-dichloroethene. The symptoms disappeared after discontinuation of exposure (Lehmann and Schmidt-Kehl 1936). No information was located regarding neurotoxicity after exposure by other routes of exposure in humans. In animals, inhalation exposure to 1,2dichloroethene was associated with behavioral changes, narcosis, and lethargy at levels ranging from 1,700 to 12,000 ppm (De Caurriz et al. 1983; Hurtt et al. 1993). Similarly, symptoms of central nervous system depression were observed in rodents after acute oral exposure to 1,2-dichloroethene (Barnes et al. 1985; Hayes et al. 1987; McCauley et al. 1990; Munson et al. 1982). The observations were restricted to behavioral tests. Further information regarding 1 ,2dichloroethene neurotoxicity in animals after exposure by inhalation, oral, and dermal routes would be valuable. Animal studies of the effects of 1,2-dichloroethene on the morphology of neurons, glial and myelinated cells, and on the synthesis and degradation of neurotransmitters would permit more accurate assessment of neurotoxic potential of this chemical.

Epidemiological and Human Dosimetry Studies. No epidemiologic studies of populations exposed to 1,2-dichloroethene were located. The general population might be exposed to low levels of 1,2-dichloroethene in contaminated urban air or in contaminated drinking water, or possibly by dermal contact. The occupationally exposed population is relatively small (285 individuals) (NIOSH 1988). The confounding exposure to other related compounds makes it difficult to perform an epidemiological study for 1,2-dichloroethene. Animal studies suggest that hematological, hepatic, neurological and reproductive effects would be the end points of concern (Barnes et al. 1985; Freundt et al. 1977; Hurtt et al. 1993; McCauley et al. 1990; McMillan 1986). Therefore, if a worker or a population with appropriate exposure can be identified, epidemiological studies could be designed to study the possibility that similar effects may be observed in humans. Studies that correlate exposure with blood or urine levels of biomarkers and/or with effects would be useful in establishing causality. The knowledge of a dose-effect relationship would be useful for monitoring individuals near hazardous waste sites for preventive purposes.

Biomarkers of Exposure and Effect.

Exposure. Methods exist for determining 1,2-dichloroethene in blood and biological tissues (Ashley et al. 1992; Hara et al. 1980; Lin et al. 1982; Raymer et al. 1990; Streete et al. 1992; Uehori et al. 1987), but specific levels of 1,2-dichloroethene have not been correlated with exposure. Exhalation of

acetone and the presence of acetone in blood have been noted in rats after inhalation exposure to cis and trans-1,2-dichloroethene, but the amounts exhaled or the levels in blood have not been correlated with exposure levels (Freundt et al. 1977). Furthermore, acetonemia is not specific for 1,2-dichloroethene; increased acetone levels were found after exposure to other chemicals (e.g., vinyl chloride and perchlorethylene) and in patients with diseases such as diabetes (Filser and Bolt 1980). Studies focusing on correlating blood or urine levels of 1,2-dichloroethene or its metabolites with exposure levels would be useful to facilitate future medical surveillance that can lead to early detection.

Effect. No known biomarkers are currently used to characterize effects caused by 1,2-dichloroethene. Rats exposed by inhalation to halogenated ethylenes, including cis- and trans-1,2-dichloroethene, were shown to exhale acetone (Filser et al. 1978, 1980; Freundt et al. 1977). Based on these studies, a possible mechanism for the production of acetone was suggested, whereby a metabolite (dichloroacetate for 1,2-dichloroethene) inhibits the enzymes of the citric acid cycle, which would lead to an increase in mitochondrial acetyl-coenzyme A and, consequently, to an alteration in lipid and fatty acid metabolism to form ketone bodies (Filser et al. 1982). Further studies that support this hypothesis might determine whether acetone exhalation could serve as a biomarker for such effects as fatty degeneration of the liver, which was observed in rats exposed by inhalation to trans-1,2-dichloroethene (Freundt et al. 1977).

Absorption, Distribution, Metabolism, and Excretion. The absorption, distribution, metabolism and excretion of a chemical can influence its toxicity. Several inhalation studies have examined the absorption of l,2dichloroethene, and they indicate that 1,2-dichloroethene vapors can be absorbed through the lung (Filser and Bolt 1979; Gargas et al. 1988, 1989; Lehmann and Schmidt-Kehl 1936). Studies by Gargas et al. (1988, 1989) and Sato and Nakajima (1979) determined 1,2-dichloroethene partition coefficients between a number of body tissues and show differences between the cis and trans isomers. The cis isomer has higher partition coefficients (tissue:air) and, therefore, greater affinity or absorption in biological tissue. These are important properties that influence toxicological effects. Absorption by the dermal route has not been investigated, although the lipophilic properties of this chemical make it likely. According to an ongoing study, trans-1,2-dichloroethene was quickly absorbed from the gastrointestinal tract of rats after oral exposure (see Section 2.10.3). No other studies on the absorption of 1,2-dichloroethene following oral exposure were located. The few oral toxicity studies support this conclusion (McCauley et al. 1990; McMillan

1986). No studies were located regarding the distribution and excretion of 1,2dichloroethene after inhalation, oral, or dermal exposure.

Cytochrome P-450 has been implicated in the initial step of metabolism of 1,2-dichloroethene in the liver. Subsequent steps are believed to be catalyzed by cytosolic and/or mitochondrial aldehyde and alcohol dehydrogenases or related enzymes (Costa and Ivanetich 1982, 1984). Differences in the metabolism rate and the metabolite profile have been reported for the cis and trans isomers, for example, the cis isomer had a 4-fold greater turnover rate in hepatic microsomes *in vitro* than the trans isomer (Bonse et al. 1975; Costa and Ivanetich 1982, 1984). The metabolism of 1,2-dichloroethene has not been extensively studied in tissues other than the liver. Distribution studies of cis- and trans-1,2-dichloroethene and metabolites would help identify those tissues, if any, that accumulate them. Excretion studies of 1,2-dichloroethene and its breakdown products would be useful for understanding the metabolic fate of this chemical and determining major routes and rates of excretion. One important question to be addressed is the difference in metabolism and excretion at low and high exposure levels.

Comparative Toxicokinetics. Although there are relatively few existing studies for comparative purposes, some general conclusions can be drawn. The human exposure studies consist of two inhalation studies from the 1930s, one of which is too sketchy to use in making any comparisons (Hamilton 1934; Lehmann and Schmidt-Kehl 1936). When two volunteers were exposed for 30 minutes to an unknown ratio of cis:trans 1,2-dichloroethene (Lehmann and Schmidt-Kehl 1936), their neurological responses were consistent with animal studies that show lethargy and drowsiness. No human toxicokinetic or dosimetry data were located. Among the animal species there is general consistency for both inhalation and oral exposure routes in the end points identified. Hepatic, hematological, and neurological end points are found in both rats and mice (Barnes et al. 1985; De Ceaurriz et al. 1983; McCauley et al. 1990; McMillan 1986). Investigation of 1,2-dichloroethene toxicokinetics in different animal species and comparison of detected metabolites with those detected in occupationally exposed individuals would be useful for determining an appropriate animal model for studying the toxicokinetics of 1,2-dichloroethene.

Methods for Reducing Toxic Effects. General recommendations for reducing the absorption and metabolic responses to 1,2-dichloroethene are based on limited mitigation studies and reports found in the primary and review/consensus literature. Few individuals have received intense exposure

to 1 ,2-dichloroethene, whether accidental, clinical or occupational. Its neurological, hepatic, hematic, and respiratory effects are similar to those of other solvents, and therefore, generalized interventions have been drawn from experience with these other solvents. Supportive measures to combat the effects of central nervous system, respiratory depression, and cardiac irritability are the clinical recommendations (TOMES 1994). There is no specific treatment for 1 ,2dichloroethene exposure, partly because its mechanisms of action are not well defined and the numbers of exposed individuals needing treatment are small.

2.10.3 Ongoing Studies

Several abstracts of studies in progress were located. A high incidence of lymphosarcoma in the lungs and histopathological lesions in the spleen and kidneys was reported in rats after 60 days of oral treatment with l/2, l/20, and l/200 of the reported LD_{50} for trans-1 ,2dichloroethene (Witmer et al. 1990). Absorption of trans-1,2-dichloroethene has been studied in rats after intravenous and oral applications (Manning et al. 1990). In these studies, trans-1,2-dichloroethene was quickly absorbed from the gastrointestinal tract reaching peak blood concentrations in 2-6 minutes after exposure.