3. HEALTH EFFECTS

3.1 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 on the toxicology of 1,1-dichloroethane. 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.

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

3.2 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 Levels of Significant Exposure (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 (LOAELs) 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.

3.2.1 Inhalation Exposure

Very little information is available regarding the health effects of 1,1-dichloroethane following inhalation exposure in humans or animals. 1,1-Dichloroethane was used in the past as an anesthetic at a pressure of 0.026 atm, which is approximately equivalent to a concentration of 105,000 mg/m^3 (26,000 ppm) (Miller et al. 1965). This use was discontinued when it was discovered that this compound induced cardiac arrhythmias at anesthetic doses (Reid and Muianga 2012).

Table 3-1 and Figure 3-1 describe the health effects observed in laboratory animals associated with inhalation exposure levels at varying time and exposure durations.

3.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to 1,1-dichloroethane. In a review paper, Smyth (1956) reported that no deaths were observed in rats exposed to 4,000 ppm for 8 hours, but an 8-hour exposure to 16,000 ppm was lethal. It has been reported in the early literature that the lethal exposure level of 1,1-dichloroethane in mice was 17,500 ppm (Reid and Muianga 2012). These values were reported in a secondary source and it is therefore impossible to assess their validity. Subchronic intermittent exposure to 500 ppm of 1,1-dichloroethane for 13 weeks followed by 1,000 ppm of 1,1-dichloroethane for an additional 13 weeks was not lethal to rats, rabbits, guinea pigs, or cats (Hofmann et al. 1971).

The highest NOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding respiratory, gastrointestinal, hematological, musculoskeletal, or dermal/ocular effects in humans or animals following inhalation exposure to 1,1-dichloroethane.

Cardiovascular Effects. A cardiostimulatory effect resulting in arrhythmias prompted the discontinuance of the use of 1,1-dichloroethane as an anesthetic in humans (Reid and Muianga 2012). This effect was noted at the relatively high dose used to induce anesthesia (0.026 atm, which is approximately equivalent to 105,000 mg/m^3, or 26,000 ppm) (Miller et al. 1965). No studies were located regarding cardiovascular effects in animals following inhalation exposure to 1,1-dichloroethane.

Hepatic Effects. No studies were located regarding hepatic effects in humans following inhalation exposure to 1,1-dichloroethane. Rats, rabbits, guinea pigs, and cats experienced no change in serum alanine aminotransferase or aspartate aminotransferase activity after intermittent 6-hour inhalation exposure to 500 ppm 1,1-dichloroethane for 13 weeks followed by 13 weeks of exposure 6 hours/day to 1,000 ppm 1,1-dichloroethane (Hofmann et al. 1971). Furthermore, no treatment-related histopathological lesions were noted in the livers of these animals after this 26-week exposure regimen. Six days after termination of a 10-day exposure to 6,000 ppm 1,1-dichloroethane (7 hours/day), a slight but statistically significant increase in relative liver weight (26% higher than controls) was observed in female Sprague-Dawley rats (Schwetz et al. 1974). However, there was no increase in aspartate aminotransferase activity over control values, and no changes in the gross appearance of the liver were noted at necropsy in these animals; the slight increase in liver weight was not considered adverse.

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to 1,1-dichloroethane. Renal injury was apparent in cats intermittently exposed 6 hours/day to 1,000 ppm 1,1-dichloroethane for 13 weeks following 13 weeks of intermittent exposure to 500 ppm 1,1-dichloroethane (Hofmann et al. 1971). Serum urea and creatinine were increased in these animals. One cat was so severely affected that it had to be removed from the study. Histopathological lesions in the kidney tubules (including crystalline precipitates and dilation) were noted in three of four cats at necropsy; renal tubular degenerations without preliminary lumen displacement and periglomerular fibrosis and tubule destruction were also observed. The ill health of these animals was also manifest by a progressive decrease in body weight. Rats, rabbits, and guinea pigs similarly exposed to 1,1-dichloroethane exhibited no adverse effects.

Table 3-1 Levels of Significant Exposure to 1,1-Dichloroethane - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Rat (Sprague-Dawley)	7 hr/d 10 d	Hepatic	6000 F			Schwetz et al. 1974	
Developmental								
2	Rat (Sprague-Dawley)	7 hr/d Gd 6-15		3000 F	6800 F (Increased incidence of delayed ossification)		Schwetz et al. 1974	
INTERMEDIATE EXPOSURE								
Systemic								
3	Rat (Sprague-Dawley)	6 hr/d 5 d/wk 26 wk	Hepatic	750			Hofmann et al. 1971 1,1-DCE	
			Renal	750				
			Bd Wt	750				
4	Gn Pig (Firbright-White)	6 hr/d 5 d/wk 26 wk	Hepatic	750			Hofmann et al. 1971 1,1-DCE	
			Renal	750				
			Bd Wt	750				
5	Rabbit (Brunte)	6 hr/d 5 d/wk 26 wk	Hepatic	750			Hofmann et al. 1971 1,1-DCE	
			Renal	750				
			Bd Wt	750				

Table 3-1 Levels of Significant Exposure to 1,1-Dichloroethane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
6	Cat (NS)	6 hr/d 5 d/wk 26 wk	Hepatic	750			Hofmann et al. 1971 1,1-DCE	
			Renal		750 (crystal precipitation and obstruction in tubule lumina)			
			Bd Wt	750				

a The number corresponds to entries in Figure 3-1.

Bd Wt = body weight; d = day(s); F = Female; Gd = gestational day; Gn pig = guinea pig; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; wk = week(s)

Figure 3-1 Levels of Significant Exposure to 1,1-Dichloroethane - Inhalation

Acute (≤14 days)

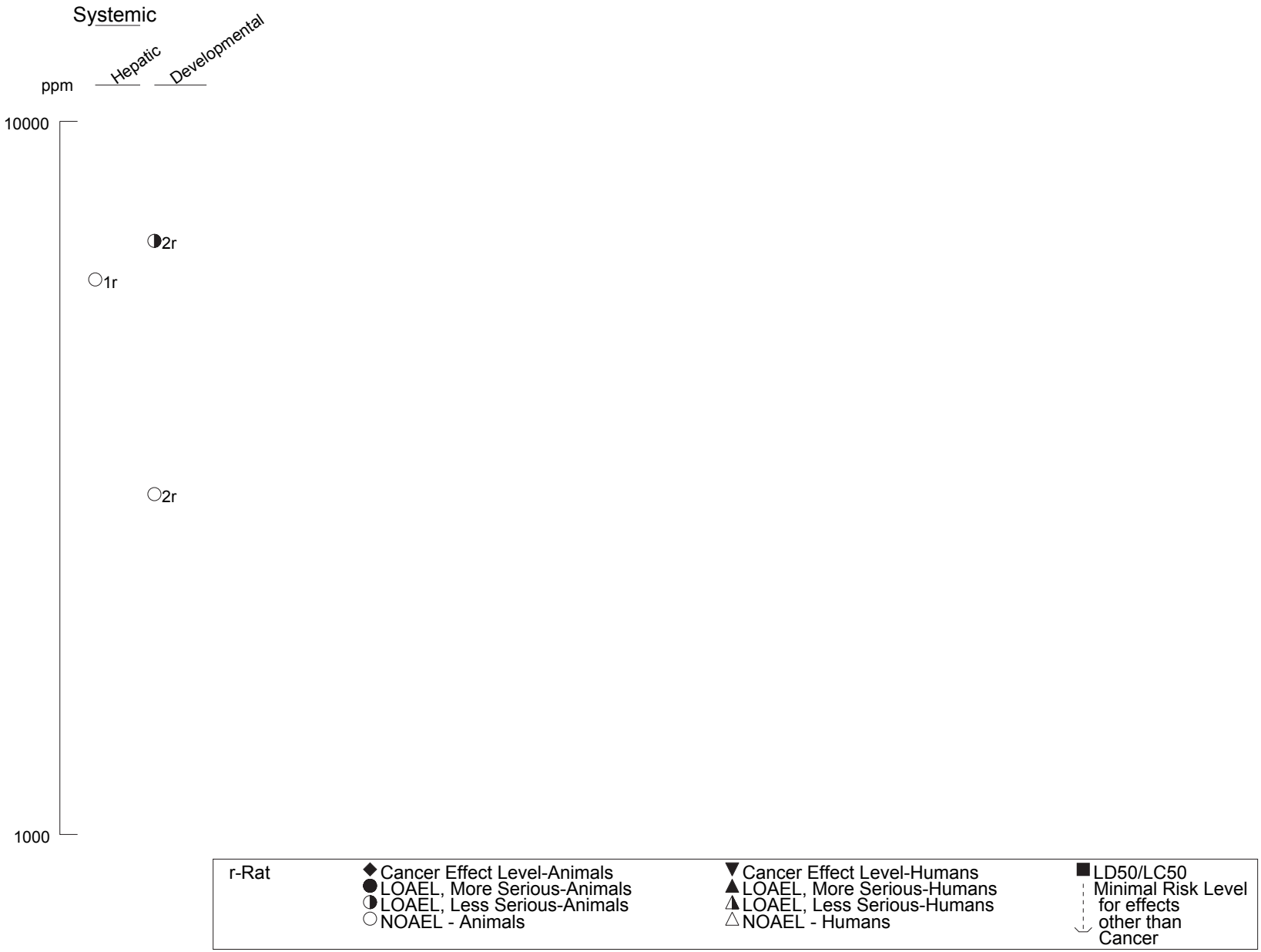
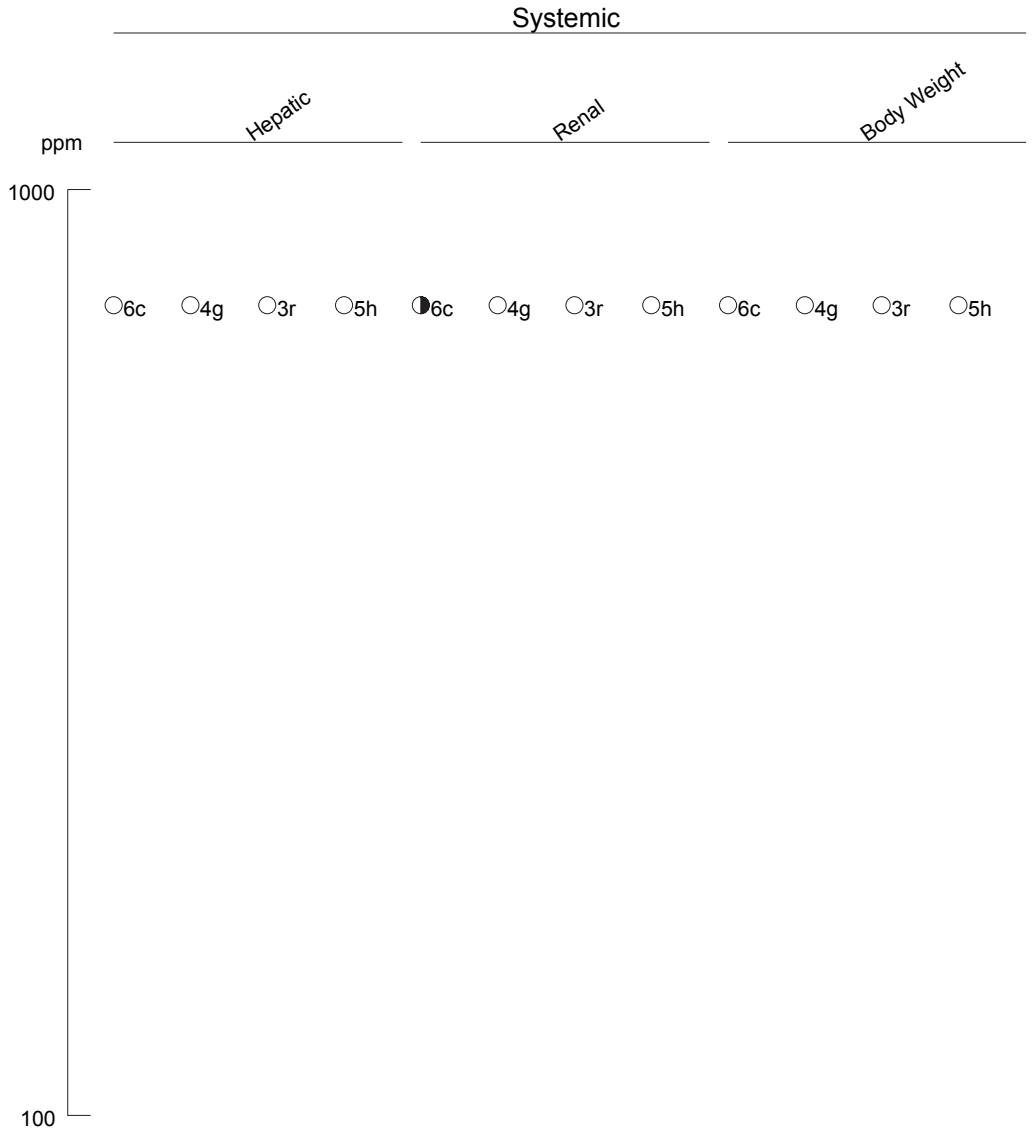


Figure 3-1 Levels of Significant Exposure to 1,1-Dichloroethane - Inhalation *(Continued)*

Intermediate (15-364 days)



c-Cat
r-Rat
h-Rabbit
g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to 1,1-dichloroethane.

3.2.1.4 Neurological Effects

Since 1,1-dichloroethane was once used as a gaseous anesthetic, it can be inferred that it causes central nervous system depression upon acute exposure. No information is available on the long-term neurologic effects of inhaled 1,1-dichloroethane in humans.

No studies were located regarding neurologic effects in animals after inhalation exposure to 1,1-dichloroethane.

3.2.1.5 Reproductive Effects

No studies were located regarding developmental effects in humans or animals following inhalation exposure to 1,1-dichloroethane.

3.2.1.6 Developmental Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to 1,1-dichloroethane.

One study examined the developmental toxic potential of 1,1-dichloroethane following inhalation exposure. No alterations in litter size, fetal resorptions, fetal growth, or incidences of gross or soft tissue anomalies were observed in the offspring of Sprague-Dawley rats exposed to 3,800 or 6,000 ppm 7 hours/day on gestation days 6–15 (Schwetz et al. 1974). A significant increase in the incidence of fetuses with delayed ossification of sternebrae was observed at 6,000 ppm. Maternal food consumption and body weight were significantly reduced in the treated animals during the exposure period but returned to normal by day 21 of gestation; on gestation day 3, dams in the 3,800 and 6,000 ppm groups weighed 8 and 11% less than controls, respectively. No other adverse effects were noted in the dams. Based on the observed effects, the LOAEL value for the developmental toxicity of 1,1-dichloroethane in rats was 6,000 ppm; the NOAEL was 3,800 ppm. These values are listed in Table 3-1 and plotted in Figure 3-1.

3.2.1.7 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to 1,1-dichloroethane.

3.2.2 Oral Exposure

Two studies were located that investigated the health effects associated with oral exposure to 1,1-dichloroethane in rats and mice (Klaunig et al. 1986; NCI 1977). With the exception of body weight depression observed in one subchronic range-finding study, neither one provided any conclusive evidence of adverse toxic effects associated with oral exposure to 1,1-dichloroethane.

Table 3-2 and Figure 3-2 describe the health effects observed in laboratory animals associated with oral exposure levels at varying time and exposure durations. No MRLs to humans for adverse effects (other than cancer) were calculated for the oral route of exposure because of the limited database.

3.2.2.1 Death

No studies were located regarding death in humans following oral exposure to 1,1-dichloroethane.

Secondary sources report the following oral LD_{50} values in rats: 725 mg/kg (Lewis 2004) and 14.1 g/kg (Archer 1978). Since these values were obtained from secondary sources, no details were available to assess the quality of these data. Survival was poor in both treated and control rats and mice in the chronic bioassay conducted by the National Cancer Institute (NCI 1977), but a significant dose-related trend for mortality was noted in the male rats and mice. The deaths could not be attributed to cancer or any other non-neoplastic lesions, although pneumonia was observed in a large percentage of the rats, and this was thought to be related to the increased mortality (NCI 1977).

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Table 3-2 Levels of Significant Exposure to 1,1-Dichloroethane - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Death								
1	Rat (Osborne-Mendel)	5 d/wk 6 wk (GO)				3160 F (2/5 rats died)	NCI 1977 1,1-DCE	
2	Mouse (B6C3F1)	5 d/wk 6 wk (GO)				5620 (4/10 deaths)	NCI 1977 1,1-DCE	
Systemic								
3	Rat (Osborne-Mendel)	5 d/wk 6 wk (GO)	Bd Wt		562 M (16% decreased body weight gain)	1000 M (29% decreased body weight gain)	NCI 1977 1,1-DCE	
4	Mouse (B6C3F1)	daily 52 wk (W)	Resp	465 M			Klaunig et al. 1986 1,1-DCE	
			Hepatic	465 M				
			Renal	465 M				
			Bd Wt	465 M				
5	Mouse (B6C3F1)	5 d/wk 6 wk (GO)	Bd Wt	2885 M			NCI 1977 1,1-DCE	

Table 3-2 Levels of Significant Exposure to 1,1-Dichloroethane - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
6	Rat (Osborne-Mendel)	5 d/wk 78 wk (GO)	Resp	764 M			NCI 1977 1,1-DCE	
			Cardio	764 M				
			Hemato	764 M				
			Musc/skel	764 M				
			Hepatic	764 M				
			Renal	764 M				
			Endocr	764 M				
			Dermal	764 M				
			Bd Wt	764 M				
7	Mouse (B6C3F1)	5 d/wk 78 wk (GO)	Resp	2885 M			NCI 1977 1,1-DCE	
			Cardio	2885 M				
			Gastro	2885 M				
			Musc/skel	2885 M				
			Hepatic	2885 M				
			Renal	2885 M				
			Endocr	2885 M				
			Dermal	2885 M				
			Bd Wt	2885 M				

a The number corresponds to entries in Figure 3-2.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; (GO) = gavage in oil; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; (W) = drinking water; wk = week(s)

Figure 3-2 Levels of Significant Exposure to 1,1-Dichloroethane - Oral

Intermediate (15-364 days)

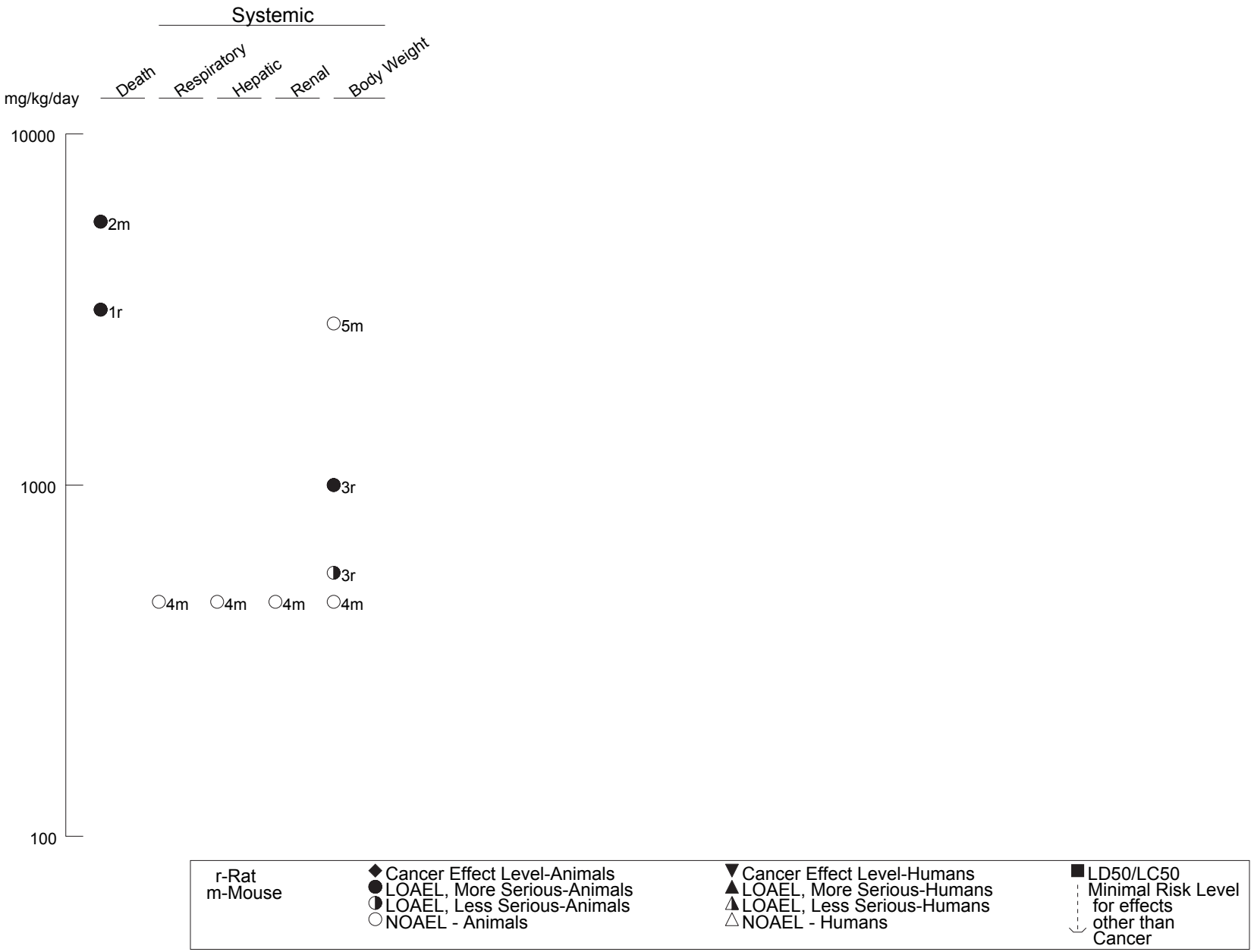
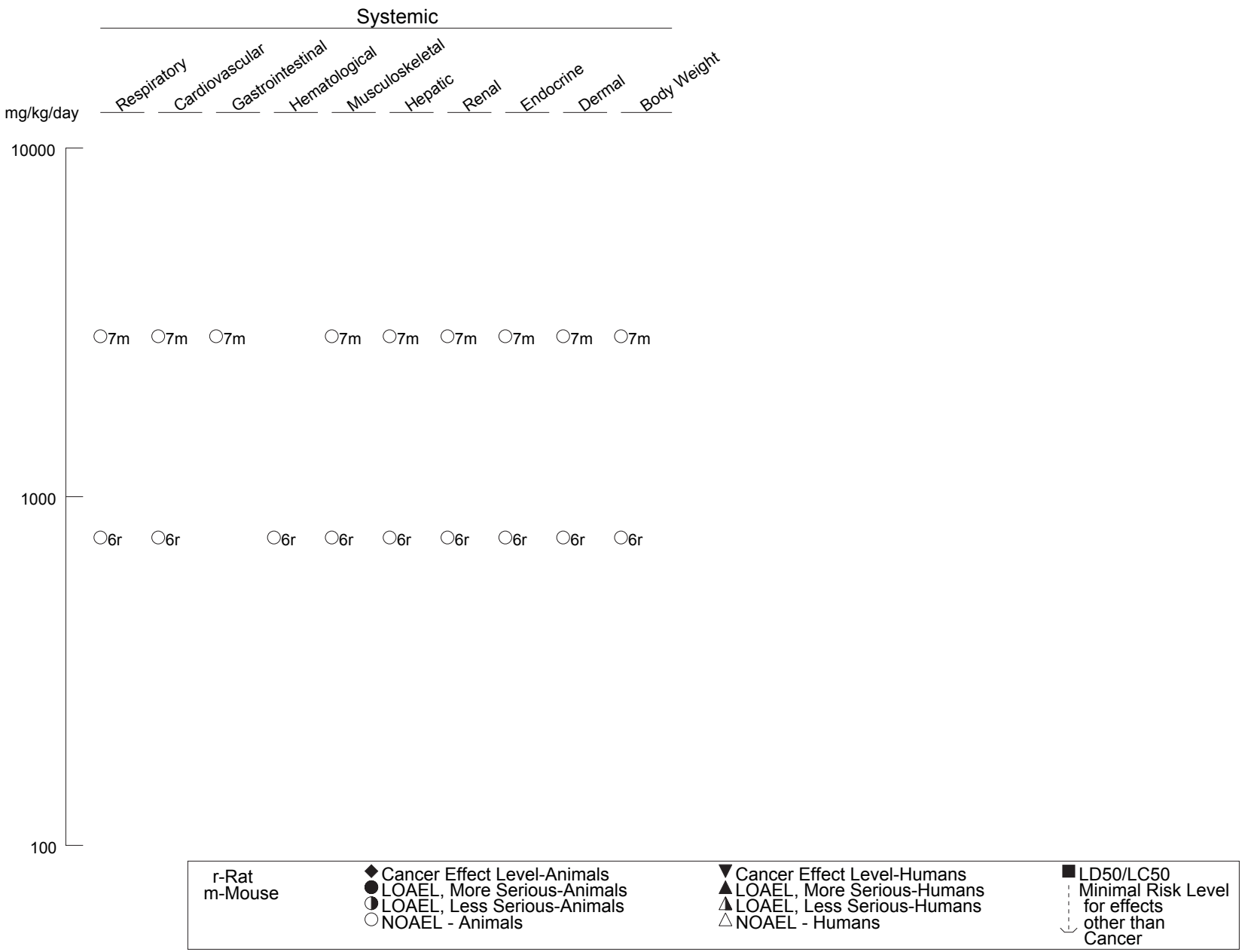


Figure 3-2 Levels of Significant Exposure to 1,1-Dichloroethane - Oral *(Continued)*

Chronic (≥365 days)



3.2.2.2 Systemic Effects

No studies were located regarding systemic effects in humans following oral exposure to 1,1-dichloroethane.

There were no treatment-related histopathological changes in the liver, kidneys, or other tissues of the rats examined in the NCI (1977) study. Similarly, no histopathological alterations were noted in the liver, kidneys, or lungs of male mice that ingested relatively high levels of 1,1-dichloroethane in drinking water (up to 2500 mg/L) for 52 weeks (Klaunig et al. 1986).

Respiratory Effects. No histological alterations were observed in the lungs of mice exposed to 465 mg/kg/day 1,1-dichloroethane in drinking water for 52 weeks (Klaunig et al. 1986). Similarly, no significant alterations in respiratory tract lesions were observed in rats or mice chronically exposed to 1,1-dichloroethane for 78 weeks (NCI 1977). The highest gavage doses were 764 and 950 mg/kg/day (5 days/week) in male and female rats, respectively, and 2,885 and 3,331 mg/kg (5 days/week) in male and female mice, respectively.

Cardiovascular Effects. The NCI (1977) chronic-duration gavage study did not find significant alterations in the incidence of lesions in the cardiovascular system.

Gastrointestinal Effects. No gastrointestinal effects were reported in rats or mice administered gavage doses of 1,1-dichloroethane for 78 weeks (NCI 1977).

Hematological Effects. No histological alterations were observed in hematological tissues in rats or mice chronically exposed to 1,1-dichloroethane (NCI 1977); however, the study did not examine the potential for alterations in erythrocyte or leukocyte counts or hemoglobin levels.

Musculoskeletal Effects. No musculoskeletal alterations were reported in the NCI (1977) chronic study of rats and mice.

Hepatic Effects. No nonneoplastic alterations were observed in mice exposed to 465 mg/kg/day via drinking water for 52 weeks (Klaunig et al. 1986) or in rats or mice administered 764/950 mg/kg/day or

2,885/3,331 mg/kg/day 1,1-dichloroethane, respectively, via gavage 5 days/week for 78 weeks (NCI 1977).

Renal Effects. Intermediate-duration drinking exposure of mice (Klaunig et al. 1986) or chronic gavage administration to rats and mice (NCI 1977) did not result in significant alteration in the occurrence of renal lesions.

Endocrine Effects. No histological alterations in endocrine tissues were observed in rats or mice chronically administered 1,1-dichloroethane (NCI 1977).

Dermal Effects. No dermal effects were noted in rats or mice administered 1,1-dichloroethane for 78 weeks (NCI 1977).

Ocular Effects. No eye damage was noted in rats or mice following chronic administration of 1,1-dichloroethane (NCI 1977).

Body Weight Effects. Administration of doses as high as 562 mg/kg/day in male rats and 1,780 mg/kg/day in female rats 5 days/week for 6 weeks resulted in decreases in body weight gain (≥16%) (NCI 1977); no alterations in body weight were observed in mice similarly exposed to doses as high as 10,000 mg/kg/day (NCI 1977). This study did not find significant decreases in body weight gain following 78 weeks of exposure (5 days/week) to 764 and 950 mg/kg/day, respectively, in male and female rats and 2,885 and 3,331 mg/kg/day, respectively, in male and female mice (NCI 1977). Similarly, no alterations in body weight gain were observed in mice exposed to 465 mg/kg/day in drinking water for 52 weeks (Klaunig et al. 1986).

No studies were located regarding the following health effects in humans or animals following oral exposure to 1,1-dichloroethane:

3.2.2.3 Immunological and Lymphoreticular Effects
3.2.2.4 Neurological Effects
3.2.2.5 Reproductive Effects
3.2.2.6 Developmental Effects

3.2.2.7 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to 1,1-dichloroethane. The results of the bioassay conducted by NCI (1977) suggest carcinogenic effects induced by 1,1-dichloroethane in rats and mice. A significant positive dose-related trend was observed for the incidence of hemangiosarcomas and mammary adenocarcinomas in female rats, hepatocellular carcinoma in male mice, and endometrial stromal polyps in female mice. However, only the incidence of endometrial stromal polyps in female mice exposed to 3,331 mg/kg/day, 5 days/week was significantly increased over the corresponding control animals. When only male mice surviving at least 52 weeks were examined, there was a significant increase in the incidence of hepatocellular carcinomas in the 2,885 mg/kg/day group. There are several limitations to this study. Survival was poor in both treated and control animals, thereby limiting the validity of these results. Although survival was significantly lower in the exposed groups, it is not clear that the increase in mortality was treatment-related. Furthermore, there were no other treatment-related effects on body weight, clinical signs, or the incidence of non-neoplastic lesions. Because of the high mortality in both the treated and control animals, the authors concluded that not enough animals survived to be at risk for late-developing tumors. Thus, though the results of this bioassay suggest that 1,1-dichloroethane is carcinogenic to rats and mice, the evidence is not conclusive.

The carcinogenicity of 1,1-dichloroethane was also examined in mice exposed to 155 or 465 mg/kg/day of the compound in the drinking water for 52 weeks (Klaunig et al. 1986). A two-stage carcinogenesis protocol was also employed in this study to assess the ability of 1,1-dichloroethane to act as a tumor promoter. Neither 1,1-dichloroethane-treated animals initiated with diethylnitrosamine (DENA) or animals treated with 1,1-dichloroethane without initiation showed a significant increase in the incidence of lung or liver tumors over their corresponding controls. However, the conclusion that 1,1-dichloroethane is not a tumor promoter may not be entirely justified since a maximal response was observed in terms of tumor incidence in the DENA-alone-treated mice (100% tumor incidence at 52 weeks). Therefore, an increase in the incidence of liver tumors due to 1,1-dichloroethane following DENA initiation, if it existed, could not have been detected. Furthermore, since measurement of water consumption and replenishment were only done once a week, there was no way to determine the extent, if any, evaporation contributed to loss of the test chemical and affected the reported level of exposure. However, precautions were taken to minimize the loss of test chemical during the 1-week period; amber bottles with Teflon stoppers and double sipper tubes were used. Since 1,1-dichloroethane is a volatile

chemical, this may present a limitation to the interpretation of results obtained from drinking water administration.

The difference in results (e.g., induction of liver tumors) between the NCI (1977) and Klaunig et al. (1986) studies may be due to the method of administration, vehicle, and/or doses used. The pharmacokinetics of 1,1-dichloroethane may vary considerably when administered in drinking water *ad libitum* over a week as compared to bolus doses given in corn oil. Evidence obtained with carbon tetrachloride indicates that corn oil likely acts as a reservoir in the gut to delay and diminish the systemic absorption of the lipophilic chemical, while such a chemical is probably rapidly absorbed when ingested in water (Kim et al. 1990a, 1990b). Furthermore, the doses given to mice by gavage were approximately 6 times higher than the drinking water concentrations. Sufficient information is not available to assess the contributions of these factors to the apparently disparate responses.

Milman et al. (1988) examined the carcinogenic potential of 1,1-dichloroethane in initiation and promotion assays. In partially hepatectomized Osborne-Mendel rats receiving a single gavage dose of 700 mg/kg 1,1-dichloroethane in corn oil followed by dietary exposure to phenobarbitol for 7 weeks, there were no alterations in gamma-glutamyltranspeptidase (GGT)-altered foci. However, in the promotion assay in which partially hepatecomized Osborne-Mendel rats received an intraperitoneal dose of diethylnitrosamine followed by gavage administration of 700 mg/kg 1,1-dichloroethane in corn oil 5 days/week for 7 weeks, there was an increase in the total number of GGT-altered foci.

3.2.3 Dermal Exposure

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

3.2.3.1 Death
3.2.3.2 Systemic Effects
3.2.3.3 Immunological and Lymphoreticular Effects
3.2.3.4 Neurological Effects
3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects
3.2.3.7 Cancer

Table 3-3. Genotoxicity of 1,1-Dichloroethane *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimuriu,m strains TA97, TA98, TA100, and TA102 (Ames assay)	Gene mutation	–	–	Nohmi et al. 1986
S. typhimurium, strains TA1535, TA1537, TA1538, TA98, and TA100 (Ames assay)	Gene mutation	–	–	Simmon et al. 1977
S. typhimurium, strains TA1537, TA98, TA100, and TA1535 (dessicator assay; vapor exposure)	Gene mutation	+	+	Riccio et al. 1983
S. typhimurium, strains TA1535, TA98, and TA100 (Ames assay; dessicator)	Gene mutation	+	+	Milman et al. 1988
Eukaryotic organisms:				
Saccharomyces cerevisiae D7	Gene mutation	–	–	Bronzetti et al. 1987
Mammalian cells				
Syrian hamster embryo (cell transformation assay; vapor exposure)	DNA viral transformation	No data	+	Hatch et al. 1983
Osborne-Mendel rat and B6C3F1 mouse hepatocytes	DNA repair	No data	+	Milman et al. 1988
BALB/C-3T3 (cell transformation assay; exposure in sealed chamber)	Cell transformation	No data	–	Tu et al. 1985
BALB/C-3T3 (cell transformation assay; exposure in sealed chamber)	Cell transformation	No data	–	Milman et al. 1998
Chinese hamster lung fibroblasts (chromosomal aberration assay; exposure in sealed chamber)	Chromosomal aberrations	–	–	Matsuoka et al. 1998)

— = negative result; + = positive result; ± = weakly positive

3.3 GENOTOXICITY

A limited number of studies have examined the genotoxicity of 1,1-dichloroethane. No studies were located regarding *in vivo* genotoxic effects in humans. The genotoxic potential of 1,1-dichloroethane has been investigated *in vitro* in bacteria, fungus, and mammalian systems; the results of these studies are summarized in Table 3-3. 1,1-Dichloroethane did not result in an increase in reverse mutations in *Salmonella typhimurium* strains with or without metabolic activation in Ames assays (Nohmi et al. 1985; Simmon et al. 1977). In contrast, Riccio et al. (1983, as reported in an abstract) and Milman et al. (1988) reported positive mutagenic alterations in *S. typhimurium* exposed to 1,1-dichloroethane vapor in a desiccator assay in the presence and absence of S9 mix. Negative findings for mutagenicity were observed in *Saccharomyes cerevisiae* exposed to 1,1-dichloroethane, with or without metabolic activation (Bronzetti et al. 1987).

Similarly, negative genotoxicity results have been observed in mammalian cell assays. *In vitro* exposure to 1,1-dichloroethane did not induce increases in cell transformations in BALB/C-3T3 cells (Milman et al. 1988; Tu et al. 1985) or chromosomal aberrations in Chinese hamster lung fibroblasts (Matsuoka et al. 1998). However, an increase in Simian adenovirus (SA7)-induced transformations was observed in Syrian hamster embryo cells (Hatch et al. 1983) and an increase in DNA repair was found in hepatocytes from Osborne-Mendel rats and B6C3F1 mice (Milman et al. 1988).

In an *in vivo* study by Colacci et al. (1985), 1,1-dichloroethane (98% purity) was found covalently bound to nucleic acids and proteins from liver, lung, kidney, and stomach of male rats and mice 22 hours following a single intraperitoneal injection of approximately 1.2 mg/kg. *In vitro* binding of 1,1-dichloroethane to nucleic acids and proteins was mediated by liver P-450 dependent microsomal mixed function oxidase system. Glutathione-S-transferase (GSH) shifted the equilibrium of the enzymatic reaction and thereby decreased binding, presumably by reducing the amount of toxic metabolite available for binding to macromolecules. On the other hand, phenobarbitone increased binding by increasing cytochrome P-450 activity, thus generating more toxic metabolites available for binding to macromolecules. Presumably, the metabolites generated from P-450 enzymatic action on 1,1-dichloroethane bind to cellular macromolecules. Lung microsomes were weakly effective whereas kidney and stomach microsomal fractions were ineffective. Therefore, the binding to macromolecules of various organs detected *in vivo* may have been due to a stable hepatic metabolite that was circulated to reach extrahepatic organs. Pretreatment with phenobarbitone enhanced the binding to DNA, microsomal RNA and proteins while addition of glutathione-s-transferase to the microsomal systems caused

suppression of binding. Because only radioactivity was measured it is difficult to determine whether the μmole bound represents 1,1-dichloroethane or its metabolite(s). However, the fact that binding is enhanced with induction of P-450 suggests that it represents the metabolite(s). Thus, GSH appears to play a detoxification role in the metabolism of 1,1-dichloroethane. The fact that 1,1-dichloroethane binds to nucleic acid suggests that it may have a potential to produce mutation in a mammalian system.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located in humans or animals regarding the absorption of inhaled 1,1-dichloroethane. However, its use as a gaseous anesthetic agent in humans provides evidence of its absorption. Furthermore, the volatile and lipophilic nature of 1,1-dichloroethane favors pulmonary absorption. Structurally related chlorinated aliphatics and gaseous anesthetics are known to be rapidly and extensively absorbed from the lung. The total amount absorbed from the lungs will be directly proportional to the concentration in inspired air, the duration of exposure, the blood/air partition coefficient of 1,1-dichloroethane, its solubility in tissues, and the individual's ventilation rate and cardiac output. One of the most important factors controlling pulmonary absorption is the blood/air partition coefficient of the chemical. The concentration of the chemical and the duration of exposure are also important determinants of the extent of systemic absorption.

It is known that an isomer of 1,1-dichloroethane, 1,2-dichloroethane, is well-absorbed following inhalation exposure. However, the blood/air partition coefficient for 1,2-dichloroethane is approximately 4 times that of 1,1-dichloroethane. This suggests that 1,1-dichloroethane would not be absorbed into the blood from air as readily as 1,2-dichloroethane, but it will still be well absorbed from the lung (Sato and Nakajima 1987).

3.4.1.2 Oral Exposure

No studies were located that quantitated the absorption of ingested 1,1-dichloroethane in humans or animals. However, when 700 mg [^{14}C]-1,1-dichloroethane/kg was orally administered to rats and mice, absorption was evidenced by the presence of radiolabel in expired air and the presence of radiolabeled

metabolites in urine, although there was no quantitative assessment made of the extent or rate of absorption (Mitoma et al. 1985).

3.4.1.3 Dermal Exposure

No studies were located regarding the absorption of 1,1-dichloroethane in humans or animals following dermal exposure. However, Reid and Muianga (2012) reported evidence that 1,1-dichloroethane penetrates the skin. 1,1-Dichloroethane was applied to the shaved abdominal skin of rabbits that were fitted with masks to prevent inhalation of the compound. Exhaled air from the rabbits was passed into pure alcohol, and the presence of halogen was tested by flaming a copper wire introduced into it. The green color observed after 1 hour indicated that the halogen ion was absorbed into the bloodstream, although no quantitative assessment of the extent or rate of absorption was possible.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located in humans or animals regarding the distribution of 1,1-dichloroethane following inhalation exposure. However, since this chemical was once used as a gaseous anesthetic, it can be assumed that it is distributed to the central nervous system as well as to the other tissues of the body. Tissue uptake of halocarbons such as 1,1-dichloroethane is governed by the affinity of each tissue for the lipophilic chemical (i.e., the higher the lipid content of a tissue, the greater its uptake of 1,1-dichloroethane) (Sato and Nakajima 1987).

3.4.2.2 Oral Exposure

No studies were located regarding the distribution of 1,1-dichloroethane following oral exposure in humans or animals.

3.4.2.3 Dermal Exposure

No studies were located regarding the distribution of 1,1-dichloroethane following dermal exposure in humans or animals.

3.4.2.4 Other Routes of Exposure

Rats and mice were intraperitoneally injected with 1.2 mg [^{14}C]-1,1-dichloroethane/kg and sacrificed 22 hours later. 1,1-Dichloroethane was covalently bound to proteins, RNA, and DNA of liver, kidney, lung, and stomach. The extent of binding was greatest in the tissue proteins and least in the DNA. Binding to rat and mouse DNA was greatest in the stomach and liver, respectively (Colacci et al. 1985). Although distribution of 1,1-dichloroethane very likely occurs to other tissues, the liver, kidney, lung, and stomach were the only tissues analyzed in this study.

3.4.3 Metabolism

The metabolism of 1,1-dichloroethane has not been extensively characterized. *In vivo* studies of the metabolism of 1,1-dichloroethane in humans and animals are very limited. Elucidation of 1,1-dichloroethane's metabolic scheme to date is primarily based on *in vitro* studies. In general, the identification of specific metabolites and the monitoring of enzyme activities indicate that the biotransformation of 1,1-dichloroethane is mediated by hepatic microsomal cytochrome P-450 system.

In rats and mice orally administered 700 or 1,800 mg/kg, respectively, 1,1-dichloroethane (5 days/week for 4 weeks followed by a single dose of radiolabelled 1,1-dichloroethane), most of the radiolabel was detected in expired air; the investigators assumed that this was parent compound (Mitoma et al. 1985). Forty-eight hours after oral administration, 7.4 and 29.3% of the radiolabel was detected in the urine, carcass, or expired carbon dioxide. The investigators assumed that this represented metabolized 1,1-dichloroethane; however, only radiolabel was measured in the carcass. It is likely that the ingested radiolabeled 1,1-dichloroethane underwent first-pass extraction by the liver. It is possible that high doses used in this study exceeded the capacity of the animals to metabolize 1,1-dichloroethane. The radiolabeled compound that was not excreted unchanged in the expired air was probably largely metabolized in the liver, followed by subsequent redistribution of labeled metabolites to other organs prior to their excretion.

An *in vitro* study demonstrated cytochrome P450 metabolism of 1,1-dichloroethane. McCall et al. (1983) demonstrated 1,1-dichloroethane binding to hepatic microsomal cytochrome P450 from rats; as compared to microsomes from untreated rats, cytochrome P450 binding was 2.25 times higher, per mole of cytochrome, in microsomes from phenobarbital-stimulated rats. Administration of β-naphthaflavone had no effect on the extent of 1,1-dichloroethane binding to cytochrome P450 binding. *In vitro* exposure of hepatic microsomal to 1,1-dichloroethane also stimulated NADPH oxidation. The rate and extent of

1,1-dichloroethane metabolism was increased 6.3 times in the hepatic microsomes of rats that were induced by chronic ethanol consumption (Sato et al. 1980).

Metabolism of 1,1-dichloroethane by hepatic microsomes resulted in the production of acetic acid as the major metabolite and 2,2-dichloroethanol, mono-, and dichloroacetic acid as minor metabolites (Table 3-4) (McCall et al. 1983). On the basis of these results, pathways for the metabolism of 1,1-dichloroethane were proposed (Figure 3-3). The initial steps in the metabolism of 1,1-dichloroethane were proposed to involve cytochrome P-450-dependent hydroxylations at either carbon. Hydroxylation at C-1 would result in the production of an unstable alpha-haloalcohol, which can lose HCl to yield acetyl chloride. An alternative, but less favorable reaction, would be a chlorine shift to yield chloroacetyl chloride. These acyl chlorides can react with water to generate free acids or react with cellular constituents. Hydroxylation at C-2 would produce 2,2-dichloroethanol, which would undergo subsequent oxidation to dichloroacetaldehyde and dichloroacetic acid (McCall et al. 1983).

Chloroethanes have been shown to undergo dechlorination by an enzyme system that is similar to the hepatic microsomal mixed function oxidase system (Van Dyke and Wineman 1971). Dechlorination was inducible by phenobarbital and required oxygen and NADPH. However, dechlorination also required a factor from the cytosolic fraction of the liver homogenate for optimal dechlorinating activity. In terms of structural requirements, dechlorination was enhanced if the carbon atom containing the chlorine had only one hydrogen. In a microsomal incubation, 13.5% of the ^{36}Cl of 1,1-dichloroethane was enzymatically removed after 30 minutes, while <0.5% of the ^{36}Cl of 1,2-dichloroethane was removed (Van Dyke and Wineman 1971).

Under hypoxic conditions, 1,1-dichloroethane gives rise to free radicals. However, its ability to develop free radicals is much less when compared to other chlorinated hydrocarbons like trichloroethane and carbon tetrachloride. It has been suggested that these free radicals possess the potential to induce toxic and carcinogenic effects. There is no correlation between the ease of free radical activation, covalent binding formation, or carcinogenic potency (Tomasi et al. 1984).

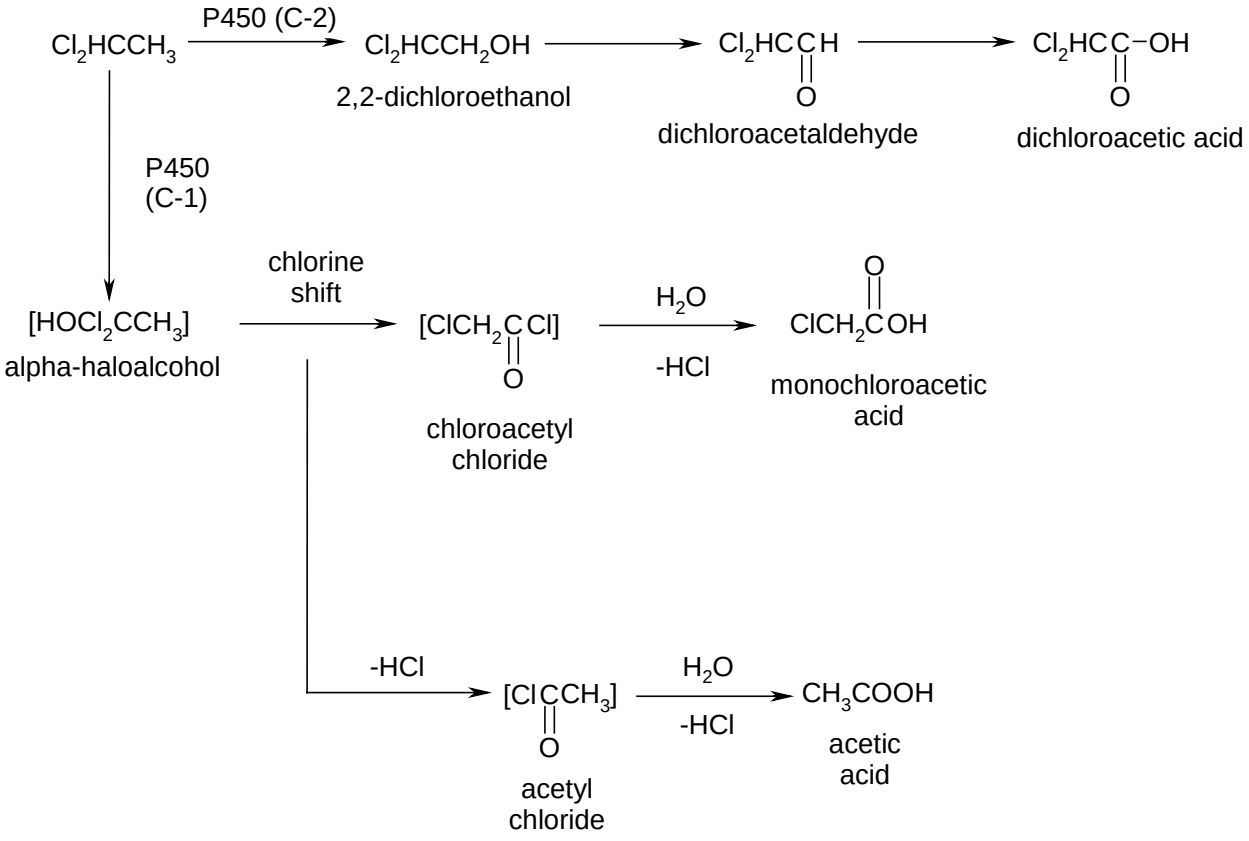
Table 3-4. Production of Metabolites from 1,1-Dichloroethane with Hepatic Microsomes from Phenobarbital-Induced Rats

Metabolites	Metabolic production[a] (nmoles/mg microsomal protein/20 minutes)
Acetic acid	179 (15)
2,2-Dichloroethane	0.12 (0.02)
Chloroacetic acid	0.22 (0.08)
Dichloroacetic acid	0.048 (0.005)
Chloroacetaldehyde	<0.07 (0.03)

[a]Values represent means (standard deviation) for determinations in triplicate on three to five separate preparations of hepatic microsomes.

Source: McCall et al. 1983

Figure 3-3. Proposed Metabolic Scheme for 1,1-Dichloroethane



Source: McCall et al. 1983

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No empirical data on the elimination of excretion of 1,1-dichloroethane in humans or animals were identified. Sato and Nakajima (1987) predicted that 59% of inhaled 1,1-dichloroethane would be metabolized and excreted in the urine and 41% would be eliminated in expired air.

3.4.4.2 Oral Exposure

Mitoma et al. (1985) examined excretion of 1,1-dichloroethane in rats and mice administered 1,1-dichloroethane via gavage 700 or 1,800 mg/kg, respectively, 5 days/week for 4 weeks followed by a single dose of radiolabelled 1,1-dichloroethane. In the rats, 86% of the administered dose was excreted in expired air 5% expired as carbon dioxide and 0.9% was detected in the urine. In mice, 70% was excreted in expired air, 25% was expired as carbon dioxide, and 1.6% was detected in urine. Because rats and mice were administered different doses, a determination cannot be made as to whether the differences in excretion and metabolism are due to species differences or are a reflection of different doses.

3.4.4.3 Dermal Exposure

No studies were located in humans or animals regarding excretion of 1,1-dichloroethane following dermal exposure

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

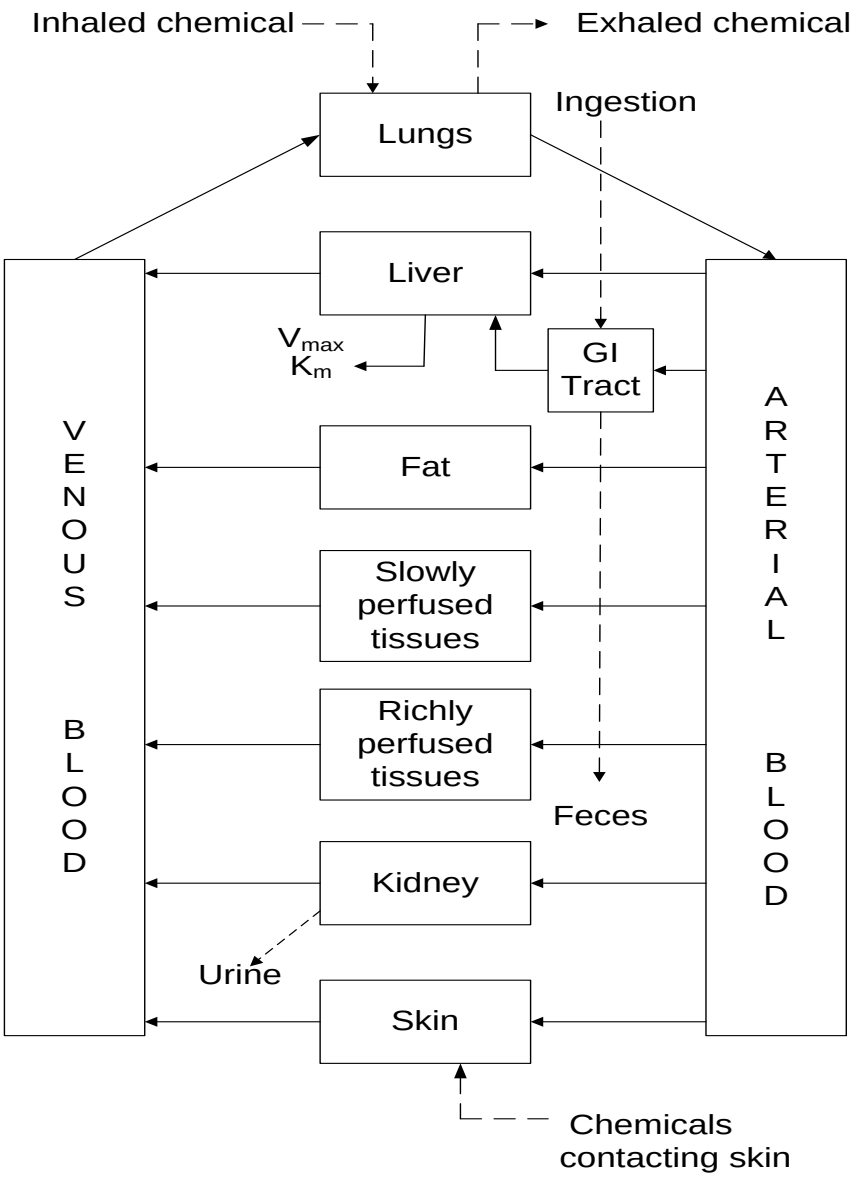
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

If PBPK models for 1,1-dichloroethane exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

No PBPK models were identified for 1,1-dichloroethane.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

No information was identified on the pharmacokinetic mechanisms of action of 1,1-dichloroethane.

3.5.2 Mechanisms of Toxicity

There are limited data to identify the critical targets of 1,1-dichloroethane toxicity or to elucidate the mode of action for the observed effects.

3.5.3 Animal-to-Human Extrapolations

The inhalation study by Hofmann et al. (1971) found species differences in the renal toxicity of 1,1-dichloroethane. Crystalline precipitations and tubular obstruction were observed in cats, but not in rats, rabbits, or guinea pigs. There are insufficient data to determine whether this would also be a relevant end point in humans and whether humans would be as sensitive to this effect as cats.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types

of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in [humans and/or animals] after exposure to 1,1-dichloroethane.

No *in vitro* studies were located regarding endocrine disruption of 1,1-dichloroethane.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The fetus/infant has an immature (developing) blood-brain barrier that past literature has often described as being leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the blood-brain barrier, there are differences between fetuses/infants and adults which are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; as it raises a very important toxicological question as to whether these mechanisms provide protection for the developing brain or do they render it more vulnerable to toxic injury. Each case of chemical exposure

should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Information on children's susceptibility to the toxic effects of 1,1-dichloroethane is limited to a developmental toxicity study in rats (Schwetz et al. 1974) that found an increase in the incidence of delayed ossifications in the fetuses of dams exposed to 6,000 ppm 1,1-dichloroethane on gestation days 6–15. An *in vitro* study (Andrews et al. 2002; only available as an abstract) utilizing rat whole embryo cultures reported eye defects in at 17.9 mM; this concentration also reported in 35% embryolethality.

3.8 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).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring. This report is available at http://www.cdc.gov/exposurereport/. The biomonitoring data for 1,1-dichloroethane from this report is discussed in Section 6.5. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, 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 1,1-dichloroethane are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well 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 1,1-dichloroethane are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to 1,1-Dichloroethane

As summarized in Section 6.5, 1,1-dichloroethane was not detected in blood samples collected from the National Health and Nutrition Examination Survey (2003–2004). No other biomarkers that could be used to identify or quantify exposure to 1,1-dichloroethane were identified.

3.8.2 Biomarkers Used to Characterize Effects Caused by 1,1-Dichloroethane

1,1-Dichloroethane was used as an anesthetic in the early part of the 20th century (Konietzko 1984; Reid and Muianga 2012). No information was available on blood levels associated with anesthesia or the occurrence of anesthesia-induced cardiac arrhythmias.

3.9 INTERACTIONS WITH OTHER CHEMICALS

No information was located regarding toxic interactions of 1,1-dichloroethane with other xenobiotics. Evidence exists to indicate that 1,1-dichloroethane is detoxified by glutathione (Colacci et al. 1985). Thus, it is likely that other substances that deplete glutathione stores such as other chlorinated hydrocarbons (e.g., 1,1-dichloroethene and 1,2-dichloroethane), acetaminophen, and bromobenzene may enhance the toxicity of 1,1-dichloroethane. Substances that alter the activity of the microsomal enzymes that are responsible for the metabolism of 1,1-dichloroethane may also affect the toxicity of this chemical. For example, it has been shown that ethanol increases the metabolism of 1,1-dichloroethane *in vitro* (Sato et al. 1980).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,1-dichloroethane than will most persons exposed to the same level of 1,1-dichloroethane in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of 1,1-dichloroethane, or compromised function of organs affected by 1,1-dichloroethane. Populations who are at greater risk due to their unusually high exposure to 1,1-dichloroethane are discussed in Section 6.7, Populations with Potentially High Exposures.

No populations unusually susceptible to 1,1-dichloroethane or chlorinated ethanes in general have been identified. NIOSH (1978) has identified the following individuals as possibly being at increased risk

from exposure to 1,1-dichloroethane: (1) individuals with skin disease because of the purported dermal irritant effects induced by 1,1-dichloroethane; (2) individuals with liver disease because of the role of this organ in the biotransformation and detoxification of xenobiotics such as 1,1-dichloroethane; (3) Individuals with impaired renal function because of the limited evidence that 1,1-dichloroethane is nephrotoxic in animals; and (4) individuals with chronic respiratory disease because of the purported respiratory irritant effects induced by 1,1-dichloroethane. Although there are no data to substantiate this, additional populations that may be unusually susceptible to 1,1-dichloroethane include children and the elderly because of immature or compromised metabolic capabilities, and phenobarbital or alcohol consumers because of the ability of these substances to alter the activity of the cytochrome P-450 system.

It should be noted that no reliable data were found regarding dermal or respiratory irritant effects of 1,1-dichloroethane.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,1-dichloroethane. 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 1,1-dichloroethane. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. No texts providing specific information about treatment following exposures to 1,1-dichloroethane were identified.

3.11.1 Reducing Peak Absorption Following Exposure

No information specific to 1,1-dichloroethane was identified.

3.11.2 Reducing Body Burden

No information specific to 1,1-dichloroethane was identified.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanisms of toxicity have not been identified for 1,1-dichloroethane.

3.12 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 1,1-dichloroethane 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 1,1-dichloroethane.

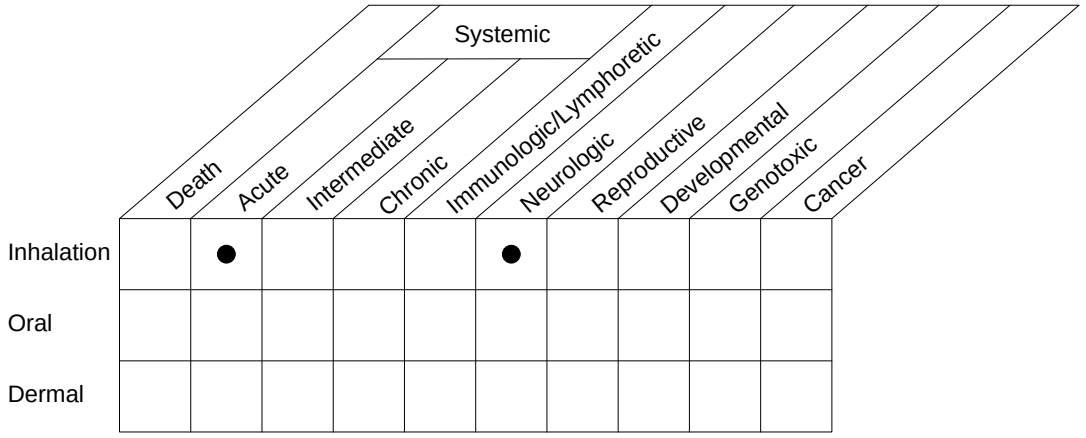
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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.

3.12.1 Existing Information on Health Effects of 1,1-Dichloroethane

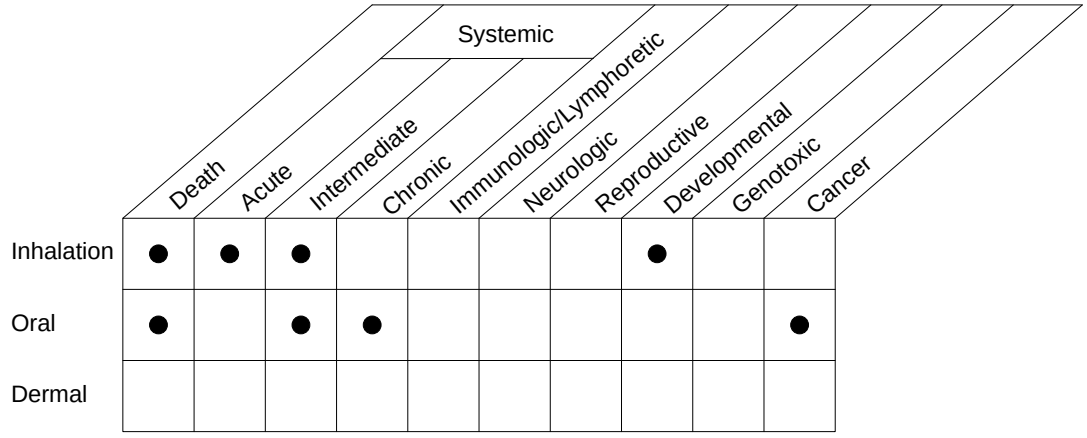
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1-dichloroethane are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,1-dichloroethane. Each dot in the figure indicates 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* (Agency for Toxic Substances and Disease Registry 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 3-5 graphically depicts the information that currently exists on the health effects of 1,1-dichloroethane. The literature reviewed concerning the health effects of 1,1-dichloroethane in humans consisted solely of an anecdotal report describing the occurrence of cardiac arrhythmias when this compound was used as a gaseous anesthetic. Chlorinated aliphatics as a class are known to cause central nervous system depression, and respiratory tract and dermal irritation when humans are exposed

Figure 3-5. Existing Information on Health Effects of 1,1-Dichloroethane



Human



Animal

● Existing Studies

by inhalation to sufficiently high levels. It has been inferred that 1,1-dichloroethane causes these effects, but no reliable data were found that verified this activity.

The database for the health effects of 1,1-dichloroethane in experimental animals is lacking, and the studies reviewed consisted primarily of one subchronic inhalation study, one inhalation developmental toxicity study, and two oral chronic bioassays. No information is available on the effects of 1,1-dichloroethane following dermal exposure. The limited information available in animals suggests that 1,1-dichloroethane may be nephrotoxic, fetotoxic, and possibly carcinogenic. The data also indicate that 1,1-dichloroethane is considerably less toxic than 1,2-dichloroethane and the tetrachlorinated aliphatics.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. No reliable information is available on the effects of acute exposure to 1,1-dichloroethane in humans. Information on the lethality of 1,1-dichloroethane following inhalation or oral exposure of animals comes from secondary sources (Archer 1978; Smyth 1956). One study examined the nonlethal toxicity of 1,1-dichloroethane following inhalation exposure (Schwetz et al. 1974); this study reported decreases in maternal weight gain and delayed ossification in the fetuses. Because the potential systemic toxicity of 1,1-dichloroethane has not been evaluated following acute inhalation or dermal exposure, the database was not considered adequate for derivation of acute-duration inhalation or oral MRLs for 1,1-dichloroethane.

Since the chlorinated aliphatics in general are known to cause central nervous system depression and irritation of respiratory and ocular mucosal epithelium following single high-level exposures, more information on the effects of acute-duration exposures to 1,1-dichloroethane by all routes would be useful to assess more fully the acute hazards of this chemical.

Intermediate-Duration Exposure. No reliable information is available on the effects of repeated exposure in humans. Limited information is available on the effects of repeated inhalation and oral exposures to 1,1-dichloroethane in animals. The studies reviewed indicate that 1,1-dichloroethane is possibly nephrotoxic, but this effect has only been demonstrated at high doses in cats, but not in rats, guinea pigs, or rabbits (Hofmann et al. 1971). No other toxic effects have been attributed to 1,1-dichloroethane following intermediate-duration inhalation exposures in animals. The lack of supporting toxicity or mechanistic data precluded using this study as the basis on an intermediate-duration inhalation MRL. More information on the systemic effects of repeated-dose exposures in animals,

particularly by the inhalation route since this is the most likely route of human exposure, would be useful to determine whether nephrotoxic effects observed in one study are an actual result of exposure to 1,1-dichloroethane, to determine if 1,1-dichloroethane reacts like other chlorinated aliphatics (e.g., causes neurotoxicity and liver toxicity), and to more fully assess potential human health hazards from repeated exposure to 1,1-dichloroethane. Two studies have examined the intermediate-duration oral toxicity of 1,1-dichloroethane. In a limited reported study, NCI (1977) found alterations in body weight gain in rats, but not mice, administered 1,1-dichloroethane for 6 weeks. In the second study, no adverse effects were observed in mice exposed to 1,1-dichloroethane in drinking water for 52 weeks (Klaunig et al. 1986). Additional oral studies are needed to identify sensitive targets of toxicity and establish dose-response relationships. Dermal studies are also necessary to evaluate the toxicity of this compound.

Chronic-Duration Exposure and Cancer. No information is available on the effects of chronic exposure to 1,1-dichloroethane in humans. No chronic-duration inhalation or dermal exposure studies were identified. In chronic-duration oral exposure studies in rats and mice (NCI1977), no nonneoplastic alterations were observed. Without information on the targets of toxicity and dose-response relationships, inhalation and oral MRLs cannot be derived. Additional chronic toxicity studies particularly by the inhalation route would be useful to fully assess potential human health hazard from long-term exposure to 1,1-dichloroethane.

Two bioassays were reviewed that investigated the potential carcinogenic effect of 1,1-dichloroethane by the oral route of exposure in animals. One study provided suggestive evidence of carcinogenicity, but because there was poor survival in this study and the statistical significance of the cancer incidence is uncertain, the results could not be considered conclusive (NCI 1977). The other bioassay yielded negative results for 1,1-dichloroethane (Klaunig et al. 1986). Given the limitations (high mortality) present in the NCI (1977) study and the observations that 1,1-dichloroethane possibly forms DNA adducts and metabolizes to free radicals, more information obtained from well-conducted carcinogenicity studies would be useful to assess more fully the carcinogenic potential of 1,1-dichloroethane in humans and animals. Studies conducted by the inhalation route would be useful.

Genotoxicity. The genotoxic potential of 1,1-dichloroethane has been investigated in *in vitro* assays; *in vivo* genotoxicity studies are necessary to evaluate the genotoxic potential of this chemical. In general, these studies provide suggestive evidence that 1,1-dichloroethane is not genotoxic. 1,1-Dichloroethane has been observed to enhance cell transformation in Syrian hamster embryo cells (Hatch et al. 1983) and results suggest that 1,1-dichloroethane or a metabolite can bind to cellular macromolecules such as DNA

(Colacci et al. 1985). More information on the genotoxic effects of 1,1-dichloroethane in animals both *in vitro* and *in vivo* would be useful to resolve the discrepancies in the present data and to assess the genotoxic hazard of this chemical in humans.

Reproductive Toxicity. No information on the reproductive effects of 1,1-dichloroethane in humans or animals is available. Reproductive toxicity studies in animals would be useful particularly by the inhalation route since this is the most likely route of human exposure.

Developmental Toxicity. No information on the developmental effects of 1,1-dichloroethane in humans is available. One study was located that investigated the developmental effects of inhaled 1,1-dichloroethane in animals (Schwetz et al. 1974). The results from this study indicated that 1,1-dichloroethane is fetotoxic in rats, causing retarded fetal development (i.e., delayed ossification of the vertebrae) in the presence of decreases in maternal food consumption and body weight gain. Additionally, well-conducted developmental toxicity studies on 1,1-dichloroethane, particularly by the inhalation route since this is the most likely route of human exposure, would be useful to verify the data from the single study that suggest this compound may cause adverse developmental effects.

Immunotoxicity. No information is available on the immunotoxic effects of 1,1-dichloroethane in humans or animals. Immunotoxicity studies in animals, particularly by the inhalation route since this is the most likely route of human exposure, would be useful to assess the potential risk for 1,1-dichloroethane-induced adverse immunologic effects in humans.

Neurotoxicity. Chlorinated aliphatics as a class are known to cause central nervous system depression in humans exposed by inhalation to sufficiently high levels. 1,1-Dichloroethane can also cause this effect, evidenced by its former use as an anesthetic. However, no reliable data were found that indicated a threshold level for this effect. No data (behavioral, histopathological, neurochemical, or neurophysiological) are available on possible neurotoxic effects of long-term low level exposures to 1,1-dichloroethane. More information on potential short- and long-term neurotoxic effects of inhaled 1,1-dichloroethane would be useful to determine whether this compound can produce neurotoxic effects following low-level, long-term exposures, and to determine the threshold exposure level for 1,1-dichloroethane-induced central nervous system depression.

Epidemiological and Human Dosimetry Studies. No epidemiological studies were located on 1,1-dichloroethane. Well-controlled epidemiological studies of people living in close proximity to areas

where 1,1-dichloroethane contamination of surface water and groundwater or air is known to have occurred, people living near hazardous waste sites, and of occupationally exposed people could add to the limited database and clarify health effects in humans induced by 1,1-dichloroethane. However, while this information would be useful, it is unlikely that it could be easily obtained from occupational studies. Other short-chain halogenated hydrocarbons are usually encountered in the same facilities where 1,1-dichloroethane is manufactured or used, thus confounding the results obtained in such a study.

Biomarkers of Exposure and Effect. For high exposure to 1,1-dichloroethane, the levels of this compound in the blood, urine, and breath may be used for biomarkers of exposure. However, these methods should be more sensitive and quantitative. The formation of DNA adducts has been suggested, and if they do occur *in vivo*, they may serve to identify long-term exposure to 1,1-dichloroethane. The development of methods for detecting metabolites in the fluids and tissue of humans is needed to indicate 1,1-dichloroethane exposure.

Biomarkers of effect would be useful for identifying 1,1-dichloroethane-specific injury (e.g., hepatotoxicity, renal toxicity, neurotoxicity) for short-, intermediate-, and long-term exposure. Presently, no biomarkers of effect are available; however, DNA adducts may be useful for indicating carcinogenicity in animals or humans following chronic exposure to 1,1-dichloroethane.

Absorption, Distribution, Metabolism, and Excretion. Studies of the toxicokinetics of 1,1-dichloroethane are very limited. Much of the information regarding the disposition of 1,1-dichloroethane is based on indirect evidence. Toxicokinetic data are useful for providing information on mechanisms of toxicity and can often support findings of toxicity studies.

Absorption of 1,1-dichloroethane occurs following exposure via all routes. The presence of a 1,1-dichloroethane metabolite in urine and expired air and its binding to tissue macromolecules provide evidence of its absorption. Studies regarding the direct analysis of the extent and rate of 1,1-dichloroethane absorption are lacking and would provide useful information on the potential health hazards associated with exposure to 1,1-dichloroethane via inhalation of contaminated air or ingestion of contaminated water.

Studies in humans and animals regarding tissue distribution of 1,1-dichloroethane are not available. Its lipophilicity suggests that the compound would be well absorbed and distributed to tissues according to their lipid content. Binding studies conducted in rats following intraperitoneal injection indicate that

1,1-dichloroethane localizes in the liver, kidney, lung, and stomach. However, analysis has been limited to these tissues. Distribution studies using routes of administration relevant to human exposure (inhalation, oral) would provide useful information on potential target organs of 1,1-dichloroethane-induced toxicity in humans.

Characterization of 1,1-dichloroethane's metabolism relies heavily on *in vitro* data. These studies reveal that the biotransformation process is mediated by cytochrome P-450 with hepatic microsomes being the most effective. Identification of products in these microsomal studies allows for the prediction of metabolic pathways. However, exposure to 1,1-dichloroethane under *in vivo* conditions may alter substrate availability and consequently alter the metabolic scheme. *In vivo* studies would provide a better understanding of the rate and extent of 1,1-dichloroethane metabolism and a more realistic perspective of its metabolic fate. This information would allow more accurate prediction of the potential of 1,1-dichloroethane to induce toxic effects, and aid in devising methods to detoxify exposed persons.

Studies regarding the excretion of 1,1-dichloroethane by humans were not available. One study was located in animals regarding the extent or rate of 1,1-dichloroethane excretion. Studies monitoring levels in blood and excretion would be useful to estimate pharmacokinetic parameters.

Comparative Toxicokinetics. The absorption, distribution, metabolism, and excretion data for 1,1-dichloroethane are all derived from animal studies. It is likely that human disposition would follow a scheme similar to that found in animals, but this conclusion is highly speculative. However, similar results obtained *in vivo* across several animal species would provide supportive evidence for the assumption that 1,1-dichloroethane is handled in a similar manner in humans.

Methods for Reducing Toxic Effects. Limited information regarding methods for reducing the toxic effects of 1,1-dichloroethane were identified. Additional information regarding the toxicity of 1,1-dichloroethane is needed prior to research on mitigating the toxicity of this compound.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

No data were identified on children's susceptibility to the toxic effects of 1,1-dichloroethane and whether there are toxicokinetic differences in the metabolism of this chemical between adults and children. As noted previously, one developmental toxicity study (Schwetz et al. 1974) reported altered fetal growth.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

No ongoing studies sponsored by NIH, NTP, or EPA were identified for 1,1-dichloroethane.