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 1,1-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.

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 (LSE) 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 (LOAELs) or exposure levels below which no adverse cffccts (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.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of 1,l -dichloroethene are indicated in Table 2-1 and Figure 2-1. Because cancer effects could occur at lower exposure levels, Figures 2-1 and 2-2 also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for 1,1-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 duration exposures 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 A). 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

No studies were located regarding death in humans after inhalation exposure to 1,1-dichloroethene. However, animal studies indicate that 1,1-dichloroethene is lethal following inhalation exposure.

The lethality of 1,1-dichloroethene in animals following inhalation exposure varies considerably and is influenced by such factors as species, strain, sex, and food intake. Differences between strains could account for the range in reported 4-hour LC_{50} values in rats with access to food (nonfasted rats) (≈6,000-8,000 ppm in males and 10,000 ppm in females) (Siegel et al. 1971; Zeller et al. 1979a, 1979b). Higher 4-hour LC_{50} values (10,000-15,000 ppm) have also been reported for nonfasted rats (sex not specified), but the animals were observed for only 24 hours (Jaeger et al. 1973c, 1974).

The LC_{50} values reported for rats that were fasted for 16 hours were generally lower than those reported for nonfasted rats. For instance, the reported 4-hour LC_{50} was 415 ppm in fasted male rats (Zeller et al. 1979b). In fasted female rats, which appear to be more resistant to the detrimental effects of starvation, the 4-hour LC_{50} was 6,545 ppm (Zeller et al. 1979b). A study by Jaeger et al. (1974) compared the effects of food intake on the lethality of male rats exposed to 1,1-dichloroethene for 24 hours. The results of the study revealed that the LC_{50} for fasted

animals was almost 30 times lower than that for nonfasted animals. The proposed mechanism by which fasting increases the toxicity of 1,1-dichloroethene is discussed in Sections 2.3 and 2.4.

Identical trends are seen in mice and hamsters (i.e., fasted vs. nonfasted and sex influence the lethality of 1,1-dichloroethene following inhalation exposure). Mice, however, are considerably more susceptible to the lethal effects of 1,1-dichloroethene than are rats. Reported 4-hour LC_{50} values in nonfasted mice range from 40 (males) to 200 ppm (females) (Henschler 1979; Oesch et al. 1983; Short et al. 1977c) and in fasted mice from 40 (males) to 115 ppm (females) (Henschler 1979). Similarly, fasted male Chinese hamsters are more susceptible than fasted females to the lethal effects of inhaled 1,1-dichloroethene (see Table 2-1) (Henschler 1979; Klimisch and Freisberg 1979a, 1979b). Death was also reported in two out of three squirrel monkeys exposed to 25 ppm 1,1-dichloroethene following intermediate exposure (Prendergast et al. 1967).

The LC_{50} values and all LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

Limited information is available on the systemic effects of inhaled 1,1-dichloroethene in humans. This information comes primarily from case reports and/or insufficiently detailed mortality studies in which the concentration and duration of exposure to 1,1-dichloroethene were not quantified. Concurrent exposure to other toxic substances cannot be ruled out in most of these cases. Given these limitations, the information available indicates that inhaled 1,1-dichloroethene can induce neurotoxicity after acute exposure (EPA 1979b) and that 1,l -dichloroethene is possibly associated with hepato- and nephrotoxicity after repeated, low-level exposure in humans (EPA 1976).

Considerable information is available on the systemic effects of 1,1-dichloroethene following both acute, intermediate, and chronic exposure in laboratory animals. The target organs or systems of 1,1-dichloroethene toxicity are reported to be the central nervous system, liver, kidney, and lungs, with adverse effects occasionally being noted in the heart.

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

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 d 4hr/d				8600 (LC50[B]) 7100 (LC50[M]) 10300 (LC50[F])	Zeller et al. 1979a
2	Rat	1 d 4hr/d				500[b] (LC50) 2500[b]	Jaeger et al. 1973c
3	Rat	1 d 4hr/d				2000	Jaeger et al. 1973a
4	Rat	1 d 4hr/d				10000[c] (LC50) 15000[c]	Jaeger et al. 1973c
5	Rat	1 d 4hr/d				2010[b] (LC50[B]) 415[b] (LC50[M]) 6545[b] (LC50[F])	Zeller et al. 1979b
6	Rat	1 d 4hr/d				600[b] (LC50) 15000[c] (LC50)	Jaeger et al. 1974
7	Mouse	1 d 4hr/d				115[c] (LC50[M]) 205[c] (LC50[F])	Henschler 1979
8	Mouse	7 d 23hr/d				98 (LC50[M]) 105 (LC50[F])	Short et al. 1977c
9	Mouse	1-8 d 6hr/d				50 (69% mortality[M])	Oesch et al. 1983
10	Mouse	4 d 22-23 hr/d				40 (70% mortality[M])	Short et al. 1977c
11	Mouse	1 d 4hr/d				40[b] (LC50[M]) 115[b] (LC50[F])	Henschler 1979

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

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
12	Hamster	1 d 4hr/d				300[b] (LC50[B]) 150[b] (LC50[M]) 455[b] (LC50[F]	Klimisch and Freisberg 1979b
13	Hamster	1 d 4hr/d				1660 (LC50[M]) 2945 (LC50[F])	Klimisch and Freisberg 1979a
Systemic							
14	Rat	1 d 4hr/d	Hepatic		250 (decreased mitochondrial glutathione level)		Jaeger 1977a
15	Rat	1 d 4hr/d	Hepatic		2000[c] (increased serum AKT)		Jaeger et al. 1974
			Hepatic		150[b] (increased serum AKT)		
16	Rat	1 d 6hr/d	Hepatic	200[c]		200[b] (necrosis)	McKenna et al. 1978b
			Renal	200[c]		200[b] (hemoglobinurea; tubular degeneration)	
17	Rat	1 d 4hr/d	Resp			5000 (pulmonary hemorrhage and congestion)	Zeller et al. 1979a
18	Rat	1 d 10 min	Cardio			25600 (cardiac arrythmias)	Siletchnik and Carlson 1974
19	Rat	1 d 4hr/d	Hepatic		2000[c] (increased SAKT activity)		Jaeger et al. 1973a
			Other			2000 (bloody ascites)	
20	Rat	1 d 4hr/d	Renal		250[b] (swelling in renal cortex)	300[b] (cortical tubular necrosis)	Jackson and Conolly 1985
21	Rat	1-3 d 23hr/d	Hepatic		60 (centrilobular degeneration)		Short et al. 1977d
			Renal	60			

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

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
22	Mouse	5 d 23hr/d	Hepatic		15 (cellular degeneration)		Short et al. 1977d
			Renal			15 (tubular nephrosis)	
23	Mouse	10 d 5d/wk 6hr/d	Hepatic		100 ([F]centrilobular swelling and pleomorphism)	200 ([F]hepatocellular degeneration and necrosis)	Henck et al. 1979
			Renal		55 (increased kidney weight)	200 ([M]renal failure)	
24	Mouse	1 d 6hr/d	Hepatic	10	50 (centrilobular swelling)		Reitz et al. 1980
			Renal			10 (nephrosis)	
25	Mouse	1 d 4hr/d	Resp			20[b] ([M]emphysema and congestion of lungs)	Zeller et al. 1979c
Developmental							
26	Rat	11 d Gd6-16 23hr/d				15 (lateral ventrical hydrocephalus)	Short et al. 1977a
27	Rat	10 d Gd6-15 7hr/d		20		80 (wavy ribs and delayed ossification of skull)	Murray et al. 1979
28	Mouse	11 d Gd6-16 23hr/d			15 (unossified incus, incompletely ossified sternebrae)		Short et al. 1977a
29	Mouse	8 d Gd8-15 23hr/d			41 (unossified incus, incompletely ossified supraoccipital)		Short et al. 1977a
30	Rabbit	13 d Gd6-18 7hr/d		80		160 (fetal resorptions)	Murray et al. 1979

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

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
31	Mouse	4 d Gd12-15 23hr/d				54 (fetal resorption)	Short et al. 1977a
Reproductive							
32	Mouse	5 d 6hr/d		30			Anderson et al. 1977
INTERMEDIATE EXPOSURE							
Death							
33	Gn pig	90 d 24hr/d				15 (3/15 died)	Prendergast et al. 1967
34	Monkey	90 d 24hr/d				25 (2/3 died)	Prendergast et al. 1967
Systemic							
35	Rat	90 d 5d/wk 6hr/d	Hepatic		25 (cytoplasmic vacuolization)		Balmer et al. 1976
36	Rat	6 mo 5d/wk 6hr/d	Resp Hemato Hepatic Derm/oc	75 75 75	25 (fatty changes in midzonal hepatic lobule)		Quast et al. 1986
37	Rat	3 wk 5d/wk 6hr/d	Resp Hepatic Other (body weight)		200 (slight nasal irritation) 500 (degeneration of liver cells) 500 (retarded weight gain)		Gage 1970

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

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
38	Rat	90 d 24hr/d	Resp Hepatic Renal	48 25 15	48 (nuclear hypertrophy of tubular epithelium)	48 (focal necrosis)	Prendergast et al. 1967
39	Rat	30 d 5d/wk 6hr/d	Hepatic		125 (centrilobular and midzonal cytoplasmic vacuolization)	200 (necrosis)	Quast 1976
40	Rat	6 wk 5d/w 6hr/d	Hemato Hepatic Renal		100 (increased plasma phosphate levels) 100 (increased liver weight) 100 (increased kidney weight; desquamation of nephric epithelial cells)		Klimisch et al. 1979
41	Rat	4 wk 7d/wk 24hr/d	Hepatic		50 (fatty changes and focal necrosis)		Plummer et al. 1990
42	Gn pig	90 d 24hr/d	Resp Hepatic	48 5[d]	48 (increased SGPT and AP enzyme activity; decreased lipid content)		Prendergast et al. 1967
43	Gn pig	6 wk 5d/wk 8hr/d	Resp Hepatic	100 100			Prendergast et al. 1967
44	Dog	90 d 24hr/d	Resp Hepatic	48 25		48 (focal necrosis of liver)	Prendergast et al. 1967

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

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
45	Dog	6 wk 5d/wk 8hr/d	Resp Hepatic	100 100			Prendergast et al. 1967
46	Monkey	6 wk 5d/wk 8hr/d	Resp Hepatic Other (body weight)	100 100	100 (5.9% decrease in body weight)		Prendergast et al. 1967
47	Monkey	90 d 24hr/d	Resp Hepatic Other (body weight)	48 25 5		48 (focal necrosis of liver) 48 (>25% decrease in body weight)	Prendergast et al. 1967
Reproductive							
48	Rat	11 wk 5d/wk 6hr/d		55			Short et al. 1977b
Cancer							
49	Dog	90 d 24hr/d				48 (adrenal cortical adenoma)	Prendergast et al. 1967
CHRONIC EXPOSURE							
Systemic							
50	Rat	18 mo 5d/wk 6hr/d	Resp Hemato Hepatic Renal	75 75 75	25 (decreased liver weight; fatty changes in the midzonal region)		Quast et al. 1986

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

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
51	Mouse	1 yr 5d/wk 6hr/d	Hemato Hepatic Renal	55		55 (hepatocellular necrosis) 55 (tubular necrosis)	Lee et al. 1977
52	Mouse	52 wk 5d/wk 4hr/d	Renal	10		25 (tubular nephrosis)	Maltoni et al. 1985
Cancer							
53	Mouse	52 wk 5d/wk 4hr/d				25 (CEL, renal adenocarcinoma)	Maltoni et al. 1985

[a]The number corresponds to entries in Figure 2-1.
[b]Animals were fasted prior to exposure.
[c]Animals were fed prior to exposure (non-fasted).
[d]Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 0.02 ppm; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability). A modifying factor of 3 was used to account for the close proximity of serious effects observed at the range of 10-25 ppm.

AKT = alanine alpha-ketoglutarate transaminase; AP = alkaline phosphatase; B = both sexes; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm/oc = dermal/ocular; Gn pig = guinea pig; F = female(s); Gd = gestation day(s); Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male(s); min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; SAKT = serum alanine alpha-ketoglutarate transaminase; SGPT = serum glutamic-pyruvic transaminase; wk = week(s); yr = year(s)

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

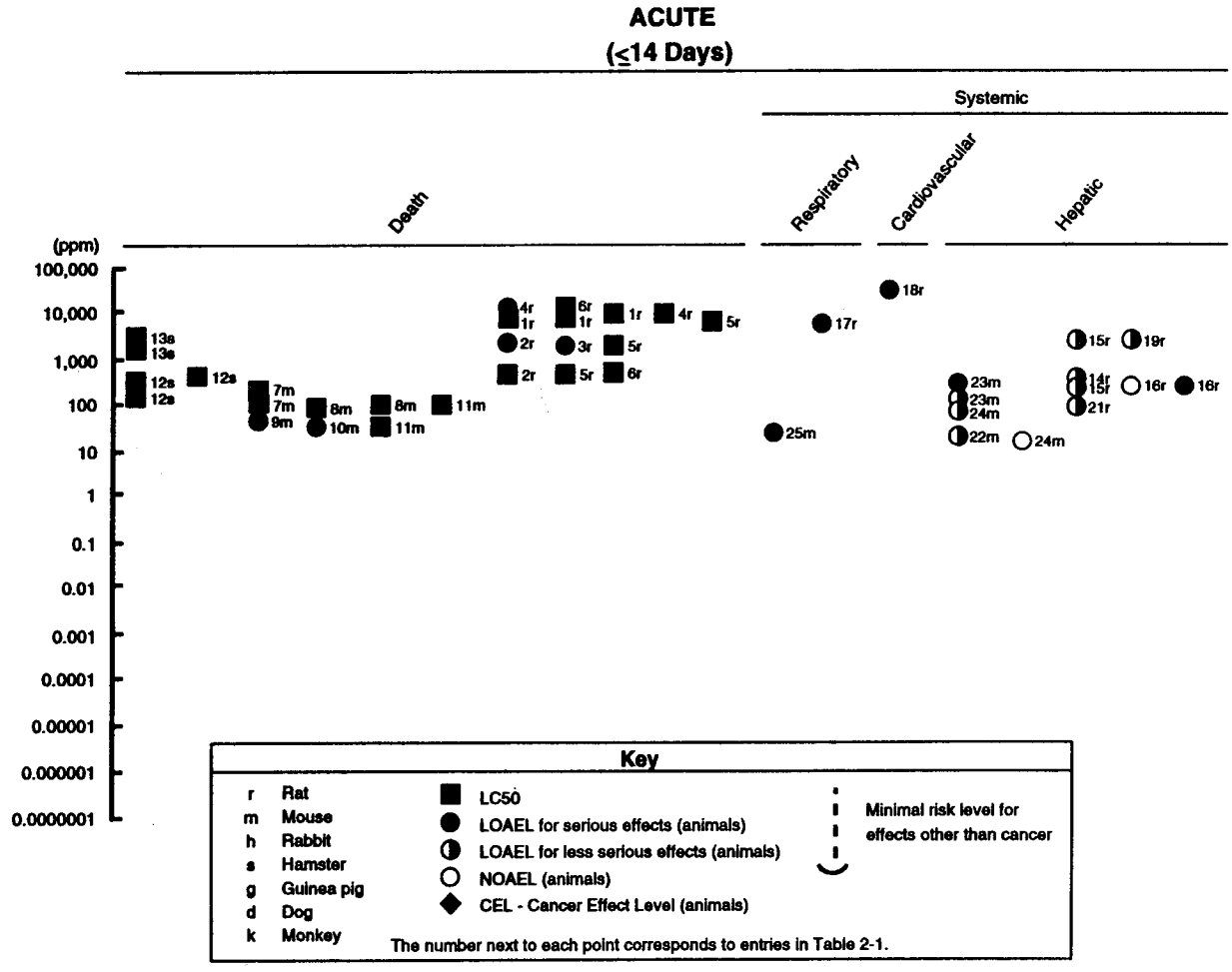


FIGURE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation *(continued)*

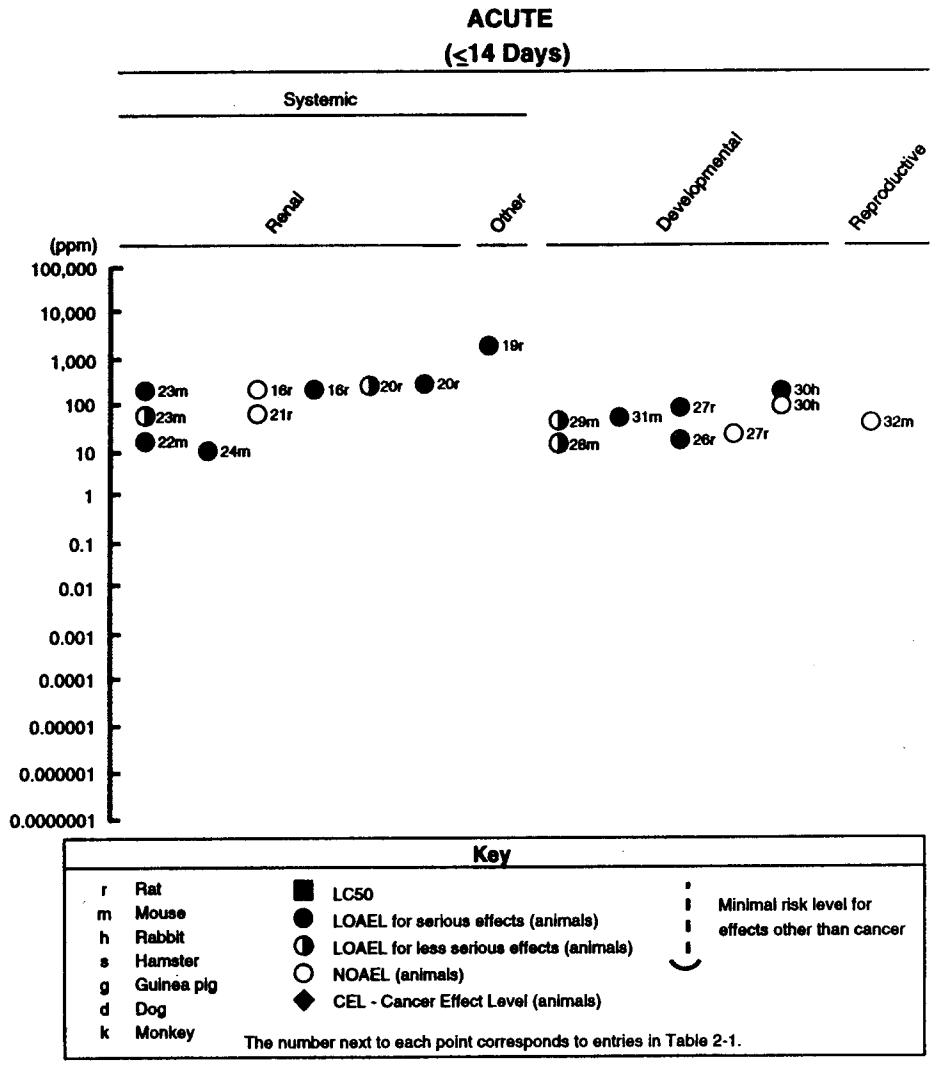


FIGURE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation *(continued)*

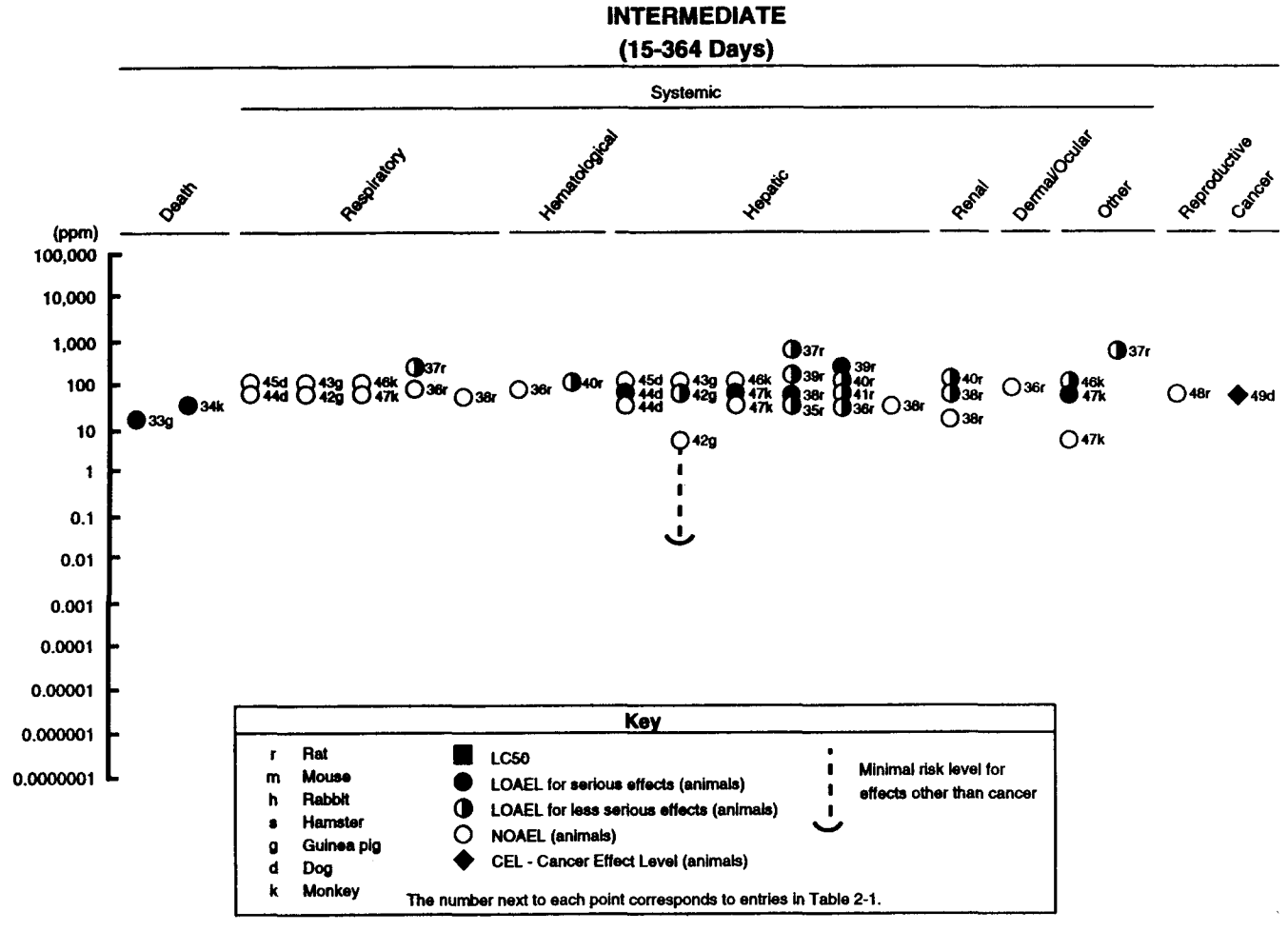
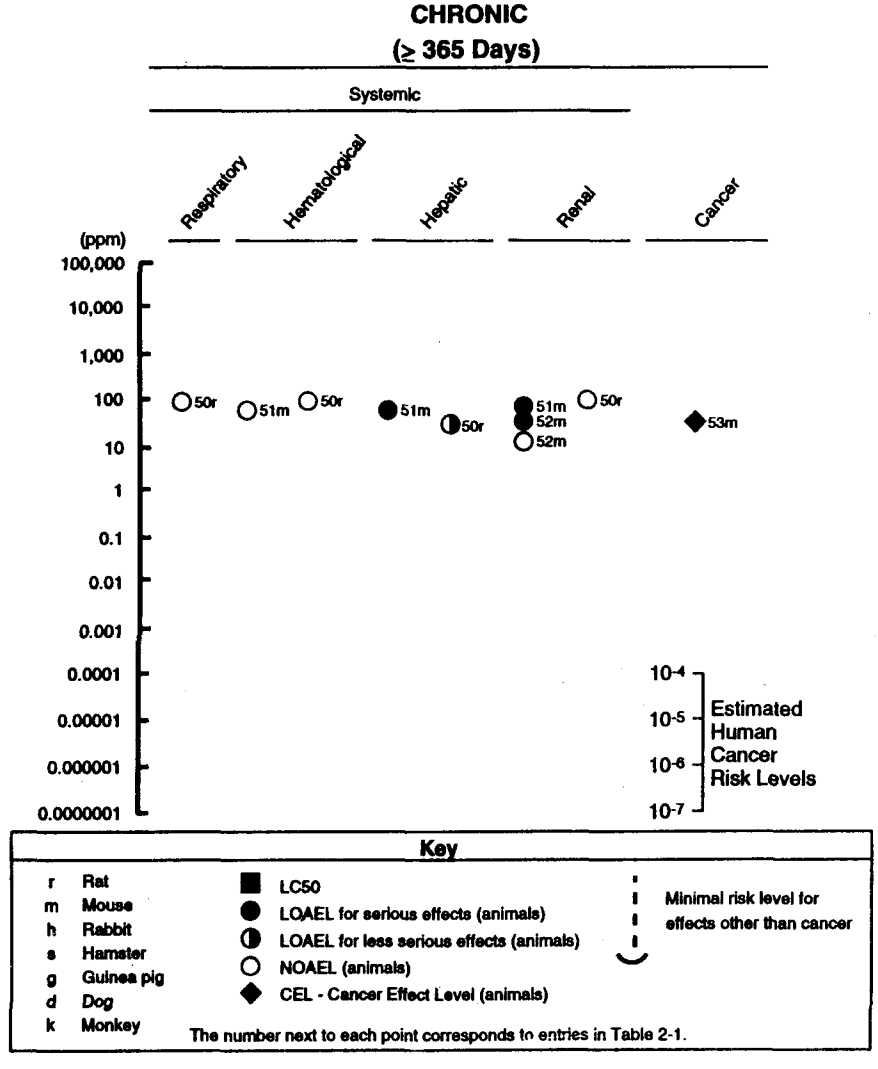


FIGURE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation *(continued)*



2. HEALTH EFFECTS

No studies were located regarding gastrointestinal or musculoskeletal effects in humans or animals after inhalation exposure to 1,1-dichloroethene.The systemic effects observed following inhalation exposure are discussed below.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. No studies were located regarding respiratory effects in humans after inhalation exposure to 1,1 -dichloroethene.

Acute swelling and localized bloody edema and congestion of the lungs are consistently seen at necropsy in rodents acutely exposed to high levels of 1,1-dichloroethene (≈500-15,000 ppm) via inhalation (Klimisch and Freisberg 1979a; Zeller et al. 1979a, 1979b); these effects were seen in hamsters (Klimisch and Freisberg 1979a, 1979b) and along with emphysema in mice (Zeller et al. 1979c) exposed to lower concentrations (150 and 20 ppm, respectively).

Nasal irritation was observed in rats exposed to 200 ppm for 3 weeks (Gage 1970). However, no histopathological effects attributed to treatment were observed in rats, monkeys, dogs, rabbits, or guinea pigs exposed to 100 ppm 1,1-dichloroethene intermittently for 6 weeks (Prendergast et al. 1967) or in rats similarly exposed to 75 ppm 1,1-dichloroethene for 18 months (Quast et al. 1986).

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

Few studies are available that describe adverse cardiovascular effects of 1,1-dichloroethene following inhalation exposure in laboratory animals. Acute exposure of rats to extremely high concentrations (25,600 ppm for 10 minutes) produced arrhythmias mediated by the sympathetic nervous system (Siletchnik and Carlson 1974). These study authors also found that 1,1-dichloroethene at 25,600 ppm increased the sensitivity of the myocardium to epinephrine, thereby providing a mechanism for the electrocardiographic changes. These effects are best characterized as nonspecific neurological effects.

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Cardiac effects such as contraction of the main vessels, and hyperemia were observed following acute, high-level exposure (≈500-15,000 ppm) to 1,1-dichloroethene (Klimisch and Freisberg 1979a, 1979b; Zeller et al. 1979b). Cardiovascular toxicity was not generally observed after more prolonged, lower-level exposure and is, therefore, most likely not a concern for prolonged lowlevel exposure in humans.

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

The available studies did not evaluate the hematological parameters following acute and intermediate exposure to 1,1-dichloroethene.No hematological alterations were observed in male rats (Quast et al. 1986) or in mice (Lee et al. 1977) exposed to 75 ppm 1,1-dichloroethene for 18 months or to 55 ppm 1,1-dichloroethene for 12 months, respectively.

Hepatic Effects. Hepatotoxicity has been observed in humans after repeated exposure to 1,1-dichloroethene, presumably by the inhalation route. Preliminary clinical findings of workers exposed to 1,1-dichloroethene for 6 years or less in a 1,1-dichloroethene polymerization plant revealed a high incidence of hepatotoxicity. Liver scans and measurements of liver enzymes revealed 50% or greater loss in liver function in 27 (59%) of the 46 exposed workers (EPA 1976). These findings must be considered only qualitative in nature since the study provided few details and no follow-up study has been reported.

In laboratory animals, the liver is a major target organ of 1,1-dichloroethene toxicity following acute and chronic inhalation exposure. Hepatotoxicity is evident by the appearance of both biochemical changes (alterations in serum enzyme levels indicative of liver injury and induction of hepatic enzymes) and marked histological changes (e.g., midzonal and centrilobular swelling of liver, degeneration, and necrosis of hepatocytes). These effects appear to follow a dose-response relationship and may also be influenced by duration of exposure. Mice exposed to 50 ppm 1,1-dichloroethene for 6 hours exhibited only slight centrilobular swelling (Reitz et al. 1980; Watanabe et al. 1980), whereas continuous inhalation exposure of mice to 15 ppm 1,1-dichloroethene for 23 hours/day for 5 days caused cellular degeneration (Short et al. 1977d). Under the same exposure regimen for 2 days, hepatic degeneration was seen at 60 ppm (Short et al. 1977d). Similar results were obtained in four strains of mice that were exposed to 55, 100, or 200 ppm

1,1-dichloroethene for 6 hours/day, 5 days/week, for 10 days. Hepatotoxic effects characterized by hepatocellular degeneration and necrosis with centrilobular hepatocellular swelling and pleomorphism at 100 and 200 ppm were observed in all strains. These effects were more severe in females (Henck et al. 1979). Severe effects were seen at higher doses in rats for even shorter-duration exposures. After inhalation exposure of rats to 200-250 ppm 1,1-dichloroethene for 4 hours the following effects were observed: increased liver weight, increased serum activities of sorbitol dehydrogenase and ornithine carbamoyl transferase (Jackson and Conolly 1985; Jaeger 1977a, 1977b), and frank hemorrhagic centrilobular necrosis (Reynolds et al. 1980).

The food intake of the organism prior to exposure influences the degree of 1,1-dichloroethene-induced hepatotoxicity, with more severe effects displayed by animals fasted overnight prior to exposure. This suggests that a relationship exists between chemical toxicity and depletion of reduced glutathione (GSH) (Reynolds et al. 1980). For example, results from an acute study in male rats demonstrated that inhalation exposures to 150 ppm 1,1-dichloroethene for up to 24 hours induced increases in serum enzyme levels indicative of liver dysfunction-alanine aketoglutarate transaminase (AKT)-in fasted animals to a greater extent compared to nonfasted animals (Jaeger et al. 1974). A significant increase in the serum enzymes (AKT) was observed in nonfasted rats exposed to 2,000 ppm or more 1,1-dichloroethene (Jaeger et al. 1974). Gross and microscopic histopathological and biochemical evidence of hepatotoxicity occurs earlier and is more extensive in fasted rats following short-term inhalation exposure to 1, 1-dichloroethene. Exposing fasted rats to 200 ppm 1,1-dichloroethene for 4 hours or less resulted in aberrations in hepatic GSH levels that preceded and/or accompanied major histological changes (Jaeger et al. 1975b; McKenna et al. 1978b; Reynolds et al. 1980). As mentioned above, the increased hepatotoxic effects of 1,1-dichloroethene following inhalation exposure seen in fasted versus nonfasted animals may be related to depletion of hepatic GSH levels in the fasted animals. GSH is known to be involved in 1,1-dichloroethene metabolism (see Section 2.3). GSH levels in rats fed *ad libitum* exhibited a marked diurnal rhythm; levels were minimal between 7 pm and 1 am and maximal between 7 am and 1 pm (Jaeger et al. 1973a). This increase was prevented in fasted rats, with maximal levels reduced by 50%. Furthermore, the I,l-dichloroethene-induced hepatotoxicity coincided with the reduction in liver GSH levels (Jaeger et al. 1973a). Nonfasted rats exposed to 1,1-dichloroethene via inhalation during the period of maximal GSH levels exhibited no signs of hepatotoxicity, but when they were exposed to similar levels of 1, I-dichloro-

ethene during the diurnal period of minimal GSH levels, 40% died and serum enzyme markers increased markedly.

The hepatotoxic effects of 1,1-dichloroethene following intermediate or chronic exposure in animals are similar to those described above for acute exposure (Gage 1970; Lee et al. 1977; Plummer et al. 1990; Quast et al. 1986). Many of the studies that describe the longer-term effects of 1,1-dichloroethene in animals are limited in that only a few experimental details were provided or only one or two doses were studied. These limitations often prevent an adequate assessment of the quality of the results. Male and female rats exposed for 6 hours/day, 5 days/week, over a day period, to 125 or 200 ppm 1,1-dichloroethene exhibited liver changes. These changes were more severe in females and were characterized by a minimal degree of centrilobular fatty degeneration or hepatocellular necrosis (Quast 1976). Mild dose-related cytoplasmic vacuolation was observed in male and female rats exposed to 25 or 75 ppm 1, 1-dichloroethene 6 hours/day, 5 days/week, for either 30 or 90 days (Balmer et al. 1976). The study authors considered this effect reversible. Fatty infiltration of the liver was reported in rats exposed to 25 ppm of 1,1-dichloroethene 6 hours/day, 5 days/week, for 6 months (Quast et al. 1986).

Animals appear to be much less tolerant of continuous exposure (23-24 hours per day) than intermittent exposure. There was no evidence of toxicity in beagle dogs exposed to 100 ppm of 1,1-dichloroethene for 8 hours/day, 5 days/week, for 42 days, but continuous exposure to 48 ppm of 1, 1-dichloroethene for 90 days caused marked liver damage (Prendergast et al. 1967). Similarly, squirrel monkeys continuously exposed to 48 ppm 1, 1-dichloroethene for 90 days exhibited marked evidence of liver damage (i.e., focal necrosis and hemosiderin deposition). However, no liver toxicity was apparent following 42 days of intermittent exposure to 100 ppm 1,1-dichloroethene (Prendergast et al. 1967). It would appear that when animals are exposed to 1,1-dichloroethene on an intermittent basis, they are better able to compensate for the toxic effects induced by this chemical. This observation supports the involvement of depletable stores of liver GSH as a possible mediator of 1,1-dichloroethene-induced hepatotoxicity.

Liver effects in guinea pigs exposed to 5, 15, 25, or 48 ppm of 1,1-dichloroethene for 24 hours per day for 90 days were mottled livers at 15 ppm, and increased SGPT and AP enzyme levels at 45 ppm (Prendergast et al. 1967). Using a NOAEL of 5 ppm based on liver changes, an

intermediate inhalation MRL of 0.02 ppm was calculated as described in the footnote in Table 2-1.

Hepatotoxic effects similar to those discussed above are seen following chronic inhalation exposure to 1,1-dichloroethene in laboratory animals (Lee et al. 1977; Quast et al. 1986). Female rats exposed to 1,1-dichloroethene via inhalation at a concentration of 25 ppm for 6 hours/day, 5 days/week, for 18 months, exhibited fatty changes in the liver (Quast et al. 1986). The results of these studies are only suggestive because of the poor presentation of the data.

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

Adverse effects have been observed in the kidneys of laboratory animals following acute, intermediate, and chronic inhalation exposure to 1,1-dichloroethene. These effects are manifested as enzyme changes (decreases in kidney monooxygenase and epoxide hydrolase levels) (Oesch et al. 1983), tubular alterations (hemoglobinuria) (McKenna et al. 1978b), gross changes (increase in organ weight) (Henck et al. 1979; Quast et al. 1986), and histological changes (tubular swelling, degeneration, and necrosis) (Henck et al. 1979; Jackson and Conolly 1985; Lee et al. 1977; McKenna et al. 1978b; Prendergast et al. 1967; Reitz et al. 1980; Short et al. 1977d; Watanabe et al. 1980). Following acute exposure, the range of 1,1-dichloroethene concentrations that produced the aforementioned effects in rats was 50-300 ppm, with the severity of the kidney lesions increasing with increasing dose and duration of exposure. Male mice appear to be more susceptible to the acute nephrotoxic effects of inhaled 1,l-dichloroethene than female mice or both sexes of rats. Severe histological lesions of the kidney were observed in mice following acute inhalation exposure to 10-50 ppm of 1,1-dichloroethene (Reitz et al. 1980; Short et al. 1977c; Watanabe et al. 1980). Similar results were obtained in four strains of mice exposed to 55, 100, or 200 ppm for 6 hours/day, 5 days/week, for 10 days. Adverse renal effects (characterized by moderate-to-severe nephrosis) were observed in all strains, with the effects observed predominantly in the male mice (Henck et al. 1979).

There is evidence that kidney damage in animals after acute inhalation exposure to 1,1-dichloroethene is reversible, though this may depend on the dose level and duration of exposure. Tubular regeneration was evident in mice after a single 6-hour exposure to 50 ppm 1,l -dichloroethene

(Reitz et al. 1980). However, reversibility of kidney damage at higher exposure concentrations has not been demonstrated.

As was seen with hepatotoxicity, the amount of food intake of the animal appears to be an important determinant of 1,1-dichloroethene-induced nephrotoxicity. Fasted male rats exposed once to 200 ppm 1,1-dichloroethene for 6 hours exhibited delayed hemoglobinuria and marked tubular degeneration, while fed male rats similarly exposed displayed no treatment-related toxic effects (McKenna et al. 1978b). GSH depletion may play an indirect role in the exacerbation of 1,l -dichloroethene-induced nephrotoxicity in the fasted rat.

The bulk of the information on 1,1-dichloroethene-induced nephrotoxicity in animals comes from acute experiments, and evidence of nephrotoxicity after intermediate exposure is limited. Continuous inhalation exposure of rats to 48 ppm 1,1-dichloroethene for 90 days resulted in nuclear hypertrophy of the renal tubular epithelium (Prendergast et al. 1967). Severe nephrotoxicity occurred in male mice exposed to 25 ppm 1, 1-dichloroethene 4 hours/day, 4-5 days/week, for 52 weeks (Maltoni et al. 1985). The reversibility of this effect was not determined. No treatment-related effects were noted in the kidneys of rats chronically exposed to a concentration of 25 or 75 ppm 1,1-dichloroethene for 6 hours/day, 5 days/week, for 18 months (Quast et al. 1986). Strain differences may account for the differential susceptibility to 1,l -dichloroethene exposure.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans following inhalation exposure to 1 ,l -dichloroethene.

No eye irritation was observed in rats exposed to an average concentration of 75 ppm 1,1-dichloroethene for 18 months (Quast et al. 1986).

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

A slight decrease in body weight was reported in rabbits exposed to 25 ppm 1,1-dichloroethene continuously for 90 days or to 100 ppm 1,1-dichloroethene intermittently for 6 weeks (Prendergast et al. 1967). Similar results were reported in monkeys exposed to 48 ppm 1,1-dichloroethene

continuously for 90 days or intermittently to 100 ppm 1,1-dichloroethene for 6 weeks (Prendergast et al. 1967). Food consumption data were not provided. A decrease in body weight was also reported in rats exposed to 500 ppm 1,1-dichloroethene intermittently for 3 weeks, but the magnitude of the effect was not reported (Gage 1970).

2.2.1.3 Immunological Effects

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

2.2.1.4 Neurological Effects

Central nervous system depression and symptoms of inebriation, which may progress to unconsciousness, have been observed in humans after acute exposure to high airborne concentrations (≈4,000 ppm) of 1,1-dichloroethene (EPA 1979b). Complete recovery generally occurs if exposure is not prolonged. However, two cases of persistent cranial nerve disorders were observed following acute inhalation exposure to 1,l -dichloroethene. These cases primarily involved the trigeminal nerve and, to a lesser extent, the hypoglossal, occipital, auricular, and cervical cutaneous nerves, as well as the innervation of muscles of mastication and eye muscles. These two patients were involved in manually cleaning tanks used in the transport of an aqueous dispersion of 1,1-dichloroethene copolymers. The effects were most likely a result of dichloroacetylene formation from 1,1-dichloroethene due to heat and the presence of alkali from the soaps used; chloroacetylenes are highly neurotoxic (Fielder et al. 1985). There is no direct evidence that 1,1-dichloroethene can produce adverse neurological effects by itself, but it is possible that similar conditions could occur (i.e., heat and an alkali environment) and cause neurotoxicity due to chloroacetylenes generated from 1,1-dichloroethene at hazardous waste sites.

Signs of central nervous system toxicity were observed in animals after acute inhalation exposure. The toxic signs are similar across species and consist primarily of central nervous system depression, dyspnea, and narcosis, ultimately resulting in death (Klimisch and Freisberg 1979a, 1979b; Zeller et al. 1979a, 1979b). These signs can also be accompanied by lethargy, rough coats, and a hunched appearance (Zeller et al. 1979b). Acute exposure of rats to extremely high

concentrations (25,600 ppm for 10 minutes) induced increased sympathetic activity, resulting in cardiac arrhythmia (Siletchnik and Carlson 1974).

2.2.1.5 Reproductive Effects

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

Premating exposure of male rats to 55 ppm l,1-dichloroethene 6 hours/day, 5 days/week, for 11 weeks did not affect their fertility (Short et al. 1977b); no pre- or post-implantation losses occurred in untreated pregnant females mated to treated males in a dominant-lethal study. Similarly, inhalation exposure of male mice to 10 or 30 ppm 1,1-dichloroethene for 6 hours/day for 5 days appeared to have no adverse effect on fertility (Anderson et al. 1977). Decreased fertility was observed in rats following inhalation exposure to 50 ppm 1,1-dichloroethene for 5 days. The study authors attributed the decrease to infertility in males that ordinarily might not have been used but had to be included in the study in order to establish a sufficient group size. However. this could not be confirmed because of lack of sufficient details.

The highest NOAEL value from a reliable study for reproductive effects in each species and duration category is recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans following inhalation exposure to 1,l -dichloroethene.

1,l -Dichloroethene appears to produce both fetotoxic and developmental effects in laboratory animals (Short et al. 1977a). Prenatal exposure resulted in soft tissue anomalies in rats and skeletal defects in rats, mice, and rabbits. Maternal toxicity, as evidenced by decreased body weight and death, was also observed al developmentally toxic doses. Doses of 1,l -dichloroethene used in these studies ranged from 15 to 449 ppm. Increased mortality was observed in both pregnant and nonpregnant mice exposed to 144 ppm or more and rats exposed to 57 ppm or more. Skeletal anomalies in rats and mice and soft tissue anomalies in rats were observed at

15 ppm. Because of the high incidence of fetal resorptions observed in these initial experiments, Short et al. (1977a) conducted additional studies in mice. Pregnant animals were exposed via inhalation to various concentrations of 1,1-dichloroethene ranging from 41 to 112 ppm. The experiments were performed over different exposure durations that covered various phases of fetal development. Statistical analysis by two sample rank tests demonstrated that treatmentinduced increases in resorption frequency were significantly reduced at the shorter exposure periods, although the treatment-related weight loss was still evident in the dams. The viable pups demonstrated a variety of soft tissue anomalies, such as hydrocephalus, microphthalmia, cleft palate, and hydronephrosis. Skeletal anomalies were also observed.

A statistically significant increase in the incidence of skeletal anomalies was observed in the litters of rats exposed to 80 and 160 ppm 1,1-dichloroethene and in the litters of rabbits exposed to 160 ppm 1,l -dichloroethene (Murray et al. 1979). Developmental effects were evidenced by wavy ribs and delayed ossification in rat fetuses and skeletal alterations in rabbit fetuses. Fetotoxicity was indicated by increased resorption. A statistically significant decrease in maternal body weight gain was also noted at these concentrations. In this study, no statistically significant adverse effects were noted in rats exposed to 20 ppm or in rabbits exposed to 80 ppm 7 hours daily during pregnancy. A NOAEL for developmental toxicity following continuous inhalation exposure was not identified.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 2-1 and plotted in' Figure 2-1.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after inhalation exposure to 1,l -dichloroethene.

Dominant lethal gene mutations have not been found to occur after inhalation of 1,1-dichloroethene vapors in animals (Anderson et al. 1977; Short et al. 1977b). However, 1, 1-dichloroethene has produced deoxyribonucleic acid (DNA) damage, as indicated by a slight increase in repair rates in mouse kidney cells in which normal replicative DNA synthesis had been inhibited (Reitz et al. 1980). Inhalation of 1,1-dichloroethene has been associated with minimal rates of DNA

alkylation in mouse and rat kidney and liver cells (Reitz et al. 1980). These data suggest that inhalation exposure of rats to 55 ppm and mice to 10, 30, and 50 ppm of 1,1-dichloroethene for 6 hours/day for 5 days does not lead to significant levels of unrepaired DNA damage in the germ cells of the testes (as shown by the lack of a dominant lethal effect). However, exposure of mice and rats to 10 and 50 ppm for 6 hours induces a low incidence of DNA damage in the kidney cells of mice and minimal alkylation in the liver and the kidney of mice and rats. 1,l -dichloroethene appears to exert genotoxic effects on somatic cells but not on germ cells.

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No relationship between the occurrence of cancer in humans and occupational exposure (primarily chronic inhalation exposure) to 1,1-dichloroethene has been demonstrated. However, only two studies were available for analysis. In addition, neither study was large enough to demonstrate a relationship between cancer and 1,1-dichloroethene unless there was an overt causality.

Chronic occupational exposure to I,l-dichloroethene was not associated with the occurrence of angiosarcoma in rubber-plant workers (Waxweiler 1981). Similarly, no association was found between occupational exposure and cancer mortality in 1,1-dichloroethene production and polymerization plant workers (Ott et al. 1976). The Ott et al. (1976) study is limited in its usefulness in assessing the cancer risk to humans exposed to 1,1-dichloroethene. The cohort size was limited, the observation period was too short, and there was a small number of deaths from specific causes. No allowance was made for a latency period; thus, potential risk was underestimated. The Ott et al. (1976) study described liver enzyme changes in two workers and gave clinical chemistry findings comparing two cohorts. None of the clinical chemistry values were significantly different between the two cohorts.

The carcinogenicity of 1,1-dichloroethene in laboratory animals following inhalation exposure has been evaluated in intermediate and chronic studies with rats, mice, and Chinese hamsters (Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977). Exposure concentrations of 1,1-dichloroethene in these studies ranged from

10 to 200 ppm. Of the long-term inhalation bioassays conducted in laboratory animals to date, only the results of a study by Maltoni et al. (1985) in mice have provided some suggestive evidence of a carcinogenic effect associated with 1,1-dichloroethene exposure.

In a study reported by Maltoni et al. (1985), male and female Swiss mice were exposed by inhalation to 0, 10, or 25 ppm 1,1-dichloroethene 4 hours/day, 4-5 days/week, for 52 weeks, and then observed until spontaneous death occurred. Increases in both malignant and nonmalignant tumors were observed. In female mice of both treatment groups (10 and 25 ppm), increases in the incidence of carcinomas of the mammary gland occurred; however, no dose-response was evident. Lung tumors (most of which were benign pulmonary adenomas) increased in males at 10 ppm and in males and females at 25 ppm. Although the study authors stated that these increases were statistically significant, no statistical analyses were presented. The study authors concluded that no dose-response relationship could be established for either increased tumor incidence. Of the 150 high-dose males in the 25-ppm group examined, 28 had renal adenocarcinomas, but no such tumors were found in either the 30 males in the low-dose (10 ppm) group or the 186 control males. Renal adenocarcinomas are rare tumors in the Swiss mouse. The kidney tumors were accompanied by severe nephrotoxic effects including nephrosis. Moreover, an increased incidence of renal tumors in the male mice was only observed at doses that induced toxicity and which approximated the acutely lethal concentration. Only one female developed kidney tumorsj but there appeared to be no difference between the sexes with regard to the incidence of regressive changes in the kidney. Thus, it does not appear that the occurrence of nephrosis necessarily predisposes the animal to the development of kidney tumors.

An increased incidence of malignant mammary tumors and leukemia was reported in rats exposed to 100 ppm 1,1-dichloroethene 4-7 hours/day, 5 days/week, for 104 weeks (Cotti et al. 1988; Maltoni et al. 1985). Pregnant female rats were exposed on gestation day 12; the exposures continued in dams and ≈50% of the offspring (in 12-day and older embryos via transplacental exposure, followed by inhalation exposure for all progeny from this group) for 104 weeks. The remaining ≈50% were exposed for 15 weeks only. The highest tumorigenic response was seen in offspring treated for 104 weeks. The study authors concluded that under these exposure conditions (high doses during and after embryonal development), 1,1-dichloroethene is carcinogenic in rats. However. the results of this study are not definitive since the, study authors

did not present statistical analyses and used ambiguous terminology (i.e., “total malignant tumors”) to present the results.

Results of other inhalation studies with laboratory animals were negative regarding carcinogenicity (Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977). In studies by Lee et al. (1977, 1978), CD-l mice and CD rats were exposed to 0 or 55 ppm 1,1-dichloroethene for 1 year. Few hepatic hemangiosarcomas, hepatomas, bronchioalveolar adenomas, and skin keratoacanthomas were observed in experimentally treated mice; however, some of the rats exposed to 55 ppm 1,1-dichloroethene developed hemangiosarcomas of the mesenteric lymph nodes and the subcutaneous tissue. The incidence of these lesions, however, was not statistically significant. In a follow-up study, curcinogenicity was examined in rats and mice during a 12-month period (Hong et al. 1981). Except for mammary tumors in female mice, no significant increase in cumulative tumor incidence was observed in either species at 55 ppm 1,1-dichloroethene. The increased tumor incidences observed in the studies by Lee et al. (1977, 1978) and Hong et al. (1981) were not statistically significant.

Male and female Sprague-Dawley rats were exposed to 0, 25, or 75 ppm 1,1-dichloroethene via inhalation for 18 months (Quast et al. 1986). A statistically significant increase ($p<0.05$) in adenocarcinomas of the mammary gland was noted in the low-dose females (25 ppm). The study authors did not consider this increase related to 1,1-dichloroethene exposure because the incidence of mammary gland adenocarcinomas in the treatment groups was within the range of historical control data and was not dose related.

Both female and male rats were exposed to 0, 10, 25, 50, 100, or 150 ppm 1,l-dichloroethene for 52 weeks (Maltoni et al. 1985). The incidence of total mammary tumors (fibroadenomas, carcinomas, sarcomas, carcinosarcomas) increased in females in the 10- and l00-ppm exposure groups. However, evidence for a carcinogenic effect from inhalation exposure to 1,1-dichloroethene in this study was inconclusive because there was no clear dose-related increase in total r mammary tumor incidence, the latency time for mammary tumor incidence was similar in all treated and control groups, the incidence (62%) of spontaneous mammary tumors in controls was high, and the incidence of mammary gland carcinomas in treated groups was lower than that of controls.

2. HEALTH EFFECTS

The effects of chronic inhalation exposure of CD-1 mice and CD rats to 55 ppm 1,1-dichloroethene for 12 months was studied by Lee et al. (1978, 1979). There was no statistically significant increase in tumors at any of the sites examined compared to the respective control animals. However, 2 of 35 treated male rats and 3 of 35 treated mice exhibited hemangiosarcomas, an uncommon tumor type, while ncme were found in the controls. The study authors claimed that rats were more resistant than mice to the carcinogenic effects of 1,1-dichloroethene, but the data do not support this since there was no significant increase in the incidence of tumors in either species and the incidence of hemangiosarcomas was practically the same for the two species. The short duration of this study may have precluded observing tumors that have a longer latency period.

In a follow-up study, CD-1 mice and CD rats were exposed to 55 ppm 1,1-dichloroethene by inhalation for 1, 3, or 6 months (mice) or 1, 3, 6, or 10 months (rats) followed by a 12-month observation period (Hong et al. 1981). There was no statistically significant increase in the incidence of tumors in any of the treated animals compared to untreated animals. However, the study was limited by the following factors: high mortality occurred; a small number of animals (three to seven per sex per group) was used which decreased the ability of the study to detect a tumorigenic response; and the exposure durations were considerably less than the expected lifetime of the mice.

The negative findings of various inhalation studies may be partially explained by inadequate test conditions. Chronic-duration animal studies at or near the maximum tolerated dose are necessary to ensure an adequate power for the detection of carcinogenic activity (EPA 1986e). Study limitations for many of these investigations included less than lifetime exposure, use of concentrations well below or above the maximum tolerated dose, small numbers of animals, and/or limited gross or microscopic examinations (Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982, 1985; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977). These limitations impair the sensitivity of a test to detect a carcinogenic response.

EPA has derived an inhalation unit risk of $5x10^{-5}$ μg /m^3 for cancer risk associated with inhalation exposure to 1,1-dichloroethene based on the study by Maltoni et al. (1985) in mice (IRIS 1992). EPA indicates, however, that it may not be appropriate to use this inhalation unit risk if the air concentration exceeds 0.05 ppm. The air concentrations associated with the upper bound for an

individual lifetime cancer risk of 10^{-4} to 10^{-7} are $5x10^{-4}$ to $5x10^{-7}$ ppm. This range is plotted in Figure 2-1. The exposure concentration associated with an increased incidence of kidney adenocarcinoma (25 ppm) in male mice is presented in Table 2-1 and plotted in Figure 2-1.

2.2.2 Oral Exposure

2.2.2.1 Death

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

Death has been observed in laboratory animals following oral exposure to 1,1-dichloroethene. The database on the lethality of ingested 1,1-dichloroethene in animals consists primarily of gavage studies in fasted rats. However, there were a few studies located regarding death in mic, or other species.

Reported oral LD_{50} values in rats are ≈1,500 mg/kg (Jenkins et al. 1972; Jones and Hathway 1978a). The threshold for mortality in male rats is 50 mg 1,1-dichloroethene/kg in corn oil (Andersen and Jenkins 1977). The limited data available for mice indicate that this species is considerably more sensitive than rats to the lethal effects of ingested 1,1-dichloroethene. Reported LD_{50} values in mice are ≈200 mg/kg (Jones and Hathway 1978a).

Since all available data are from fasted animals, it is not possible to determine whether the amount of food intake of the animal influenced the lethality of ingested 1,1-dichloroethene, as it does during inhalation exposure. It has been demonstrated by Jenkins et al. (1972) that adrenalectomy in rats exacerbates the lethal effects of ingested 1,1-dichloroethene. These investigators reported an oral LD_{50} of 81 mg/kg for 1,1-dichloroethene in adrenalectomized rats. The mechanism and significance of this effect are unclear but probably involves a compromise in the animal's response to stress.

Oral administration of a single dose of 1,1-dichloroethene to fasted rats revealed that young male rats (100-200 g) appeared to be more susceptible than older rats to its lethal effects (Andersen and Jenkins 1977). This age-dependent difference in toxicity was not seen in females. Male mice

fasted before inhalation exposure showed signs of enhanced 1,1-dichloroethene toxicity compared to nonfasted rats.

In summary, ingested 1,1-dichloroethene is very toxic in at least two species of laboratory animals. Young animals and those with compromised stress responses appear to be most susceptible to these effects (Gosselin et al. 1984).

All LD_{50} values and LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located regarding systemic effects in humans following oral exposure.

1,1-dichloroethene has been shown to adversely affect several organ systems in laboratory animals. The major target organs of 1,1-dichloroethene toxicity in animals are the liver and kidney. In addition, some studies suggest that 1,1-dichloroethene may induce adverse effects on the respiratory and gastrointestinal systems following oral exposure.

No studies were located regarding cardiovascular, musculoskeletal, or dermal/ocular effects in animals following oral exposure to 1,l -dichloroethene. The systemic effects observed after oral exposure are discussed below.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No histopathological changes were observed in the lungs of nonfasted or fasted rats administered a single gavage dose of 200 mg/kg 1,1-dichloroethene in either corn oil, mineral oil, or an aqueous solvent (Chieco et al. 1981).

Pulmonary injury was observed in mice exposed to a single oral dose of 200 mg/kg (Forkert et al. 1985). Histopathological changes were observed in Clara cells within 24 hours, and these were accompanied by pulmonary edema, and hemorrhage. This damage appeared to be reversible;

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

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(G)	Once				1550 (LD50)	Jones and Hathway 1978a
2	Rat	(G)	Once				50 (LD_{LO}, 10% died)	Andersen and Jenkins 1977
3	Rat	(G)	Once				1510 (LD50)	Jenkins et al. 1972
4	Mouse	(G)	Once				194 (LD50[F]) 217 (LD50[M])	Jones and Hathway 1978a
Systemic								
5	Rat	(GO)	Once	Hepatic			100 (centrilobular and midzonal necrosis)	Kanz et al. 1991
6	Rat	(G)	Once	Hepatic	100[b]	400[b] (increased plasma levels of LDH, SDH, and transaminases)		Jenkins and Andersen 1978
				Renal	200[b]		400[b] (tubular necrosis; increased plasma creatinin and urea nitrogen)	
7	Rat	(G)	Once	Hepatic		25[b] (morphological changes in bile canaliculi and plasma membranes)		Kanz and Reynolds 1986

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

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
8	Rat	(GO)	Once	Hepatic		100[b] (decreased G6Pase and increased SAKT activity)		Jaeger et al. 1973b
9	Rat	(G)	Once	Hepatic		200[b] (decreased bile flow, increased plasma levels of GOT and LDH)		Moslen et al. 1985
10	Rat	(G)	Once	Resp	200			Chieco et al. 1981
				Cardio	200			
				Gastro		200 (edema of forestomach)		
				Hemato		200[b] (increased hemoglobin level)		
				Hepatic			200[b] (hemorrhagic liver and midzonal necrosis)	
				Renal		200[b] (granular "heme" casts in Henle's loop)		
				Other (body weight)	200			
11	Rat	(G)	Once	Hepatic		50[b] (increased SGOT and SGPT activity)		Chieco et al. 1981
12	Mouse	(G)	Once	Resp		200 (reversible damage and disruption of Clara cells)		Forkert et al. 1985
Developmental								
13	Rat	(W)	10 d Gd6-15 ad lib		40			Murray et al. 1979

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

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
INTERMEDIATE EXPOSURE								
Systemic								
14	Dog	(W)	97 d ad lib	Hemato Hepatic Renal	25 25 25			Quast et al. 1983
CHRONIC EXPOSURE								
Systemic								
15	Rat	(W)	2 yr ad lib	Hemato Hepatic Renal	19.3 10 19.3	19.3 (cytoplasmic vacuolization)		Rampy et al. 1977
16	Rat	(W)	2 yr ad lib	Hepatic		9 (hepatocellular fatty changes, accentuated hepatic lobular pattern)		Nitschke et al. 1983
17	Rat	(W)	2 yr ad lib	Hemato Hepatic	20 10	20 (hepatocellular swelling with midzonal fatty changes)		Quast et al. 1983
18	Rat	(W)	2 yr ad lib	Hemato Hepatic	30	9[c] (hepatocellular swelling with midzonal fatty changes)		Quast et al. 1983

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

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
19	Rat	(W)	2 yr ad lib	Hemato	25.6			Rampy et al. 1977
				Hepatic	12.6	25.6 (cytoplasmic vacuolization)		
				Renal	25.6			
Reproductive								
20	Rat	(W)	2 yr ad lib		30			Nitschke et al. 1983

[a]The number corresponds to entries in Figure 2-2.
[b]Animals were fasted prior to exposure.
[c]Used to derive a chronic Minimal Risk Level (MRL) of 0.009 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

ad lib = ad libitum; Cardio = cardiovascular; d = day(s); F = female(s); (G) = gavage; Gastro = gastrointestinal; Gd = gestation day(s); (GO) = gavage oil; GOT = glutamate-oxalacetate transaminase; Hemato = hematological; LD50 = lethal dose, 50% kill; LD_{LO} = lowest lethal dose; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; SAKT = serum alpha-ketoglutarate transaminase; SDH = sorbitol dehydrogenase; SGOT = serum glutamate-oxalacetate transaminase; SGPT = serum glutamic pyruvic transaminase; (W) = water; yr = year(s)

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

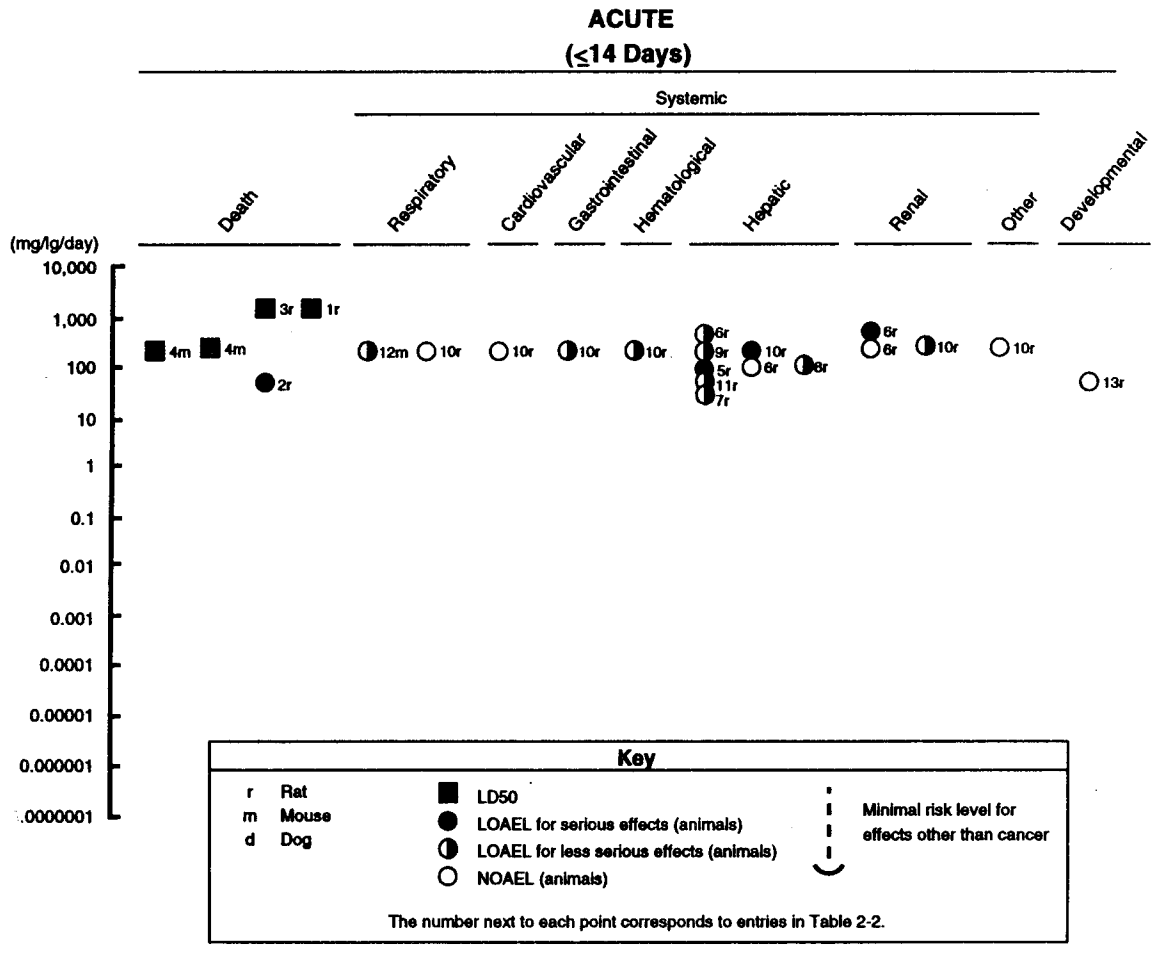
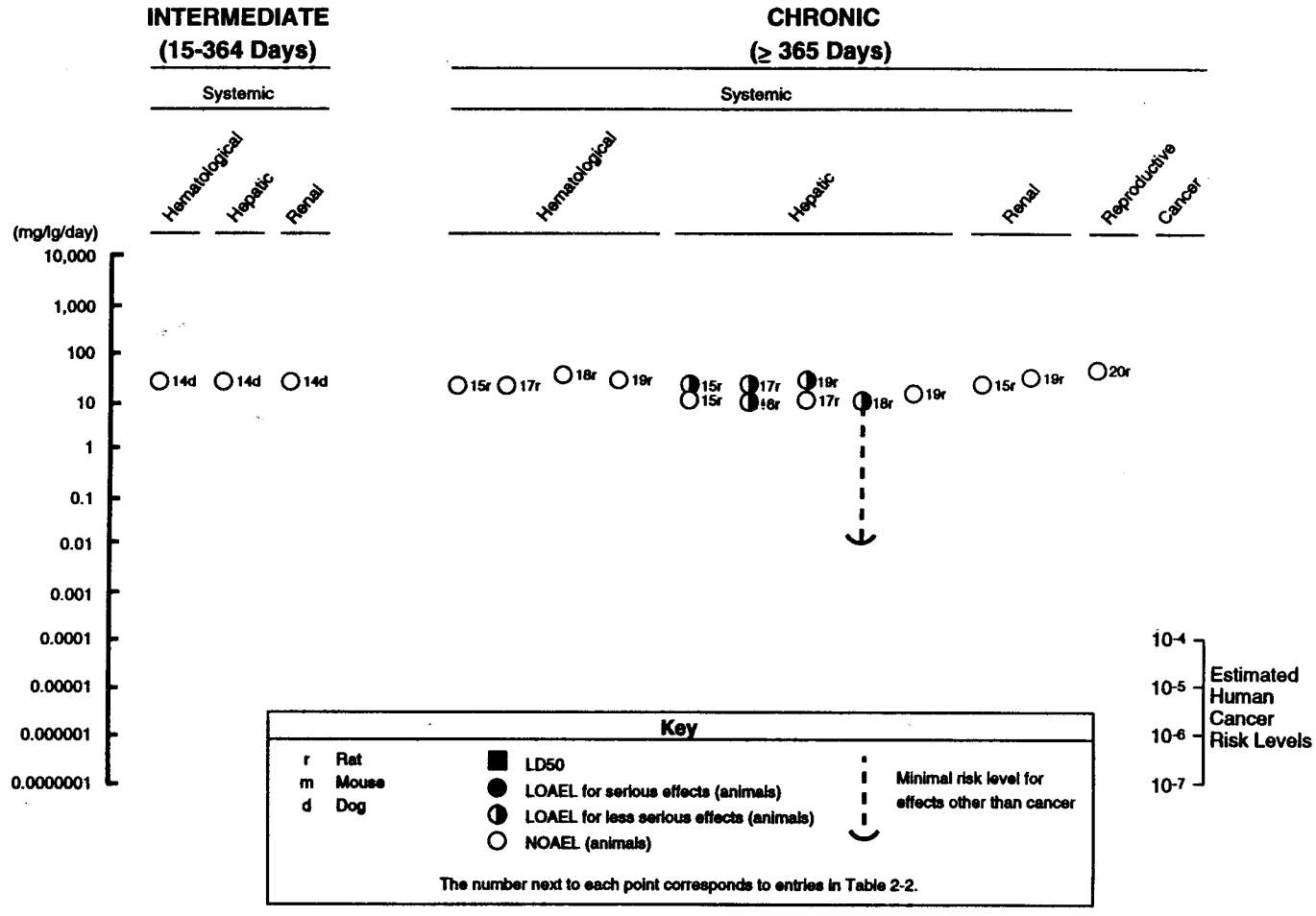


FIGURE 2-2. Levels of Significant Exposure to 1,1-Dichloroethene - Oral *(continued)*



cellular regeneration was evident within 5 days of treatment. The relevance of these findings to human exposure is questionable.

Gastrointestinal Effects. Edema of the forestomach was observed in fasted and nonfasted rats after a single gavage dose of 200 mg/kg (Chieco et al. (1981). However, this alteration was not associated with any discernible degenerative changes, and its relevance to human exposure is unknown. No acute-duration studies of 1,1-dichloroethene administered in food were located.

Hematological Effects. A significant increase ($p<0.001$) in plasma free hemoglobin was observed in fasted rats administered a single dose of 200 mg/kg 1,1-dichloroethene in mineral oil or in corn oil (Chieco et al. 1981). The effect was not as marked, although still significant ($p<0.05$), when 1,1-dichloroethene was given to nonfasted rats in either vehicle. According to the investigators, the effect does not represent a true hematological effect but is due to hemolysis of red cells trapped in the congested sinusoids of the injured liver.

No significant changes in hematological or clinical chemistry parameters were observed in dogs exposed to 25 mg/kg/day 1,1-dichloroethene in drinking water for 97 days (Quast et al. 1983). Similar results were observed in rats exposed to $\leq$30 mg/kg/day in drinking water for 2 years (Quast et al. 1983; Rampy et al. 1977).

Hepatic Effects. 1,1-dichloroethene is hepatotoxic in laboratory animals, particularly after ingestion of an acute dose. A complete spectrum of effects indicative of liver toxicity has been observed in animals following acute oral administration of 1,1-dichloroethene, and their incidence and severity tend to be dose related. Significant increases in serum enzyme markers of liver damage or dysfunction (aspartate transaminase, ALT and alanine transaminase, AST) have been noted in fasted rats after the ingestion of a single dose of 50 mg/kg or more (Andersen and Jenkins 1977; Jenkins and Andersen 1978; Moslen et al. 1989b). Acute exposure to 25 mg/kg or more induced bile canalicular injury in fasted rats (Kanz and Reynolds 1986; Moslen et al. 1989a). Histological evidence of liver damage as seen by the presence of pyknotic cells was noted following oral administration of 100 mg/kg to rats (Kanz et al. 1991). Ultrastructural changes in hepatocellular organelles such as morphological changes in bile canaliculi and plasma membranes have also been noted in fasted rats after a single dose of 25 mg/kg (Kanz and Reynolds 1986).

2. HEALTH EFFECTS

The food intake of animals and the dosing vehicle influence the hepatotoxicity of orally administered 1,l -dichloroethene in animals. Fasting exacerbates 1,l -dichloroethene-induced hepatotoxicity; nonfasted animals exhibit only mild effects at comparable doses (i.e., increases in organ weight) (Andersen and Jenkins 1977; Andersen et al. 1980; Chieco et al. 1981; Jenkins and Andersen 1978). The hepatotoxic effects of 1,1-dichloroethene in rats tend to be more severe when administered in mineral or corn oil than in 0.5% aqueous Tween 80 (Chieco et al. 1981). Study authors have suggested that an aqueous solution of Tween 80 facilitates the clearance of 1,l -dichloroethene from the body.

One study was located regarding hepatic effects in animals after intermediate exposure to 1,1-dichloroethene. No exposure-related gross or histopathological changes were observed in the livers of beagle dogs given 25 mg/kg/day in drinking water for 97 days (Quast et al. 1983).

Chronic studies have been performed in rats ingesting low levels (9-20 mg/kg/day) of 1,l-dichloro-ethene for 2 years. The results indicated few treatment-related changes. After 1 year of treatment, only a minimal increase in cytoplasmic vacuolation of hepatocytes was noted (Rampy et al. 1977). After 2 years, a minimal amount of hepatocellular swelling with midzonal fatty change was reported (Quast et al. 1983). Slight hepatocellular changes were observed in rats exposed to 1,1-dichloroethene in the drinking water at levels of 9 mg/kg/day *in utero*, during lactation, and through weaning into adulthood (Nitschke et al. 1983). A chronic oral MRL of 0.009 mg/kg (Quast et al. 1983) was calculated for 1,1-dichloroethene, as described in the footnote in Table 2-2.

Renal Effects. Evidence for 1,1-dichloroethene-induced kidney dysfunction has been observed in laboratory animals following acute oral exposure. Fasted rats given single gavage doses of 200 mg/kg or more in corn oil exhibited increased plasma urea and creatinine levels (at 400 mg/kg) (Jenkins and Andersen 1978). Histopathological changes (vacuolizalion, pigmentation, tubular dilation, and necrosis) were observed at 400 mg/kg. These changes were more severe in females, though some recovery was evident in females 96 hours after exposure. Histological changes such as granular heme casts in Henle's loop were observed in the kidneys of nonfasted and fasted rats administered single doses of 200 mg/kg by gavage in either corn oil, mineral oil, or an aqueous solvent (Chieco et al. 1981). As noted for hepatic effects, fasting exacerbates

1,l -dichloroethene-induced nephrotoxicity in animals; no renal effects were observed in nonfasted animals administered single doses of 400 mg/kg (Jenkins and Andersen 1978).

No renal effects were noted in animals following intermediate (Quast et al. 1983) or chronic (Rampy et al. 1977) oral exposure to 1,1-dichloroethene at doses of 30 mg/kg/day or less.

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

No effect on body weight was reported in rats following acute oral exposure to 200 mg/kg/day (Chieco et al. 1981).

2.2.2.3 Immunological Effects

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

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to 1,l -dichloroethene.

No adverse neurological effects on were identified after oral administration of 1,1-dichloroethene for any exposure duration in animals. The appearance and demeanor of the test animals were not affected in either an intermediate feeding study in dogs (25 mg/kg/day for 97 days) or a chronic study in rats (30 mg/kg/day or less for 2 years) (Quast et al. 1983). However, these results are only suggestive because no sensitive neurological tests were performed.

2.2.2.5 Reproductive Effects

Only one human study was located regarding neural tube defects in newborns after transplacental exposure to 1,l-dichloroethene via contaminated water (NJDH 1992a, 1992b). However, these data provide only suggestive evidence and therefore, should be interpreted with caution.

1,1-dichloroethene (99.5% purity) was administered in the drinking water of rats at dosages of 30 mg/kg/day or less for three generations. No dose-related changes were seen in reproduction or neonatal development (Nitschke et al. 1983). The study employed sufficient number of animals and used three dose levels. The NOAEL value for reproductive effects is listed in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

Only one human study was located regarding neural tube defects in newborns after transplacental exposure to 1,1-dichloroethene via contaminated water (NJDH 1992a, 1992b). However, these data provide only suggestive evidence and, therefore, should be interpreted with caution.

No effect on the number of implantations, live fetuses, or resorptions, sex ratio, or fetal weight were observed among the offspring of rats administered 40 mg/kg/day in the drinking water on gestation days 6 through 15 (Murray et al. 1979). The incidence of malformations, considered individually or collectively, among the rats given 1,1-dichloroethene was not significantly different from that of controls. There was, however, a marginal increase in crown-rump length in treated rats; the significance of this effect is unclear.

The highest NOAEL values for developmental effects in rats after acute exposure are listed in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

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

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

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

2. HEALTH EFFECTS

A number of chronic studies in rats and mice have evaluated the carcinogenicity of 1,1-dichloroethene by oral exposure (Maltoni et al. 1982, 1985; NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983; Rampy et al. 1977). Dosages of 1,1-dichloroethene in these studies ranged from 0.5 to 150 mg/kg/day. Administration was by gavage with the exception of two studies in which 1,1-dichloroethene was administered daily in the drinking water (Quast et al. 19%; Rampy et al. 1977). Major organs and tissues of treated and control animals in these investigations were subjected to both gross and microscopic examination.

A trend toward increased incidence of malignant and nonmalignant tumors in 1,1-dichloroethene-treated animals has been reported (NTP 1982; Ponomarkov and Tomatis 1980; and Quast et al. 1983). For example, rats exposed in *utero* to a single dose of 150 mg/kg I,l-dichloroethene and given weekly gavage doses of 50 mg/kg 1,1-dichloroethene from weanilg until 120 weeks of age had increased incidences of meningiomas and liver cell adenomas and {arcinomas compared to controls, but the difference was not statistically significant (Ponomarkob and Tomatis 1980). However, hyperplastic nodules of the liver in these animals were significantly increased ($p=0.04$). No significant increase in tumor incidence was seen in dams receiving a single oral dose of 150 mg/kg 1,1-dichloroethene (Ponomarkov and Tomatis 1980). Another study showed that male rats treated by gavage with 5 mg/kg 1,1-dichloroethene for 2 years had an increased incidence of pheochromocytomas, but when compared with control animals, the difference was not statistically significant (NTP 1982).

Statistically significant increases in certain types of tumors and cancers have been reported in bioassays in which rats and beagles were orally exposed to 1,1-dichloroethene (Quast et al. 1983); however, investigators discounted these results for various reasons. In a 2-year study by Quast et al. (1983), doses of 7, 10, and 20 mg/kg/day and 9, 14, and 30 mg/kg/day were administered in the drinking water of male and female rats, respectively. A statistically significant increase ($p<0.05$) in the incidence of combined mammary gland fibroadenomas and adenofibromas was noted in low-dose females. Because the incidence of these types of tumors was within the normal range of historical control data and because these tumors were not observed in higher-dose females or in treated males, the study authors did not consider these increases to be related to 1,1-dichloroethene ingestion. Thus, the results of the study are of questionable biological significance.

Clinical signs of toxicity were not generally observed in the various oral carcinogenicity studies on 1,1-dichloroethene; consequently, maximum tolerated doses may not have been achieved (NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983; Rampy et al. 1977). Chronic-duration animal studies at or near the maximum tolerated dose are necessary to ensure an adequate power for the detection of carcinogenic activity (EPA 1986e). Two of the oral carcinogenicity studies also used exposure periods that were less than lifetime (52-59 weeks); however, the animals were observed for 136 or 147 weeks allowing an adequate latency period for the development of lateappearing tumors (Maltoni et al. 1982, 1985).

EPA has derived an oral cancer slope factor (q_1*) of 0.6 $(mg/kg/day)^{-1}$ for cancer risk associated with oral exposure to l,l-dichloroethene based on the study by NTP (1982) in rats (IRIS 1992). The doses associated with the upper bound for individual lifetime cancer risk of 10^{-4} to 10^{-7} are $1.7x10^{-4}$ to $1.7x10^{-7}$ mg/kg/day. This range is plotted in Figure 2-2. At the highest dose level tested, 5 mg/kg/day, the incidence of pheochromocytomas increased in male rats, but the increase was not statistically significant.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to 1,l -dichloroethene.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to 1,l -dichloroethene. The dermal/ocular effects observed after dermal expostire are discussed below.

Dermal/Ocular Effects. Liquid 1,1-dichloroethene is irritating when applied to the skin of humans (EPA 1979b) and animals (Torkelson and Rowe 1981) after exposures lasting only a few minutes. Details concerning these studies are lacking, but it has been suggested that these irritant effects may be due to the inhibitor,*p*-hydroxyanisole (monomethyl ether of hydroquinone,

MEHQ), present in these formulations. MEHQ is an antioxidant which on contact results in skin depigmentation at concentrations of 0.25% or more (Busch 1985). Similarly, 1,1-dichloroethene is an ocular irritant in humans (EPA 1979b); this effect has also been ascribed to MEHQ.

2.2.3.3 Immunological Effects

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

2.2.3.4 Neurological Effects

Two cases of persistent nerve disorders were reported in subjects involved in manually cleaning tanks used to transport 1,1-dichloroethene copolymers (Fielder et al. 1985). The study is limited by a small sample size, lack of details regarding concentration, and a possible exposure via inhalation route.

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

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

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

The carcinogenicity of 1,1-dichloroethene following dermal exposure has been evaluated by Van Duuren et al. (1979). In this study, 1,1-dichloroethene doses of 40 or 121 mg (1,333 or 4,033 mg/kg, respectively) in acetone were applied three times weekly for 588 days or less to the skin of Swiss mice. No skin tumors were noted in treated animals. Increased incidences of

pulmonary papillomas and squamous-cell carcinomas of the forestomach were observed in treated mice; the incidences of these tumors, however, were not statistically different from controls. The results suggest 1,1-dichloroethene is inactive as a complete carcinogen (an agent that, if applied in sufficient concentrations, can induce tumors by itself) when applied repeatedly to the mouse skin.

The ability of 1,1-dichloroethene to act as a tumor initiator in the skin of Swiss mice was evaluated by Van Duuren et al. (1979). In two-stage tumorigenesis, a subthreshold dose of a tumor initiator is applied. An initiator does not generally produce tumors at this dose but causes "dormant" cell changes so that later repeated applications of a promoter (an agent that by itself will not produce tumors) will induce benign and malignant tumors at the site of application. 1,1-dichloroethene (121 mg or 4,033 mg/kg) in acetone was applied to the skin once, followed 2 weeks later by dermal application of the tumor promotor, phorbol myristate acetate (TPA), three times a week for 576 days or less. Untreated, vehicle-treated, and TPA-only-treated animals served as negative controls. A statistically significant ($p<0.005$) increase in the incidence of skin papillomas was recorded in treated mice compared to controls. These results indicate that 1,1-dichloroethene is a tumor-initiating agent in the Swiss mouse skin test.

2.3 TOXICOKINETICS

Data regarding toxicokinetics of 1,1-dichloroethene in humans are not available. Studies in animals indicate that 1,1-dichloroethene is readily absorbed and rapidly distributed in the body following inhalation and oral exposure. The oral absorption rate greatly depends on the type of vehicle used. Oily vehicles facilitate uptake. Uptake of 1,1-dichloroethene vapors is duration and dose dependent. However, the percentage of 1,1-dichloroethene uptake decreases as the exposure concentration increases, until an equilibrium is reached. 1,1-dichloroethene distributes mainly to the liver and kidney and does not appear to be stored or accumulated in the tissues. It is metabolized by the hepatic microsomal cytochrome P-450 system. This process gives rise to several possible reactive intermediates thought to be responsible for 1,1-dichloroethene toxicity. The major detoxification route for these intermediates are hydroxylation and conjugation with GSH. Therefore, metabolic interventions that deplete GSH (treatment with drugs, fasting, etc.) tend to increase 1,1-dichloroethene toxicity. Excretion of metabolites occurs primarily via the urine and exhaled air. Unmetabolized parent compound may also be eliminated via exhaled air. After high-level exposures, greater percentages of the dose are exhaled as unchanged 1,1-dichloro-

ethene. The physical/chemical properties of 1,1-dichloroethene indicate that absorption of 1,l -dichloroethene via dermal exposure is possible in humans. Information on the disposition and metabolism of 1,1-dichloroethene following chronic-duration exposures was not available.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding the absorption of 1,1-dichloroethene in humans following inhalation exposure.

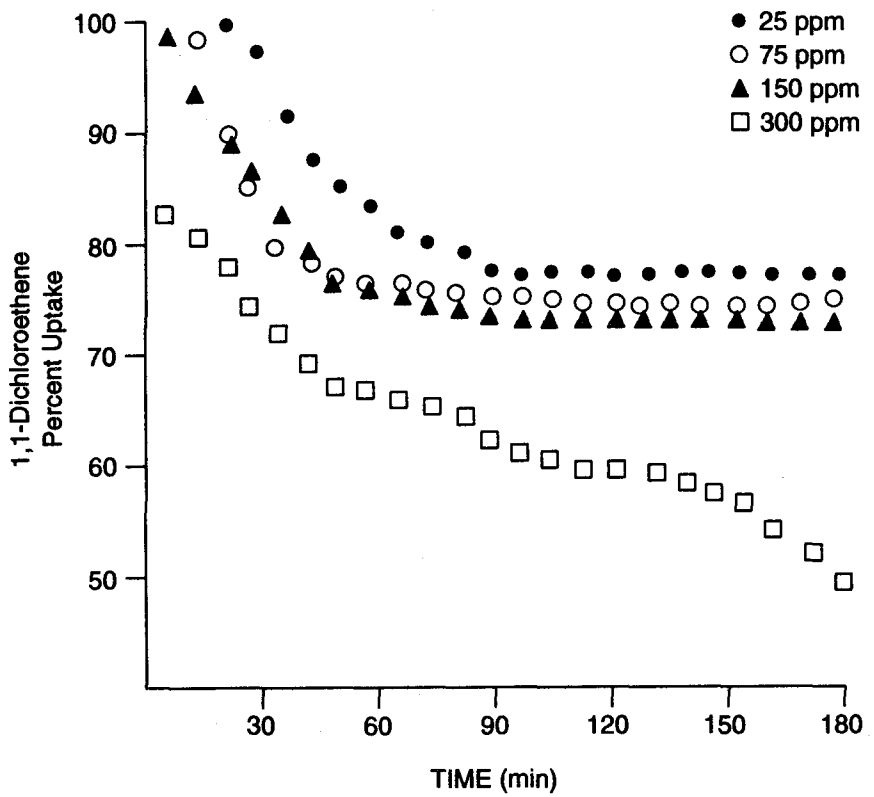
Studies in laboratory animals have demonstrated that 1,1-dichloroethene was rapidly absorbed following inhalation exposure (Dallas et al. 1983; McKenna et al. 1978b). No studies were located that described transport mechanisms for 1,1-dichloroethene absorption. Since 1,1-dichloroethene is a small organic molecule with chemical and physical properties similar to lipid soluble anesthetics, it is expected to penetrate pulmonary membranes easily and to enter the blood stream rapidly. Substantial levels of the parent compound were found in the venous blood of rats within 2 minutes after inhalation exposure (Dallas et al. 1983). Absorption of 1,l-dichloroethene was duration and dose-dependent, as shown in Figure 2-3. The percentage of systemic uptake decreased with time from the onset of exposure until an equilibrium was reached within 1 hour. Once equilibrium was reached, percentage uptake varied inversely with dose. The cumulative uptake of 1,1-dichloroethene following inhalation exposure was linear for levels of 150 ppm or less. However, at 300 ppm a steady state was never achieved. This finding indicates that 1,1-dichloroethene absorption following inhalation exposure was saturable at high levels, and the kinetics at these levels are best described by a cubic curve (Dallas et al. 1983).

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to 1,1-dichloroethene.

Studies in animals clearly indicated that doses of 1,1-dichloroethene ranging from 10 to 100 mg/kg were rapidly and almost completely absorbed from the gastrointestinal tract of rats and mice following oral administration in corn oil (Jones and Hathway 1978a; Putcha et al. 1986). Rapid

FIGURE 2-3. Percent Systemic Uptake of 1,1-Dichloroethene During Inhalation Exposures*



* Rats were exposed to 25, 75, 150, or 300 ppm 1,1-Dichloroethene for 3 hours. Percentage uptake was determined at 8-minute intervals. Each point represents the mean percentage uptake in four animals per group. Standard deviation brackets are omitted for the sake of clarity. Adapted from Dallas et al. 1983.

absorption occurred following oral administration of 200 mg/kg in an aqueous emulsion, as evidenced by the observation that the largest percentage of the dose was exhaled during the initial 15-minute period (Chieco et al, 1981). Peak blood levels were achieved in rats within 2-8 minutes after oral administration (Putcha et al. 1986). When 0.5-50 mg/kg of radiolabeled 1,1-dichloroethene was given to female rats, ≈10% of the parent compound was recovered in the expired air by 1 hour after exposure, indicating that oral absorption was rapid (Reichert et al. 1979). After oral administration to rats of 1,1-dichloroethene labeled with radioactive carbon (^{14}C), 81-99.8% of the administered radioactivity was recovered within 72 hours (Reichert et al. 1979). Studies have shown that 9-21% was recovered in the expired air, 53.9% in urine, 14.5% in feces, 2.8% in the carcass, and 7.5% in the cage rinse following oral administration of 1 or 5 mg ^{14}C-1,1-dichloroethene/kg (McKenna et al. 1978a; Reichert et al. 1979). After a dose of 50 mg ^{14}C-1,1-dichloroethene/kg, 19% and 29% of the parent compound was excreted via lungs in nonfasted and fasted rats, respectively (McKenna et al. 1978a). These results suggest that 1,1 -dichloroethene may be rapidly and completely absorbed in humans following oral exposure (e.g., via ingestion of contaminated groundwater).

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after dermal exposure to 1,l -dichloroethene. Nonetheless, the physical/chemical properties of 1,l -dichloroethene indicate that dermal absorption of 1,1-dichloroethene is probable. 1,1-dichloroethene is a small organic molecule with properties similar to the lipid-soluble anesthetics. Thus, liquid 1,1-dichloroethene is expected to readily penetrate the skin, which is a lipid-rich tissue. However, with a vapor pressure of greater than 500 torr at room temperature, the rate of evaporation would be rapid leaving only a short time for skin penetration.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans after inhalation exposure to 1,l-dichloroethene.

Following inhalation exposure of rats to 10 or 200 ppm of ^{14}C-labeled 1,1-dichloroethene, the highest level of radioactivity was found in the liver and kidneys after 72 hours, with only very small amounts present in other tissues (McKenna et al. 1978b). These authors found that the tissue burden/g of tissue (mg equivalents of ^{14}C-1,1-dichloroethene/g of tissue/total mg equivalents recovered per rat) in the liver, kidneys, and lungs of fasted rats were significantly greater than in nonfasted rats at both exposure levels, even though the total accumulation of ^{14}C in fasted rats was less than in nonfasted rats. The results of this study suggest that in fasted rats the ^{14}C is retained in specific target tissues and not distributed randomly in all tissues.

Preferential accumulation of radioactivity was reported in the kidney and liver of rats exposed to 2,000 ppm radiolabeled 1,1-dichloroethene for 2 hours (Jaeger 1977a). Fasted rats had higher levels of label than nonfasted rats in these tissues. Examination of ^{14}C activity at the subcellular level in these two tissues revealed that significantly more water-soluble ^{14}C activity was present in the cytosolic fractions of fasted rats. This observation suggests that distribution pathways for metabolism differ according to the amount of food ingested by the animals.

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to 1,1-dichloroethene.

1,1-dichloroethene was rapidly distributed to all tissues examined following a single oral dose of the ^{14}C-labeled compound to rats (Jones and Hathway 1978b). The highest amount of radioactivity was found in the liver and kidneys within 30 minutes of administration. More general redistribution throughout the soft tissues of the body followed.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to 1.1-dichloroethene.

2.3.2.4 Other Routes of Exposure

In a study by Okine et al. (1985) in which mice were administered a single intraperitoneal injection of 125 mg/kg of ^{14}C-l ,l -dichloroethene, radioactivity was distributed to some extent to all examined tissues with peak levels seen 6 hours after administration. The highest levels of radioactivity were found in the kidney, liver, and lung with lesser amounts in the skeletal muscle, heart, spleen, and gut.

2.3.3 Metabolism

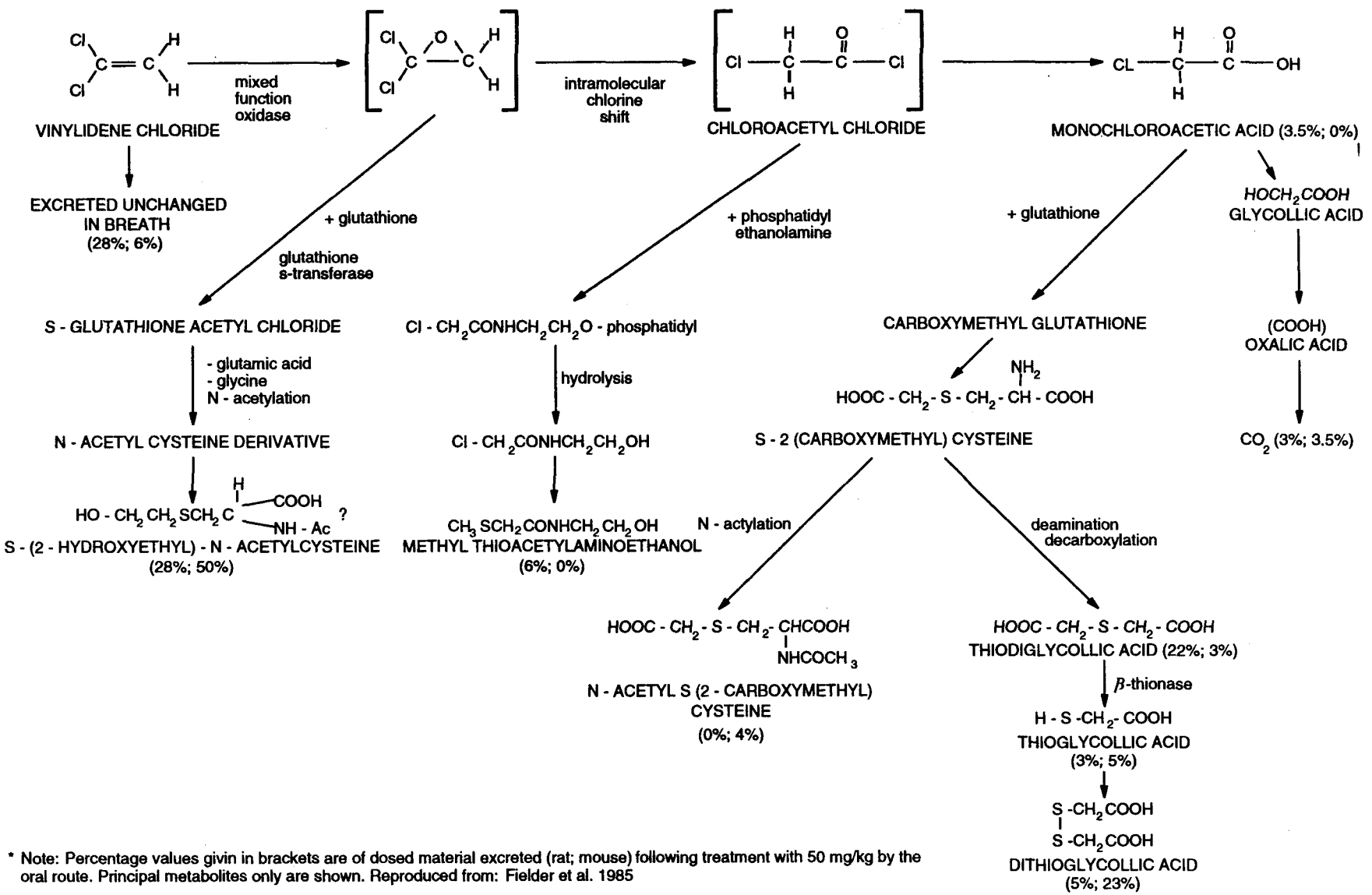
No studies were located regarding metabolism in humans following inhalation, oral, or dermal exposure to 1,1-dichloroethene.

Some evidence from animal studies suggests that at least the initial metabolic transformations in humans may be similar to those described in animals. Liver cells from a human subject together with Arochlor- pretreated S-9-activated 1,1-dichloroethene induced unspecified mutagenic metabolites in *Salrnonella typhimutium* assay (Jones and Hathway 1978c). This suggests that reactive metabolites may also be produced in humans.

The metabolism of 1,1-dichloroethene following oral administration in rats has been extensively studied (Jones and Hathway 1978a, 1978b; McKenna et al. 1978a; Reichert et al. 1979). These studies demonstrate that 1,l-dichloroethene undergoes biotransformation, and several metabolites have been identified. An overall summary of the metabolic pathway of 1,1-dichloroethene in animals is presented in Figure 2-4.

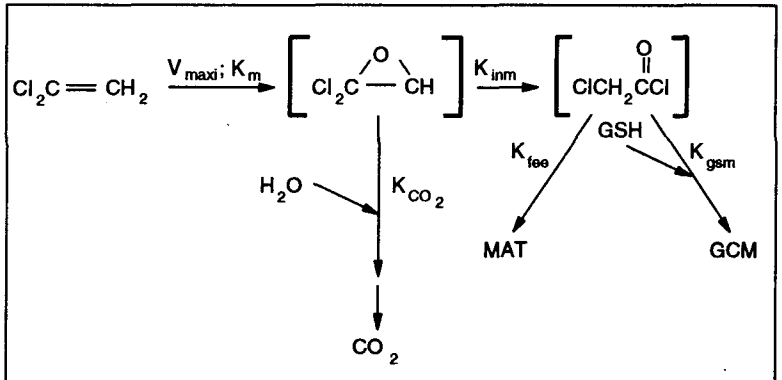
A physiologically based pharmacokinetic model for 1,1-dichloroethene based on its oxidative metabolism by the P-450 cytochrome system and subsequent conjugation with GSH, a principal pathway, was developed by D'Souza and Anderson (1988) (see Figure 2-5). Their model demonstrates that because 1,l-dichloroethene has a low blood-to-air partition coefficient and saturable metabolism, the metabolism of 1,1-dichloroethene is sensitive to the rate of absorption. Furthermore, 1,1-dichloroethene's metabolic pathway (i.e., the percentage of l,l-dichloroethenc exhaled, metabolized, and conjugated with GSH) is different for different routes of exposure and

FIGURE 2-4. Metabolic Pathway of 1,1-Dichloroethene in Animals*

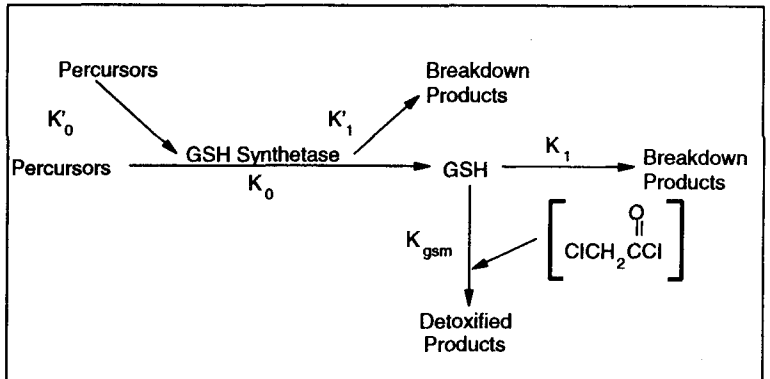


* Note: Percentage values givin in brackets are of dosed material excreted (rat; mouse) following treatment with 50 mg/kg by the oral route. Principal metabolites only are shown. Reproduced from: Fielder et al. 1985

FIGURE 2-5. Physiologically Based Pharmacokinetic Model for 1,1-Dichloroethene*



Scheme I. Model for 1,1-Dichloroethene metabolism pathways.



Scheme II. GSH synthesis and depletion by chloroacetyl chloride.

GCM Glutathione - conjugated metabolite.

GSH Glutathione concentration

K_{fee} First-order rate constant for formation of MAT.

K_{gsm} First-order rate constant for formation of GCM.

K_{inm} First-order rate constant for chloroacetyl chloride formation.

K_m Michaelis constant for oxidative pathway.

K_0 Zero-order glutathione synthesis, time and GSH dependent.

$K_{0'}$ Glutathione synthetase formation.

K_1 First-order rate constant for glutathione breakdown.

$K_{1'}$ First-order rate constant for glutathione synthetase breakdown.

MAT Metabolite available for toxicity.

V_{max} Maximum velocity of oxidative pathway.

* Reproduced from: D'Souza and Anderson 1988.

Parameters Used In The 1,1-Dichloroethene PB-PK Model	
Partition Coefficients	
Liver:blood	1.1
Richly perfused:blood	1.1
Slowly perfused:blood	0.6
Fat:blood	18.4
Blood:air	5.0
Kinetic Constants	
V_{max} (mg hr^{-1})	2.6
K_m (mg $liter^{-1}$)	0.25
K_{gsm} ($\mu M^{-1} hr^{-1}$)	0.33
K_{fee} (hr^{-1})	50
K_{inm} (hr^{-1})	9000
K_{co_2} ($M^{-1} hr^{-1}$)	1.82×10^{-5}
H_2O (M)	55

dose levels. This model, which the study authors verified experimentally, is useful in predicting the kinetics and potential toxicity of 1,1-dichloroethene under various exposure conditions.

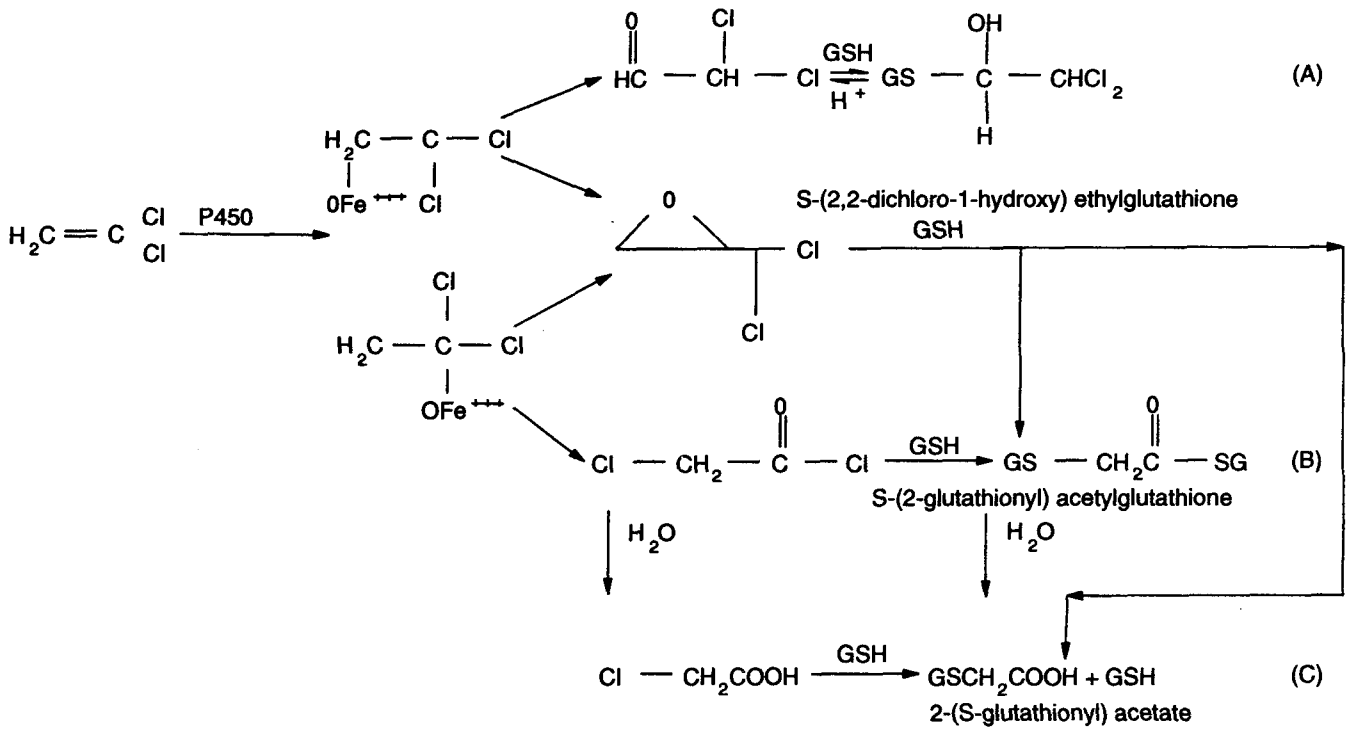
The hepatic cytochrome P-450 isozyme, P-450 2E1, is believed to play a role in the metabolic toxification of DCE in the liver (Kainz et al. 1993). An initial step in the metabolism of 1,1-dichloroethene may be the formation of the epoxide (oxirane) intermediate, 1,1-dichloroethylene oxide; however, this reactive compound has never been isolated after 1,1-dichloroethene administration in laboratory animals (Jones and Hathway 1978b; McKenna et al. 1977; Reichert et al. 1979).

An alternate metabolic scheme that does not go through the epoxide intermediate was proposed based on studies in isolated hepatocytes by Liebler et al. (1985, 1988) and is presented in Figure 2-6.

The main biotransformation pathways for 1,1-dichloroethene in the rat may involve conjugation with GSH, either with the epoxide or following rearrangement of the epoxide to chloroacetylchloride, with subsequent hydrolysis to monochloroacetic acid. This is consistent with the observation that exposure to 1,1-dichloroethene depletes GSH levels in the liver (Jaeger et al. 1974; Reichert et al. 1978; Reynolds et al. 1980). For example, Reynolds et al. (1980) reported a linear relationship in rats between intraperitoneally administered 1,1-dichloroethene and GSH depletion over the range of 20-100 mg/kg; above this level GSH depletion reached a plateau. The maximum reduction seen (70%) occurred 4 hours after treatment, with a subsequent gradual recovery to normal levels within 24 hours. These findings have led several investigators to suggest that 1,1-dichloroethene-induced hepatotoxicity is related to the depletion of hepatic GSH levels, thereby permitting the reactive intermediate to bind to and alkylate hepatic macromolecules instead of being detoxified, ultimately leading to cell death (Jaeger et al. 1974; McKenna et al. 1977, 1978a; Reynolds et al. 1980).

Conjugation of monochloroacetic acid with GSH followed by β-thionase activity appeared to be the major metabolic route on a quantitative basis in rats since thiodiglycollic acid was the predominant urinary metabolite (Jones and Hathway 1978a), this metabolite, however, only comprised 25% of ^{14}C urinary activity in another study (McKenna et al. 1978c). Forty-five percent of the activity was contributed by *S*-(2-hydroethyl)-*N*-acetylcysteine. Other metabolites

FIGURE 2-6. General Proposed Scheme for Oxidative Conjugative Metabolism of 1,1-Dichloroethene Not Metabolized Via the Epoxide Intermediate*



*Reproduced from Liebler et al. (1985)

identified in this pathway include monochloroacetic acid itself, thioglycolic acid, and dithioglycollic acid. However, direct GSH detoxication of the epoxide also apparently occurred to a significant degree, as demonstrated by the formation of glutathionyl acetyl chloride with subsequent breakdown to an *N*-acetyl cysteine derivative.

Evidence suggests that enzymatic hydration of the epoxide by epoxide hydrolase is a minor pathway in the metabolism of 1,1-dichloroethene in rats. Exacerbation of 1,1-dichloroetheneinduced toxicity in rats by diethyl maleate and various epoxide inhibitors following inhalation exposure was directly related to their ability to decrease GSH levels, rather than their ability to competitively inhibit epoxide hydrolase (Andersen et al. 1980).

An alternative metabolic pathway (i.e., one not involving GSH conjugation) to account for the presence of the metabolite methylthioacetylaminoethanol was proposed by Reichert et al. (1979). They suggested that chloroacetylchloride, instead of being hydrolyzed to monochloroacetic acid, reacts with membrane phosphatidyl ethanolamine, which is enzymatically cleaved to yield the ethanolamine derivative of chloroacetic acid. The thiomethyl group is then probably transferred from methionine to the metabolite as a result of direct nucleophilic attack.

The pathways of 1,1-dichloroethene metabolism in the mouse were similar to those seen in the rat except that the rate of metabolism was greater in the mouse (i.e., a greater proportion of administered 1,1-dichloroethene was metabolized per given dose level by the mouse than the rat) (Jones and Hathway 1978a). A predominant urinary metabolite of 1,1-dichloroethene found in mice was the *N*-acetylcysteine derivative produced by GSH conjugation to detoxify the epoxide intermediate. In mice there were quantitatively greater amounts of water-soluble urinary metabolites present in the urine (and consequently less parent compound in the expired air) attesting to a greater metabolic capacity. Furthermore, β-thionase activity was more pronounced since more dithioglycollic acid was found than thiodiglycollic acid (Jones and Hathway 1978a). In addition, Oesch et al. (1983) pointed out that 1,1-dichloroethene may have different effects on cytosolic GSH transferase activity and that this difference may have contributed to the species differences observed.

^{14}C- 1,1-DICHLOROETHENE covalently binds preferentially to liver and kidney tissues following administration, which may provide a basis f& the toxic effects seen in these organs (Jaeger et al.

1977a; McKenna et al. 1977, 1978a). A linear increase in the amount of covalently nound radioactivity in the liver of rats exposed to 10-200 ppm ^{14}C- 1,l -dichloroethene by inhalation for 6 hours was reported by McKenna et al. (1977). However, GSH depletion plateaued at about 200 ppm. Therefore, the actual amount of reactive metabolite formed and available for binding was probably determined by a combination of both activation and detoxication pathways.

The increased severity of hepatotoxic and nephrotoxic effects induced by 1,1-dichloroethene in the mouse, compared to the rat, may be partially explained by the observation that greater amounts of covalently bound reactive material were found in these two tissues in the mouse than in the rat following exposure to the same dose of 1,1-dichloroethene (McKenna et al. 1977). Levels of covalently bound material were six times higher in the mouse kidney than in the rat kidney (McKenna et al. 1977). Similar results were reported by Short et al. (1977d) when a single dose of ^{14}C-1,1-dichloroethene was injected intraperitoneally into mice. The highest level of covalently bound radioactivity was seen in the mouse kidney. The study authors found that pretreatment with disulfiram also reduced the amount of covalent binding. The study authors speculated that disulfiram may reduce the activation of 1,1-dichloroethene and increase the extent of its detoxification. Thus conjugation of reactive intermediates of l,l-dichloroethetle with GSH is a major detoxification mechanism in laboratory animals because it reduces the amount of reactive material available to covalently bind to cellular macromolecules.

1,1-dichloroethene can also potentially form adducts with hemoglobin, as has been observed with ethylene oxide (Tornyvist et al. 1986). Electrophilic intermediates, such as the epoxide formed in 1,1-dichloroethene metabolism, may bind to proteins in hemoglobin, similar to reactions demonstrated for liver and kidney (McKenna et al. 1977).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion in humans following inhalation exposure to 1,l -dichloroethene.

Elimination of 1,1-dichloroethene by rats following inhalation exposure to low levels is rapid, with the majority of the compound eliminated as metabolites in the urine, and very little (1% of the administered dose) eliminated as the unchanged parent compound in the expired air (McKenna et al. 1973). After exposure to low levels (25-150 ppm) of 1,1-dichloroethene, steady-state levels of 1,1-dichloroethene in the expired air are achieved within 30-45 minutes, indicating that elimination is first-order at low levels of exposure (Dallas et al. 1983). Steady-state levels of 1,1-dichloroethene in expired air are never reached when exposure levels approach 200-300 ppm because metabolic processes are saturated. When metabolic processes become saturated, increased amounts of 1,1-dichloroethene can easily be eliminated unchanged via the lung, since 1,1-dichloroethene is volatile (VP=500 torr at 20°C) and relatively insoluble in blood. Following cessation of exposure, concentrations of 1,1-dichloroethene in both blood and breath were observed to fall rapidly (Dallas et al. 1983). Similar results were reported by McKenna et al. (1978b).

1, 1-dichloroethene exhibited a biphasic elimination profile following inhalation exposure in rats (McKenna et al. 1978b). The first phase had a half-life of about 20 minutes for the elimination of unchanged 1,1-dichloroethene in breath and 3 hours for the elimination of water-soluble metabolites in urine. The second phase had a half-life of about 4 hours in breath and 20 hours in urine. The bulk of the material was eliminated in both the breath and the urine during the rapid phase. Fasting did not appear to affect the elimination kinetics of 1,1-dichloroethene following inhalation exposure in rats (McKenna et al. 1978b).

Information is limited on elimination in mice following inhalation exposure to 1,1-dichloroethene. However, McKenna et al. (1977) reported that at low levels of exposure (10 ppm for 6 hours), somewhat smaller amounts of unchanged 1,1-dichloroethene were eliminated in the expired air of mice and larger amounts of water-soluble metabolites were found in the urine of mice compared to levels observed in rats. This indicates that mice metabolize 1,1-dichloroethene at a greater rate than rats.

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans following oral exposure to 1,1-dichloroethene.

2. HEALTH EFFECTS

Elimination of 1,1-dichloroethene and its metabolites following oral administration in rats is very similar to that seen following inhalation exposure. Following oral administration of 1 mg/kg ^{14}C-1,1-dichloroethene in corn oil, less than 1% of the administered dose was excreted unchanged in the expired air, with 8-14% of the administered dose recovered as ^{14}C-carbon dioxide. The bulk of the administered ^{14}C-1,1-dichloroethene (44-W% of the administered dose) was eliminated in the urine within 3 days, most within the first 24 hours. Smaller amounts of water-soluble metabolites (8-16% of the administered dose) were found in the feces (Jones and Hathway 1978b; McKenna et al. 1978a; Reichert et al. 1979). Following the oral administration of higher doses to rats (50 mg/kg ^{14}C-1,1-dichloroethene), a higher proportion of unchanged parent compound (16-30% of the administered dose) was excreted in the breath with a concomitant reduction in the amount of expired carbon dioxide (3-6% of the administered dose) and urine metabolites (35-42% of the administered dose) (Jones and Hathway 1978b; McKenna et al. 1978a; Reichert et al. 1979). Similar but more marked trends were observed at even higher doses (Chieco et al. 1981; Jones and Hathway 1978b). Thus, metabolic processes become saturated at rather low dose levels.

The elimination of orally administered 1,1-dichloroethene is triphasic according to Putcha et al. (1986); however, McKenna et al. (1978b) and Reichert et al. (1979) reported that elimination is biphasic. The first phase identified by Putcha et al. (1986) occurred almost immediately, within the first few minutes after exposure, and the second two phases corresponded to those observed by the other investigators. Half-lives for the two phases of elimination after inhalation exposure were 20 minutes and 1 hour in the breath and 6 hours and 17 hours in the urine.

The amount of food ingested in the previous 24 hours slightly modifies the elimination of 1,1-dichloroethene by rats after oral administration. It was found that 19% of a 50-mg/kg dose was excreted unchanged via the lungs of nonfasted rats, whereas 29% was excreted by fasted rats (McKenna et al. 1978b). This finding provides evidence that fasted rats eliminate unchanged 1,1-dichloroethene to a greater extent than nonfasted rats. However, elimination of nonvolatile metabolites was slightly greater in nonfasted animals than in fasted animals, indicating a reduced capacity for metabolism in fasted rats.

Mice eliminate more 1,1-dichloroethene as water-soluble metabolites in the urine than do rats at comparable doses (Jones and Hathway 1978a). These results suggest that mice also metabolize orally administered 1,1-dichloroethene to a greater extent than rats.

2.3.4.3 Dermal Exposure

No studies were located regarding the excretion of 1,1-dichloroethene in humans or animals following dermal exposure to 1,1-dichloroethene.

2.3.4.4 Other Routes of Exposure

Using the physiologically based pharmacokinetic model developed for 1,l -dichloroethene discussed in Section 2.33, D'Souza and Anderson (1988) demonstrated that the half-life of 1,1-dichloroethene in blood is not representative of metabolism rates, but rather more closely corresponds to reeyuilibration of 1,1-dichloroethene from fat. Consequently, rats with a greater amount of fat deposits had longer 1,1-dichloroethene blood half-lives following intravenous administration. This finding could have important implications for obese individuals exposed to high levels of 1,1-dichloroethene.

2.3.5 Mechanisms of Action

The specific mechanism by which 1,1-dichloroethene is transported across the gastrointestinal wall or across the pulmonary epithelium is not known. However, because of its high lipid solubility, it is expected that 1,1-dichloroethene will easily penetrate biological membranes following a concentration gradient. Similarly, no information was found regarding the mechanism by which 1,1-dichloroethene is transported in the blood; however, it is reasonable to assume that I,1 dichloroethene will dissolve in the lipid fraction of the blood.

It is well known that the toxicity of 1, 1-dichloroethene is due to biotransformed 1,1-dichloroethene and not to the parent compound (Andersen et al. 1978, 1980; Jaeger et al. 1977a; Jones and Hathway 1978c). 1,1-dichloroethene is initially oxidized by the hepatic cytochrome P-450 system with the formation of reactive and electrophilic products such as epoxides, acyl chlorides, and halogenated aldehydes, which are responsible for the liver toxicity via alkylation of

macromolecules (Forkert et al 1986). These reactive intermediates form GSH *S*-conjugates by the action of glutathione *S*-transferases located in the hepatic cytosol and microsomes. GSH *S*-conjugates that are primarily secreted from the hepatocytes into plasma and *S*-conjugates entering the circulation after reabsorption from the small intestine are ultimately delivered to the kidney where they undergo glomerular filtration (Dekant et al. 1989). In the kidney, GSH Sconjugates may be metabolized to the corresponding cysteine S-conjugate, which may be acetylated to form the corresponding mercapturic acid and excreted in the urine (Vamvakas and Anders 1990). However, cysteine S-conjugates may also be metabolized by β-lyase, an enzyme located in the renal proximal tubule cells; the resulting unstable thiols in turn yield electrophilic products whose interactions with macromolecules are associated with nephrotoxicity. In summary, GSH *S*-conjugate formation of nephrotoxic haloalkenes competes with hepatic cytochrome P-450 for substrates. The relative extent of these reactions *in vivo* appears to be decisive for the initiation of adverse effects either in the liver (via oxidation products generated by P-450 system) or in the kidney (via formation and renal processing of S-conjugates).

2.4 RELEVANCE TO PUBLIC HEALTH

Exposure to 1,l -dichloroethene in an occupational setting is most likely to occur via a combination of the inhalation and dermal routes. The general population is most likely to be exposed to 1,1-dichloroethene by inhalation of contamination and oral consumption of contaminated food or water. Limited information is available on the human health effects following exposure to 1,1-dichloroethene. This information comes primarily from case reports and/or insufficiently detailed mortality studies wherein the concentration and duration of exposure to 1,1-dichloroethene were not quantified. Concurrent exposure to other toxic substances cannot be ruled out in most of these cases. Nevertheless, the information available indicates that relatively high concentrations of inhaled 1,1-dichloroethene can induce adverse neurological effects after acute-duration exposure, and that 1,1-dichloroethene is associated with liver and kidney toxicity in humans after repeated, low-level exposure. Considerable information exists regarding the effects of 1,1-dichloroethene in animals after inhalation and oral exposure. The liver and kidney, and possibly the lungs, can be considered target organs for 1,1-dichloroethene by both routes of exposure. In addition, cardiovascular, neurological, developmental, and genotoxic effects were reported after inhalation of 1,1-dichloroethene, and gastrointestinal effects occurred after oral exposure. The evidence for 1,1-dichloroethene carcinogenicity is inadequate in humans

and is limited in animals. Information regarding toxicokinetics in animals suggests that 1,1-dichloroethene does not tend to accumulate in the body. Background levels found in air and drinking water supplies (see Section 5.4) are not likely to cause adverse health effects in humans. For populations living near waste sites and/or facilities that manufacture or store 1,1-dichloroethene, the most likely routes of exposure are inhalation and oral (through contaminated water).

There is convincing evidence from animal studies to indicate that 1,1-dichloroethene toxicity is mediated by metabolism to reactive intermediates that act at the cellular level to ultimately compromise the viability of the target tissues. While the metabolic pathways for 1,l -dichloroethene are similar in the rat and mouse, the rate of metabolism is greater in the mouse, resulting in greater concentrations of toxic metabolites. Thus, the severity of 1,1-dichloroethene-induced toxicity in humans probably depends on the extent to which 1,1-dichloroethene is metabolized and which intermediates are formed.

Groups of people who should be specifically cautioned against exposure to 1,1-dichloroethene include the very young; the elderly; pregnant women; those who ingest alcohol; people using phenobarbital (or possibly other hepatic enzyme-inducing drugs); people who, for whatever reason, are fasting; and those with cardiac, hepatic, renal, and certain central nervous system dysfunctions.

Minimal Risk Levels for 1,1-Dichloroethene

Inhalation MRLs

- An MRL of 0.02 ppm has been derived for intermediate-duration inhalation exposure (15-364 days) to 1,1-dichloroethene. This MRL is based on a NOAEL of 5 ppm for hepatic effects in guinea pigs continuously exposed to 1,1-dichloroethene (Prendergast et al. 1967). Increased SGPT and alkaline phosphatase activity and decreased lipid content were observed at 48 ppm.

An MRL has not been derived for acute inhalation exposure (14 days or less) to 1,1-dichloroethene. A study by Reitz et al (1980) reported adverse kidney effects in mice exposed to 10 ppm for 6 hours. This appears to be the most sensitive end point identified; however, study limitations,

such as the small number of animals used (three to six males) and the ambiguous description of the incidence of the lesions (0-20% of the animals), precluded derivation of an acute-duration inhalation MRL. In addition, an acute-duration MRL could not have been derived since the renal effects occurred at a lower concentration than did effects following intermediate-duration exposure to 1,l -dichloroethene.

An MRL has not been derived for chronic inhalation exposure (365 days or more) to 1,1-dichloroethene. Adverse hepatic effects were observed in rats exposed to a concentration of 25 ppm 1,1-dichloroethene 6 hours/day, 5 days/week, for 18 months (Quast et al. 1986). Few chronic inhalation studies were identified, and the one conducted by Quast et al. (1986) provided the most complete information and identified the most sensitive end point. However, a serious LOAEL of 15 ppm for developmental effects in rats and mice following acute exposure to 1,1-dichloroethene was reported by Short et al. (1977a) which precluded derivation of a chronic-duration inhalation MRL.

Oral MRLs

- An MRL of 0.009 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to 1,1-dichloroethene. This MRL is based on the development of hepatocellular changes observed in rats exposed to 50 ppm 1,1-dichloroethene (converted by the investigators to a dose of 9 mg/kg/day based on body weight and water consumption data) in *utero*, during lactation, and through weaning into adulthood (Quast et al. 1983). These results are supported by several other chronic-duration studies that fc>und similar hepatic effects in rats at comparable doses of 1,1-dichloroethene.

An MRL has not been derived for acute oral exposure (14 days or less) to 1,1-dichloroethene. With the exception of a developmental study in rats (Murray et al. 1979), all the acute-duration studies administered a single dose of 1,1-dichloroethene, and although Murray et al. (1979) defined a NOAEL of 40 mg/kg/day, this NOAEL is too close to the 50-mg/kg dose that caused death in fasted rats (Andersen and Jenkins 1977).

2. HEALTH EFFECTS

An MRL has not been derived for intermediate oral exposure (15-364 days) to 1,1-dichloroethene. Only one study reported data after intermediate-duration exposure to 1,1-dichloroethene (Quast et al. 1983). This study could not define a dose-response relationship for any examined end point and reported a NOAEL of 25 mg/kg/day.

Death. No deaths have been reported in humans following 1,1-dichloroethene exposure.

1,1-dichloroethene was lethal to animals following acute exposures to high levels via the inhalation or oral routes. 1,1-dichloroethene-induced lethality appeared to be influenced by the fasting of the animal regardless of exposure route, with LD_{50} values for fasted animals generally significantly lower than those reported for nonfasted animals (e.g., Chieco et al. 1981; Jaeger et al. 1973c; Jenkins and Andersen 1978; Siegel et al. 1971). Young males appeared to be affected to a greater extent by fasting than females. Experimental evidence suggests that this enhanced toxicity in fasted animals resulted from increased levels of reactive intermediates of 1,1-dichloroethene available for binding to macromolecules in target tissues after fasting (McKenna et al. 1978b). Nonfasted rats that were exposed to 20,000 or 32,000 ppm of 1,1-dichloroethene by inhalation for 1 hour survived for at least 24 hours (Carlson and Fuller 1972). However, when comparable animals were pretreated with the microsomal enzyme inducers phenobarbital or methylcholanthrene, these exposure levels were lethal to nearly all of the animals within 2 hours, suggesting that lethality was due to increased formation of toxic metabolites. However, Carlson and Fuller (1972) found that pretreating rats with two different inhibitors of microsomal metabolism, which presumably would reduce the formation of reactive intermediates (SKF 525A and Lilly 18947), prior to inhalation exposure to 1,1-dichloroethene also reduced the survival time. Other inhibitors of microsomal metabolism (carbon disulfide and diethyldithiocarbamate) were found to protect mice against all 1,1-dichloroethene-induced toxic effects at low doses following intraperitoneal injection (Masuda and Nakayama 1983). These results indicate that biotransformation plays an important role in the expression of 1,1-dichloroethene-induced effects. Increased susceptibility of fasted animals to the lethal effects of 1,1-dichloroethene may occur because fasting depleted GSH in the target tissues and less GSH was available to bind to the active intermediate (Jaeger et al. 1973a).

Mice are more sensitive than rats to the lethal effects of inhaled 1,1-dichloroethene (see Figure 2-1) (Jaeger et al. 1974). This differential sensitivity also has been observed by the oral

exposure route (Jenkins et al. 1972; Jones and Hathway 1978a). Pharmacokinetic studies suggest that, relative to rats, the rate of metabolism is higher in mice, resulting in a greater degree of damage from the increased levels of electrophilic species capable of reacting with intracellular macromolecules (McKenna et al. 1977; Reitz et al. 1980).

Although animal studies indicate that amount of food ingested affects 1,1-dichloroethene-induced lethality, how the amount of food ingested prior to exposure affects the susceptibility of humans to the toxic effects of 1,1-dichloroethene is not known. Human subpopulations probably exist with differing biochemical capacities for 1,1-dichloroethene metabolism and thereby are more or less able to form reactive intermediates. It is not known whether these differing biochemical capacities would affect an individual's susceptibility to 1,1-dichloroethene-induced lethality. Orally ingested 1,l-dichloroethene at sufficiently high doses is likely to cause death in humans, and younger members (particularly males) of the population at hazardous waste sites may be at higher risk.

Systemic Effects

Respiratory Effects. No information regarding respiratory effects in humans was located.

Irritation of the mucous membranes of the upper respiratory tract and pulmonary congestion, hyperemia, and morphological changes were seen at necropsy in rats and mice acutely exposed to high levels of 1,1-dichloroethene via inhalation (Henschler 1979; Klimisch and Freisberg 1979a; Zeller et al. 1979b). Chronic inhalation exposure to 1,1-dichloroethene was associated with similar adverse respiratory effects (Gage 1970; Prendergast et al. 1967; Quast et al. 1986). These effects appeared to be rather nonspecific and probably resulted from 1,1-dichloroethene's irritating properties. Therefore, these data suggest that any possible nongenotoxic respiratory effects associated with inhalation exposure to 1,1-dichloroethene (particularly acute exposure) in humans may be a consequence of local nonspecific irritation.

However, a local nonspecific irritant effect cannot explain the pulmonary injury observed in mice following the oral administration of a single-dose of 1,1-dichloroethene. The effects seen included histopathological changes in Clara cells. These effects were considered reversible since cellular regeneration was evident within 3 days of treatment (Forkert et al. 1985). Clara cell

degeneration, increases in covalent binding, and decreases in GSH content were also seen in mice following acute intraperitoneal administration of 1,1-dichloroethene (Forkert et al. 1986, 1990; Krijgsheld et al. 1984; Moussa and Forkert 1992). The relevance of these findings to prolonged human exposure is not known because the findings in the one oral study are not substantiated by other studies and because intraperitoneal administration is not a relevant route of administration in humans.

Cardiovascular Effects. No information was located regarding cardiovascular effects of 1,1-dichloroethene in humans.

Results obtained in experimental animals suggest that at high concentrations the myocardium is sensitized by 1,1-dichloroethene (Siletchnik and Carlson 1974). However, the relevance of these findings to prolonged human exposure is not known because the findings are not substantiated by other studies.

Hematological Effects. No information was found regarding hematological effects of 1,1-dichloroethene in humans.

Increased hemoglobin levels were reported in an acute oral study in rats fed 200 mg/kg/day 1,1-dichloroethene (Chieco et al. 1981). Given the lack of effects noted in animals in chronic-duration studies by the inhalation (Lee et al. 1977; Quast et al. 1986) and oral routes (Quast et al. 1983; Rampy et al. 1977), it seems unlikely that 1,1-dichloroethene would cause adverse hematological effects in humans.

Hepatic Effects. Information regarding hepatic effects of 1,1-dichloroethene in humans was limited to a reports of increased serum enzymes (indicative of liver injury) in occupationally exposed workers (Ott et al. 1976; EPA 1976). However, because of the incomplete reporting of the results, a clear relationship between exposure to 1,1-dichloroethene and development of adverse hepatic effects in humans could not be established.

Results from animal as well as human studies indicate that the liver is a primary target organ for 1,1-dichloroethene-induced toxicity. Hepatotoxicity in animals following both inhalation and oral exposure to 1,1-dichloroethene was manifested by biochemical changes (i.e., increases in serum

enzyme markers of liver damage and induction of hepatic enzymes), and mild to marked histological changes (e.g., midzonal and/or centrilobular vacuolization, swelling, degeneration and necrosis). More severe hepatotoxic effects were seen in fasted animals (particularly males), compared to fed animals (Andersen and Jenkins 1977; Andersen et al. 1978, 1980; Chieco et al. 1981; Jaeger et al. 1974, 1975b; Jenkins and Andersen 1978; McKenna et al. 1978a; Reynolds et al. 1980). The increased susceptibility to 1,1-dichloroethene-induced hepatotoxicity seen in fasted rats is probably related to the depletion of GSH levels. The hepatotoxic effects of 1,1-dichloroethene were also found to be dependent on the vehicle used. For example, increased liver toxicity was observed in fasted rats given 1,1-dichloroethene in mineral oil or corn oil compared to administration of 1,1-dichloroethene in an aqueous solution (Chieco et al. 1981). This information has important implications with regard to humans, since oral exposure to 1,1-dichloroethene, particularly in individuals in close proximity to hazardous waste sites, will most likely be from groundwater.

Indirect evidence of the role of GSH in 1,1-dichloroethene-induced hepatotoxicity is provided by Jaeger et al. (1974) who demonstrated that diethyl maleate, a substance that depletes liver GSH levels, potentiates liver toxicity in nonfasted rats exposed to 1,1-dichloroethene via inhalation. Decreased levels of hepatic GSH were also reported in mice treated with 1,1-dichloroethene intraperitoneally (Forkert and Moussa 1991). In addition, thyroidectomy, a surgical procedure that results in increased liver GSH levels, has protected against 1,1-dichloroethene-induced hepatotoxicity and lethality, whereas thyroxine replacement restored or even potentiated the susceptibility of thyroidectomized animals to 1,1-dichloroethene-induced hepatotoxicity (Jaeger et al. 1977b; Szabo et al. 1977).

Results from *in vivo* studies suggest that 1,1-dichloroethene-induced hepatic injury may result from the formation of a reactive epoxide or other intermediate *in vivo* (Andersen et al. 1978, 1980; Jaeger et al. 1977a; Jones and Hathway 1978c), which in turn binds to macromolecules in the target tissues. These intermediates are believed to be generated via the cytochrome P-450 mixed function oxidase system (Forkert et al. 1986).

Other subcellular mechanisms of 1,1-dichloroethene-induced toxicity have been proposed. For example, it has been suggested that 1,1-dichloroethene-induced inhibition of calcium-dependent ATPase may be the initial biochemical insult that triggers a sequence of events that may

culminate in cell death (Luthra et al. 1984). Results of *in vitro* studies in liver perfusates have suggested that 1,1-dichloroethene metabolism reduces the viability of liver cells (Reichert et al. 1978). This was demonstrated by Kainz et al. (1993) who determined that mouse hepatocytes incubated with 1,1-dichloroethene experienced a concentration-dependent leakage of lactate dehydrogenase (LDH) into the cellular medium. Histochemical and biochemical evidence support the concept that plasma membranes and mitochondrial membranes may be the primary foci of acute hepatocellular injury in fasted rats (Jaeger 1977; Reynolds et al. 1980). Phospholipase A2 activation may also be part of the sequence of events (Glende and Recknagel 1992).

In conclusion, 1,1-dichloroethene induces hepatotoxicity in humans. This is supported by evidence in animals following both inhalation and acute and repeated oral exposures. However, humans, particularly those exposed by inhalation to high levels of 1,1-dichloroethene in occupational settings or in areas surrounding hazardous waste sites and those with compromised hepatic function, may be at risk for 1,1-dichloroethene-induced liver toxicity.

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

Renal toxicity (e.g., enzyme changes, hemoglobinuria, increases in organ weight, and tubular swelling, degeneration, and necrosis) has been observed following both inhalation and oral exposure to 1,1-dichloroethene in animals (Jackson and Conolly 1985; Lee et al. 1977; McKenna et al. 1978a; Oesch et al. 1983; Short et al. 1977d). Fasted animals (particularly males) were again more susceptible to these effects than nonfasted animals (Chieco et al. 1981; McKenna et al. 1978b), and mice were more susceptible than rats, as was seen for 1,1-dichloroethene-induced hepatotoxicity (Reitz et al. 1980; Short et al. 1977c; Watanabe et al. 1980). There is some evidence that the kidney damage induced by acutely inhaled or ingested 1,1-dichloroethene may be reversible (Jenkins and Andersen 1978; Reitz et al. 1980), and the amount of reversibility is concentration and duration dependent. As indicated in Section 23.5, kidney toxicity has been attributed to the formation of cysteine S-conjugates that may be metabolized by β-lyase, located in the proximal tubule cells, to unstable thiols that yield electrophilic products that interact with macromolecules.

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Though data on kidney toxicity in humans following exposure to 1,1-dichloroethene do not currently exist, evidence from animal studies in two species suggest that nephrotoxicity may also occur in humans, particularly following acute exposure to 1,1-dichloroethene. The fact that adverse renal effects were rarely seen following more prolonged exposure to 1,l-dichloroethene (except in male mice), coupled with the observation that the acute nephrotoxic effects at lower doses were reversible, suggest that up to a point the damaged cells can be replaced. The renal effects of chronic-duration exposure to 1,1-dichloroethene in humans are not known but are probably minimal at concentrations generally experienced.

Immunological Effects. No studies were located regarding immunological effects in humans and animals after 1,1-dichloroethene exposure by any route. Therefore, the potential for 1,1-dichloroethene to cause immunological effects in humans exposed in the environment or at hazardous waste sites cannot be assessed.

Neurological Effects. Central nervous system toxicity has been observed in humans acutely exposed to high concentrations (≈4,000 ppm) of inhaled 1,1-dichloroethene (EPA 1979b). Complete recovery occurred if exposure was not prolonged.

In addition, signs of central nervous system toxicity were the predominant effects observed in animals after acute inhalation exposure to high concentrations of 1,1-dichloroethene. These signs and symptoms observed in humans and in animals are consistent with a narcotic effect of 1,1-dichloroethene, which is observed with many other organic solvents. Effects on the nervous system were not observed following lower oral dose or repeated inhalation exposures to 1,1-dichloroethene in animals. However, these studies did not utilize comprehensive neurological testing that may have detected subtle neurological effects. The available information is insufficient to predict whether or not exposure to low levels of 1,1-dichloroethene by the inhalation, oral, or dermal routes of exposure represent a neurological hazard for humans.

Reproductive Effects. The only study reported in humans regarding reproductive effects of 1,1-dichloroethene provides only suggestive evidence of neural tube defects in newborns (NJDH 1992a, 1992b). Therefore, these data should be interpreted with caution.

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Premating exposure of male rats to 1,1-dichloroethene by the inhalation route had no effect on reproductive end points (Anderson et al. 1977; Short et al. 1977b). Similarly, no reproductive effects were reported in a three-generation drinking water study with 1,1-dichloroethene in rats (Nitschke et al. 1983). The biological significance of these findings in animals with regard to potential reproductive effects of 1,1-dichloroethene in humans is not known.

Developmental Effects. The only study reported in humans regarding reproductive effects of 1,1-dichloroethene provides very weak suggestive evidence of neural tube defects in newborns (NJDH 1992a, 1992b). Therefore, these data should be interpreted with caution. An increased incidence of congenital cardiac malformations was observed in infants born to mothers who had consumed water contaminated mainly with trichloroethylene and to a lesser extent with 1,1 dichloroethene and chromium during the first trimester of pregnancy (Goldberg et al. 1990).

Although exposure to other chemicals was simultaneous, this finding may be relevant since 1,1-dichloroethene induced a dose-related increase in various congenital cardiac defects in rat fetuses after intrauterine administration of 1,1-dichloroethene to the dams (Dawson et al. 1990). Since 1,1-dichloroethene was not supplied by a natural route of exposure, the results of this study should be interpreted with caution (Dawson et al. 1990). Based on studies by Short et al. (1977a), 1,1-dichloroethene has weak teratogenic effects in laboratory animals (rats and mice). Developmental toxicity was enhanced following inhalation exposure to 1,1-dichloroethene, compared to oral exposure. Developmental toxicity was often observed at doses of 1,1-dichloroethene that also induce maternal toxicity in animals. Studies by Murray et al. (1979) demonstrated that the sensitivity of pregnant rats to 1,1-dichloroethene was greater by inhalation than by ingestion. After inhalation exposure at 80 and 160 ppm for 7 hours/day on gestation days 6-18, 1,1-dichloroethene produced maternal toxicity, increased resorption and skeletal alterations. Except for a marginal increase in mean fetal crown-rump length in the offspring, no adverse effects were noted in rats receiving 40 mg/kg/day in drinking water. The author hypothesized a possible mechanism to explain the route-dependent differences in 1,1-dichloroethene-induced toxicity was as follows: since detoxication of 1,1-dichloroethene occurred via conjugation of its active metabolites with GSH (McKenna et al. 1977) and GSH levels undergo diurnal variations (Jaeger et al. 1973a), was speculated that sufficient GSH levels were available to detoxify 40 mg/kg administered in drinking water over a 24-hour period, but not when the animals were exposed via inhalation between 8:30 am and 3:30 pm (Murray et al. 1979). When

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1,l -dichloroethene doses are converted into equivalent units, animals exposed by inhalation received ≈76.6 and 153 mg/kg/day (assuming all 1,1-dichloroethene was absorbed by the lungs) compared to 40 mg/kg/day in drinking water. Thus, a difference in total dose may also explain the greater toxicity seen following inhalation exposure.

Based on studies in laboratory animals, it is prudent to consider that potential adverse maternal and developmental effects could occur in humans exposed to 1,1-dichloroethene.

Genotoxic Effects. The available data suggest that 1,1-dichloroethene produces genotoxic effects in a number of test systems. The results of *in vitro* and *in vivo* studies indicate that 1,1 -dichloroethene exhibited mutagenic properties upon metabolic activation (i.e., the presence of an exogenous mammalian metabolic system was required) in bacteria and yeast and that it induced gene conversion in yeast. It was also widely mutagenic in plant cells without activation by mammalian metabolic systems. 1,1-dichloroethene induced chromosome aberrations and sister chromatid exchanges in cultured mammalian cells *in vitro* and DNA damage in mice *in vivo.*

1,1-dichloroethene was genotoxic in several *in vitro* test systems. A metabolic activation system is usually required for activity. Results of *in vitro* genotoxicity studies are shown in Table 2-3. Gene mutations were observed in bacteria, yeast, and plant cells (Bartsch et al. 1975, 1979; Bronzetti et al. 1981; Greim et al. 1975; Jones and Hathway 1978c; Oesch et al. 1983; Van't Hof and Schairer 1982) and it induced gene conversion in yeast (Bronzetti et al. 1981; Koch et al. 1988). Dose-dependent increases in the frequency of euploid whole chromosome segregants were noted in *Aspergillus nidulans* (Crebelli et al. 1992). Both base-pair substitution and frameshift mutations were reported in *Salmonella typhimurium* after continuous exposure to 1,1-dichloroethene vapors (Bartsch et al. 1975, 1979; Jones and Hathway 1978c; Oesch et al. 1983). Another study reported negative results from tests in *Salmonella* (Mortelmans et al. 1986). However, the Mortelmans et al. (1986) study incorporated single doses of 1,1-dichloroethene into warmed incubation medium instead of exposing the bacteria continuously to vapor. Given that l,l-dichloroelhene is very volatile and would be expected to escape from the culture, continuous exposure to vapor is considered a mere reliable method. 1,1-dichloroethene was mutagenic in *Salmonella* after metabolic activation with an exogenous activation system derived from human liver cells (Jones and Hathway 1978c), thus supporting the ccmcept that the human liver is capable of activating 1,1-dichloroethene into mutagenic metabolites.

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

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium (desiccator test for exposure to gases)	Gene mutation	+	No data	Bartsch et al. 1979
S. typhimurium (gas exposure)	Gene mutation	+	-	Oesch et al. 1983
S. typhimurium (gas exposure)	Gene mutation	+	-	Bartsch et al. 1975
S. typhimurium (gas exposure)	Gene mutation	+	No data	Jones and Hathway 1978c
S. typhimurium (liquid preincubation test)	Gene mutation	-	-	Mortelmans et al. 1986
S. typhimurium (liquid preincubation test)	Gene mutation	+	-	Roldan-Arjona et al. 1991
Escherichia coli WP2	Gene mutation	+	-	Oesch et al. 1983
E. coli K12	Gene mutation	+	-	Greim et al. 1975
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae D7	Gene mutation	+	-	Bronzetti et al. 1981
S. cerevisiae D7	Gene conversion	+	-	Bronzetti et al. 1981
S. cerevisiae D7	Gene conversion	-	-	Koch et al. 1988
S. cerevisiae D7	Gene mutation	+	-	Koch et al. 1988
S. cerevisiae D61.M	Mitotic malsegregation	+	+	Koch et al. 1988
Aspergillus nidulans	Chromosome segregation	+	No data	Crebelli et al. 1992
Plant:				
Tradescantia clone 4430	Gene mutation	No data	(+)	Van't Hoff and Schairer 1982
Mammalian cells:				
Chinese hamster V79 cells	Gene mutation	-	No data	Drevon and Kuroki 1979
Chinese hamster CHL cells	Chromosomal	+	-	Sawada et al. 1987
Chinese hamster CHL cells	Sister chromatid exchange	(+)	-	Sawada et al. 1987
Mouse L5178Y lymphoma cells	Gene mutation	+	(+)	McGregor et al. 1991

- = negative result; + = positive result; (+) = weakly positive result

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In cultured mammalian cells, 1,1-dichloroethene was negative in a point mutation assay in 8-azaguanine and ouabain-resistant V79 Chinese hamster lung cells (Drevon and Kuroki 1979), but it produced chromosomal aberrations and sister chromatid exchanges in a Chinese hamster lung fibroblast cell line (Sawada et al. 1987) and in mouse lymphoma cells (McGregor et al. 1991) in the presence of a metabolic activation system.

1,1-dichloroethene has also been tested in several *in vivo* studies in animals. Results of *in vivo* genotoxicity studies are shown in Table 2-4. Negative results were reported in assays for dominant lethal mutations in mice (Anderson et al. 1977) and rats (Short et al. 1977b) and in a micronucleus test in mice using both the bone marrow assay system following gavage administration and the transplacental assay system following intraperitoneal administration to pregnant mothers (Sawada et al. 1987). 1,1-dichloroethene inhalation was associated with low rates of DNA alkylation in the livers and kidneys of mice and rats, compared to dimethylnitrosamine-treated controls. Furthermore, DNA repair mechanisms were induced in the kidneys of mice in cells in which normal replicative DNA synthesis had been inhibited. A significant increase in DNA repair rates was not observed in 1,1-dichloroethene treated mouse liver nor in the kidneys or liver of rats (Reitz et al. 1980). In a mouse host-mediated assay system, 1,1-dichloroethene was mutagenic and induced gene conversion in yeast (Bronzetti et al. 1981).

In vitro and *in vivo* studies indicate that 1,1-dichloroethene exhibits some mutagenic properties upon metabolic activation. But there is no direct evidence that exposure to 1,1-dichloroethene causes genotoxic effects in humans. However, the evidence that a metabolizing enzyme system derived from human liver could activate 1,1-dichloroethene into mutagenic metabolites (Jones and Hathway 1978c) suggests that 1,1-dichloroethene may be considered a potential genotoxic threat to humans. It must be mentioned, however, that human liver cells overlaid with mammalian tissue post-mitochondrial SC) (prepared from Aroclor 1254-induced rats) were activated, and human tissue not overlaid with S9 did not activate 1,1-dichloroethene into mutagenic metabolites (Jones and Hathaway 1978c).

Cancer. Data regarding carcinogenic effects of 1,1-dichloroethene in humans were limited to results from an occupational exposure study (Ott et al. 1976). The assumption is made that

TABLE 2-4. Genotoxicity of 1,1-Dichloroethene *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Mouse	Dominant lethals	-	Anderson et al. 1977
Rat	Dominant lethals	-	Short et al. 1977b
Mouse bone marrow	Micronuclei	-	Sawada et al. 1987
Mouse fetal liver and blood	Micronuclei	-	Sawada et al. 1987
Mouse kidney (DNA repair)	DNA damage	(+)	Reitz et al. 1980
Host-mediated assays:			
Saccharomyces cerevisiae (mouse host-mediated assay)	Gene mutation	+	Bronzetti et al. 1981
S. cerevisiae (mouse host-mediated assay)	Gene conversion	+	Bronzetti et al. 1981

- = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid

exposure occurred mainly via inhalation, although dermal contact cannot be ruled out. Limitations in these studies, such as small cohort size and short observation periods greatly diminished their usefulness for assessing the carcinogenic potential of 1,1-dichloroethene in humans.

The carcinogenicity of 1,1-dichloroethene following inhalation, oral, dermal, and subcutaneous exposure has been evaluated in mice (Hong et al. 1981; Lee et al. 1978; Maltoni et al. 1985; Van Duuren et al. 1979) rats (Hong et al. 1981; Maltoni et al. 1982, 1985; NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983, 1986; Rampy et al. 1977; Viola and Caputo 1977) and Chinese hamsters (Maltoni et al. 1985). Of the carcinogenicity bioassays conducted to date, only the results of a single inhalation study in mice by Maltoni et al. (1985) provide evidence of a positive carcinogenic effect from 1,1-dichloroethene exposure. In this study, increases in renal adenocarcinomas were noted in male Swiss mice exposed to 25 ppm 1,1-dichloroethene via inhalation. Mammary gland carcinomas and lung tumors, most of which were benign pulmonary adenomas, were also observed in this study. Results of all other carcinogenicity studies with laboratory animals have been negative. Increases in a variety of malignant and nonmalignant tumors were reported in studies involving inhalation and oral exposure; however, these increases either were not statistically significant or were not considered by the respective authors to be exposure related (Lee et al. 1977, 1978; Maltoni et al. 1985; NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983, 1986). Study limitations for several of the investigations included less than lifetime exposure, use of doses below the maximum tolerated dose, small numbers of animals, and limited gross and microscopic examinations. Such limitations reduce the sensitivity of a bioassay system to detect a carcinogenic response.

The carcinogenicity of 1,1-dichloruethene in mice treated by dermal application and by subcutaneous injection was evaluated by (Van Duuren et al. 1979). 1,1-dichloroethene was inactive as a complete carcinogen when applied repeatedly for a lifetime to the skin of mice and did not induce local malignancies when administered chronically to mice by subcutaneous injection. However, a dermal initiation-promotion study with Swiss mice has shown that 1,1-dichloroethene was active as a tumor-initiating agent. A statistically significant increase in the incidence of skin papillomas was noted in Swiss mice treated dermally initially with 1,1-dichloroethene and subsequently with the tumor-promoting agent phorbol myristate acetate (Van Duuren et al. 1979).

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On the basis of the suggestive inhalation study by Maltoni et al. (1985), 1,1-dichloroethene should be regarded as a possible animal carcinogen and, therefore, as a possible human carcinogen. Results of studies with laboratory animals indicating nonsignificant or non-dose-related increases in various malignant and nonmalignant tumors following oral or inhalation exposure provide limited but suggestive support that 1,1-dichloroethene may be a weak carcinogen (Lee et al. 1978, 1977; Maltoni et al. 1985; Ponomarkov and Tomatis 1980; Quast et al. 1986, 1983). The positive initiation-promotion study by Van Duuren et al. (1979) also suggests that 1,1-dichloroethene in concert with tumor-promoting agents can induce cancer, but a relationship between this test and human cancer has not been demonstrated.

In experimental studies with mice, it has been observed that doses of 1,1-dichloroethene that induce renal tumors also induce renal tissue damage (degeneration and necrosis) (Maltoni et al. 1985; Reitz et al. 1980; Watanabe et al. 1980). These tumorigenic doses, however, are associated in mice with only minimal DNA alkylation and DNA repair (Reitz et al. 1980). These findings suggest that kidney toxicity may play a contributing role in the induction of renal tumors (Watanabe et al. 1980), and that tumors observed in mice exposed to 1,1-dichloroethene may be the result of the chemical's toxic effect upon nongenetic carcinogenic mechanisms (Reitz et al. 1980). However, 1,1-dichloroethene is mutagenic in lower organisms and the same nephroses present in males was present in females but no tumors developed.

It has been suggested that the toxic and carcinogenic effects of 1,1-dichloroethene may depend on species, strain, and sex of the tested animals (Maltoni et al. 1985). Results of studies suggest that male Swiss mice are more susceptible to the toxic effects of 1,1-dichloroethene than female Swiss mice, rats, or hamsters (Maltoni et al. 1985; Oesch et al. 1983). Pharmacokinetic studies also suggest that compared to rats, mice have a greater rate of 1,1-dichloroethene activation to electrophilic species capable of reacting with intracellular macromolecules (McKenna et al. 1977; Reitz et al. 1980).

NTP originally described the carcinogenic effects of oral administration of 1,1-dichloroethene in both sexes of Fischer-344 rats and $B6C3F_1$ mice as negative. This term has subsequently been changed to no evidence. EPA (IRIS 1992) has classified 1,1-dichloroethene as a Group C agent (possible human carcinogen). This category applies to chemicals for which there is limited evidence of carcinogenicity in animals and inadequate evidence in humans. IARC (1987) has

classified 1,1-dichloroethene as a Group 3 chemical (not classifiable as to human carcinogenicity). 1,1-Dichloroethene is not included in the Sixth Annual Report on Carcinogens, which is a list of compounds that may reasonably be anticipated to be carcinogens published by the U.S. Public Health Service (NTP 1991).

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time 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,l -dichloroethene are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well 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-dichloroethene are discussed in Section 2.5.2.

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

2.5.1 Biomarkers Used to Identify or Quantify Exposure to 1,1-dichloroethene

Exposure to 1,1-dichloroethene can be determined by the appearance of 1,1-dichloroethene in exhaled air and/or the appearance of metabolites such as dithioglycollic acid in urine (see Section 6.1). However, because 1,1-dichloroethene is rapidly eliminated from the body, such determinations can prove useful only for detecting recent exposure (within days). Furthermore, because other structurally similar compounds such as vinyl chloride can give rise to the same metabolic products as 1, 1-dichloroethene, formation of adducts with hemoglobin and detection of urinary metabolites cannot be considered as specific biomarkers of exposure to 1,l-dichloroethene.

Data from available studies have been insufficient to correlate levels of 1,1-dichloroethene in the environment with levels in breath. In an investigation of trace organic compounds in human breath, a 60-minute: sampling period yielded 13.0 μg of 1,1-dichloroethene in the breath (volume unspecified) of one individual (Conkle et al. 1975). This value was corrected for the amount of 1,l-dichloroethene in the air supplied to the individual during the sampling period. The study authors attributed the amount of 1,1-dichloroethene in the individuals's breath to previous exposure; however, no levels of previous exposure to 1,1-dichloroethene were reported for the test subject. The breath of 1 out of 12 subjects tested by Wallace et al. (1984) contained 1,1-dichloroethene; however, the levels were not specified. No environmental levels of 1,l-dichloroethene were reported for this study. Twelve percent of breath samples from 50 residents of New Jersey contained measurable amounts of 1,1-dichloroethene, ranging from 0.2 to 2 $\mu g/m^3$ of expired air (Wallace et al. 1986). Increased liver enzyme (AST, ALT)

activities were reported in two workers exposed to 1,1-dichloroethene (Ott et al. 1976). However, these enzyme markers are not specific to 1,1-dichloroethene induced liver toxicity because they can be indicative of the detoxification process.

2.5.2 Biomarkers Used to Characterize Effects Caused by 1 ,I -Dichloroethene

As indicated in Sections 2.2 and 2.3, the liver and kidney are primary target organs for 1,l -dichloroethene exposure. Exposure to 1,1-dichloroethene (depending on dose and duration of exposure) increases serum levels of certain liver enzymes such as SGOT (AST), SGPT (ALT), and others, which is taken as an indication of liver injury. However, this effect is caused by other halogenated alkenes as well such as vinyl chloride, and cannot be considered as a specific indicator of 1,l -dichloroethene effects.

Occupational exposure studies have investigated health effects associated with exposure to 1,1-dichloroethene. Because of the small cohort size and concurrent exposure to other compounds, the information from these studies is not sufficient to correlate levels of 1,1-dichloroethene in the environment with health effects. A study of 138 workers exposed to 1,1-dichloroethene (time-weighted-average concentrations ranging from <5 to 70 ppm) and copolymers other than 1,l -dichloroethene reported no statistically-related changes attributable to 1,l -dichloroethene in long-term mortality or health-inventory findings (Ott et al. 1976). No association between occupational exposure to 1,1-dichloroethene (with concurrent exposure to other chemicals) and incidence of angiosarcomas of the liver in workers was found by Waxweiler (1981).

Inhalation exposure to 50 ppm 1,1-dichloroethene was associated with minimal rates of DNA alkylation in liver and kidney cells of experimental rats and mice (Reitz et al. 1980).

Additional details regarding biomarkers of effects for 1,1-dichloroethene may be found in the CDC/ATSDR Subcommittee Report on Biological Indicators of Organ Damage (CDC/ATSDR 1990) or in the Office of Technology Assessment report on neurotoxicity (OTA 1990). A more detailed discussion of health effects attributed to exposure to 1,1-dichloroethene can be found in Section 2.2 of Chapter 2 in this document.

2.6 INTERACTIONS WITH OTHER CHEMICALS

As discussed in previous sections, it is apparent that the toxicity of 1,1-dichloroethene is largely due to the formation of toxic intermediates during metabolism *in vivo*. The production and biotransformation of toxic metabolic intermediates of 1,1-dichloroethene can be greatly influenced by various metabolic inhibitors and inducers, and by the availability of precursors of compounds involved in detoxication, such as GSH.

Microsomal mixed-function oxidases (MFOs) are a group of enzymes involved in the biotransformation and detoxication of xenobiotics such as 1,1-dichloroethene. Inhibitors of some microsomal MFOs include the compound SKF-525-A, disulfiram, and other dithiocarbamates, such as thiram and diethyldithiocarbamate. These compounds reduce the toxic effects of 1,1-dichlorethene in the liver, probably by inhibiting the enzymes responsible for the formation of reactive toxic intermediates (Masuda and Nakayama 1983; Short et al. 1977c). Pretreatment with intracellular cysteine precursor, L-2-oxothiazolidine-4-carboxylate is also used to protect against 1,1-dichloroethene toxicity in this way (Moslen et al. 1989b). Inhibitors of metabolic enzymes responsible for the breakdown of these reactive intermediates may also enhance the toxicity of 1,1-dichloroethene. For example, 1,1,1-trichloropropane and other inhibitors of epoxide hydrolase can potentiate the toxicity of 1,1-dichloroethene (Jaeger 1977). Other chemicals that reduce the activity of metabolic enzymes and show some protective effects against the toxicity of 1,1-dichloroethene include pyrazole, 3-aminotriazol (Andersen et al. 1978).

Pretreatment of rats with acetaminophen greatly increased lethality and the hepatotoxic effects of 1,1-dichloroethene (Wright and Moore 1991). Although the depletion of glutathione was not discussed, the study authors concluded that acetaminophen produces alterations that make hepatocytes more susceptible to 1,l-dichloroethene injury.

Enzyme inducers (enhancers) may either protect against or exacerbate the toxicity of 1,1-dichloroethene. Induction of enzymes involved in the formation of toxic intermediates potentiates 1,l -dichloroethene-induced toxicity following 1,1-dichloroethene exposure; conversely, induction of enzymes responsible for the biodegradation of the toxic intermediate(s) decreases toxicity. Examples of compounds that induce MFOs and increase toxic effects upon exposure to 1,1-dichloroethene include ethanol and acetone (Charbonneau et al. 1991; Hewitt and Plaa 1983;

Kainz et al. 1993; Sato et al. 1983). In acetone-pretreated rats, mixtures containing chloroform or carbon tetrachloride plus 1,1-dichloroethene increased hepatotoxic responses additively (Charbonneau et al. 1991).

Many inducers of MFO enzymes (e.g. P-450) do not increase the hepatotoxicity of l,l-dichlorocthene, perhaps because they stimulate enzyme systems not involved in the metabolism of 1,1-dichloroethene. An example of a P-450 inducer is phenobarbital (Carlson and Fuller 1972). Jenkins et al. (1971) found that pretreatment of rats with phenobarbital followed by oral administration with 1,1-dichloroethene had a protective effect against liver damage, while Carlson and Fuller (1972) found that pretreatment of rats with phenobarbital followed by inhalation exposure to 1,1-dichloroethene increased mortality but had no effect on hepatotoxicity. This discrepancy may be due to differences in routes of administration and indicators of toxicity examined.

Thyroidectomy protected rats from the hepatotoxic effects of 1,1-dichloroethene, probably by increasing the amount of hepatic GSH (Szabo et al. 1977). Thyroxine replacement in thyroidectomized rats exacerbated the liver damage seen upon subsequent exposure to 1,1-dichloroethene (Szabo et al. 1977).

Pretreatment of animals with compounds that deplete GSH levels (such as buthionine sulfoximine) increases the amount of liver damage caused by 1,1-dichloroethene exposure (Reichert et al. 1978). Conversely, pretreatment of animals with supplements containing high concentrations of the amino acids cysteine and/or methionine, both of which are metabolic contributors of the sulfhydryl group required for GSH biosynthesis, has had a protective effect against the toxicity of 1,1-dichloroethene (Short et al. 1977d).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,1-dichloroethene than will most persons exposed to the same level of 1,1-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 preexisting 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.

Specific information regarding human subpopulations that are unusually susceptible to the toxic effects of 1,1-dichloroethene were not located. However, animal studies have suggested that there are factors that may predispose some groups of the population to an increased risk for the toxic effects of 1,1-dichloroethene. These factors are discussed below.
The influence that dietary intake can have upon the metabolism and detoxification of xenobiotics

has been well documented. Fasting is known to modify the metabolism and toxicity of a variety of halogenated alkenes (Andersen et al. 1978; Nakajima et al. 1982). As discussed in previous sections, the liver MFO activity in fasted animals or animals kept on a low carbohydrate diet was enhanced when exposed to 1,1-dichloroethene, compared to that in similarly exposed control (carbohydrate-fed) animals (McKenna et al. 1978a; Nakajima et al. 1982). Fasting prior to 1,1-dichloroethene exposure resulted in an earlier appearance of hepatic lesions, a more extensive distribution of lesions and a reduced ability to metabolize high doses of 1,1-dichloroethene when compared to control (nonfasted) rats (Jaeger et al. 1974; McKenna et al. 1978a; Reynolds and Moslen 1977).

Sex differences in the toxic response to 1,1-dichloroethene have been observed in animals. For example, in a chronic inhalation exposure study in rats, hepatotoxic effects occurred at lower 1,1-dichloroethene concentrations in female rats than in male rats (25 and 75 ppm, respectively) (Quast et al. 1986). Fasted male animals, particularly young males, appear to be more susceptible to the toxic effects of 1,1-dichloroethene than fasted females, as evidenced by their enhanced responses at lower doses of 1,1-dichloroethene.

Individuals taking certain drugs or who have pre-existing liver, kidney, thyroid, or cardiac disease may be at greater risk for 1,1-dichloroethene-induced toxicity. Acetaminophen is prescribed to

some rheumatic patients at doses up to 4 grams per day (Insel 1990). Such individuals may be highly susceptible to the effects of 1,l-dichloroethene (Wright and Moore 1991). Phenobarbital, even though somewhat protective against 1,1-dichloroethene-generated liver damage (Carlson and Fuller 1972), has sensitized the heart to 1,l -dichloroethene-induced arrhythmias (Siletchnik and Carlson 1974). Since phenobarbital is sometimes used as a soporific, and by those with various forms of epilepsy or seizure disorders, people who are taking this medication or those with pre-existing arrhythmic heart conditions should not be exposed to high levels of 1,l-dichloroethene. Ethanol increases the amount of 1,1-dichloroethene-induced hepatotoxicity observed in rats, which suggests that alcohol ingestion could exacerbate 1,1-dichloroethene-induced toxicity in exposed individuals. Therefore, individuals taking medicine that contains alcohol or individuals drinking alcoholic beverages may be more susceptible to the toxic effects of 1,1-dichloroethene. Thyroidectomy, either chemical or surgical, can protect against the hepatotoxicity associated with inhalation of 1,1-dichloroethene. Conversely, thyroxine treatment to replace or supplement normal thyroid function increases the amount of liver damage upon subsequent exposure to 1,1-dichloroethene in animals (Szabo et al. 1977). Individuals with liver or kidney disease or those with an acute hypersensitivity to 1,1-dichloroethene should avoid exposure to 1,1-dichloroethene.

Specific data concerning teratogenicity in humans exposed to 1,l-dichloroethene were not found in the literature. 1,1-dichloroethene has been described as a possible teratogen responsible for soft-tissue anomalies in rats and skeletal defects in mice, rats, and rabbits, often at levels that produced clear evidence of toxicity in the dam. It would be prudent for pregnant women to avoid exposure to 1,1-dichloroethene.

To conclude, groups of people who should be specifically cautioned against exposure to 1,1-dichloroethene include the very young; the elderly; the pregnant; those ingesting large amounts of acetaminophen as medication; those that ingest large amounts of alcohol; people using phenobarbital (or possibly other hepatic enzyme-inducing drugs); those receiving thyroid replacement therapy or those who are hyperthyroid; people who, for whatever reason, are fasting; and those with cardiac, hepatic, renal, and certain central nervous system dysfunctions.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,l -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 1,1-dichloroethene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

Treatment for exposure to 1,1-dichloroethene is essentially supportive after the individual is removed from the contaminated environment (Haddad and Winchester 1990). The following steps have been suggested in an acute exposure situation to reduce the possibility of 1,1-dichloroethene absorption. If 1,1-dichloroethene is swallowed and the victim is conscious, water or milk can be administered to minimize mucosal irritation (Anonymous 1991). Activated charcoal can be administered to inhibit absorption in the intestine. Following dermal contact, the affected areas are flushed with water. No specific information was located regarding reducing peak absorption of 1,l -dichloroethene following inhalation exposure.

2.8.2 Reducing Body Burden

No information was located regarding retention of 1,1-dichloroethene or its metabolites in humans exposed to 1,1-dichloroethene. However, if the toxicokinetic mechanisms described in animals are suggestive for humans, the metabolites are eliminated mainly in the urine. Therefore, increasing diuresis may be a way of reducing the body burden of 1,1-dichloroethene metabolites.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

No information was located in the available literature regarding clinical or experimental methods that can block the mechanism of toxic action of 1,1-dichloroethene in humans.

Although the exact mechanism of action of 1,1-dichloroethene in humans is not known both humans and animal studies have identified the liver as the target organ for 1,1-dichloroethene. In

experimental animals, 1,1-dichloroethene-induced hepatotoxicity is primarily due to reactive metabolic products that arise from biotransformation reactions initiated by the cytochrome P-450 enzymatic system. It is, therefore, not unreasonable to assume that 1,1-dichloroethene-induced liver toxicity in humans is also caused by 1,1-dichloroethene metabolites. If this premise is accepted, then two general types of biochemical manipulations could be envisioned to reduce 1,1-dichloroethene-induced toxicity. The first one would be to prevent biotransformation into reactive intermediates. This could be done by inhibiting enzymes responsible for these processes. The second alternative would be to ensure that adequate amounts of GSH are available (for example by administering precursors of GSH) in the liver in order to form S-conjugates with metabolic intermediates that can be eliminated in the urine. In fact, such interventions have been shown to protect against 1,1-dichloroethene-induced liver damage in rats (Moslen et al. 1989c). Based on the fact that I,l-dichloroethene does not appear to accumulate in tissues, these experimental procedures are likely to be more useful shortly after exposure to 1,1-dichloroethene rather than after prolonged exposure to low levels of 1,1-dichloroethene, which may occur to populations near waste sites.

2.9 ADEQUACY OF THE DATABASE

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

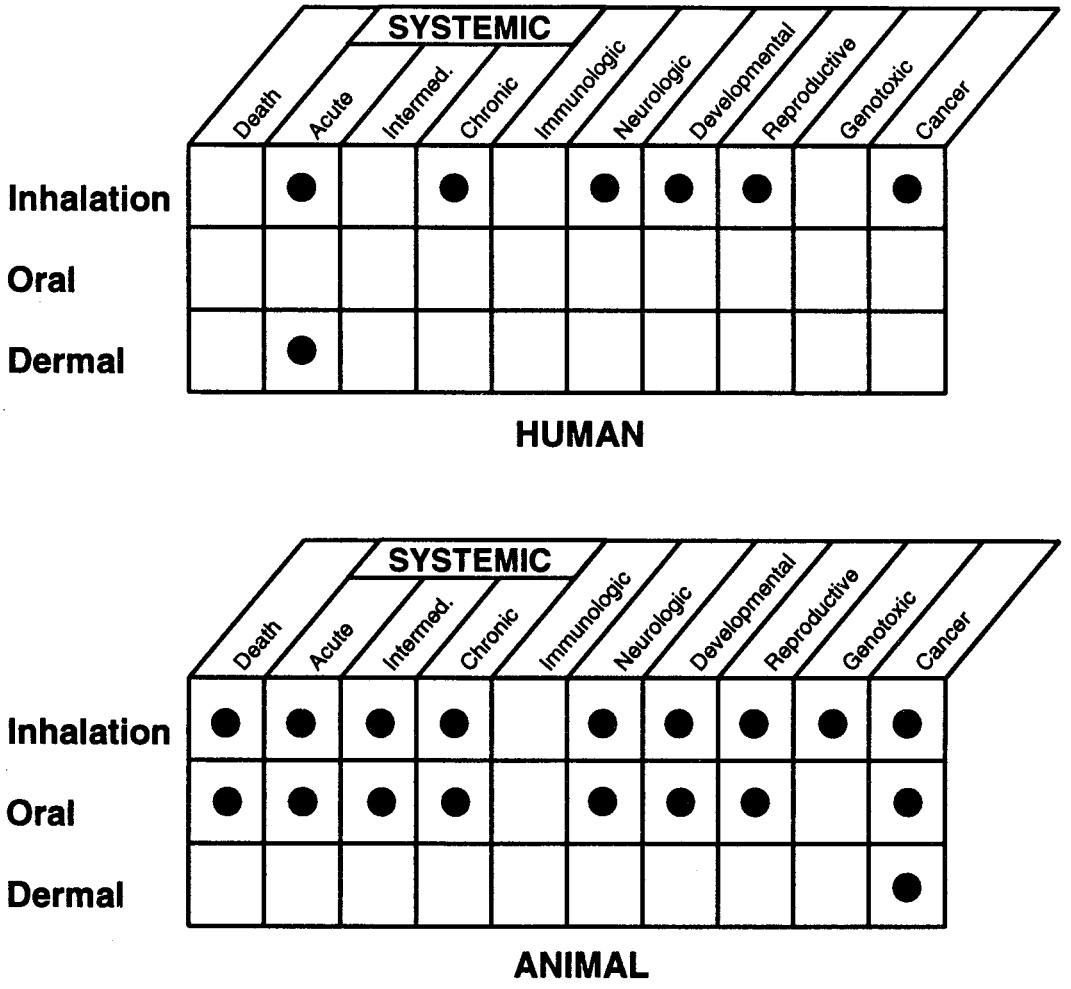
2.9.1 Existing Information on Health Effects of 1,1-Dichloroethene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1-dichloroethene are summarized in Figure 2-7. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,1-dichloroethene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs." 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 2-7 depicts the existing health effects information on 1,1-dichloroethene for a specific route and duration of exposure. There is little information available concerning the long-term health effects of 1,1-dichloroethene in humans following inhalation exposure. Most of the information concerning health effects in humans is reported in occupational studies that are difficult to interpret because of limitations in study design (e.g., exposure levels and duration cannot be quantified and concurrent exposure to other toxic substances cannot be ruled out). No information concerning oral or dermal exposure to 1,1-dichloroethene in humans was found in the reviewed literature.

The systemic effects of 1,1-dichloroethene in animals following inhalation and oral exposure have been studied in a variety of species following acute, intermediate, and chronic exposure durations. No studies were located regarding immunological effects in humans or animals following inhalation or oral exposure. One oral exposure study reported observations of the "appearance" and "demeanor" of test animals, but this was not considered a good analysis of possible neurological or behavioral effects. Genetic effect end points were examined following inhalation exposure only. Carcinogenicity studies in animals following exposure by the oral, inhalation, and dermal routes are available.

FIGURE 2-7. Existing Information on Health Effects of 1,1-Dichloroethene



● Existing Studies

2.9.2 Identification of Data Needs

Acute-Duration Exposure. No data were located indicating specific organs or systems as targets for 1,l -dichloroethene in humans by any route of exposure. The data in experimental animals such as rats and mice suggest that the liver and kidneys are the primary targets for acute-duration exposure to 1,1-dichloroethene by inhalation and oral routes of exposure (Anderson et al. 1980; Chieco et al. 1982; Henck et al. 1979; Jenkins and Anderson 1978; McKenna et al. 1975; Moslen et al. 1989b; Reynolds et al. 1980). Data regarding the dermal route of exposure were not located. Although the kidney was. identified as the most sensitive organ in acute inhalation studies (Henck et al. 1979; McKenna et al. 1978b; Reitz et al. 1980), these studies were considered inadequate for derivation of an acute inhalation MRL, largely because of the small numbers of animals used and lack of clarity in the presentation of the results. The data in experimental animals were insufficient to derive an acute oral MRL mainly because the lowest dose associated with systemic effects (Moslen et al. 1989a) was also found to cause lethality in fasted rats (Anderson and Jenkins 1977). Information regarding the cause of death in the acuteduration studies would be useful. Acute-duration studies by the dermal route using ^{14}C-1,l -dichloroethene would provide useful information regarding absorption, distribution and kinetics of excretion. Results of these studies coupled with available knowledge on the toxicity and toxicokinetics should suffice. This information may be relevant for populations surrounding hazardous waste sites that might be exposed to 1,1-dichloroethene for brief periods. Acute industrial exposure is, however, more likely. Pharmacokinetic data do not suggest route-specific target organs. Since 1,1-dichloroethene is rapidly excreted, it is not expected to accumulate in tissues.

Intermediate-Duration Exposure. No data were located that identified target organs in humans following intermediate exposure to 1,1-dichloroethene by any route of exposure. Information is available on the systemic toxicity of 1,1-dichloroethene following inhalation and oral exposure in rats, guinea pigs, dogs, and monkeys. These data indicate that the liver and kidneys are target organs for intermediate exposure to 1,1-dichloroethene (Prendergast et al. 1967). An MRL was derived for inhalation exposure based on hepatic effects in guinea pigs (Prendergast et al. 1967). Only one study was identified that described the effects of 1,1-dichloroethene in animals (dogs) after oral intermediate exposure (Quast et al. 1983). The lack of supporting data precluded derivation of an oral MRL. Additional studies conducted in rats via oral route for intermediate

exposure would be useful for setting the maximum tolerated dose for oral chronic studies. Data on dermal exposure in animals are not needed. This information may be relevant for populations surrounding hazardous waste sites that might be exposed to 1,1-dichloroethene for brief periods. There are no pharmacokinetic data that would suggest route-specific target organs.

Chronic-Duration Exposure and Cancer. No data were located that identified target organs in humans following chronic exposure to 1,1-dichloroethene by the oral and dermal routes. Hepatic effects described in occupationally exposed humans (EPA 1976) are supported by data in animals (Quast et al. 1983, 1986) but data from animal studies are sparse. An MRL was derived for oral exposure based on hepatic effects in rats (Quast et al. 1983). There are no pharmacokinetic data that would suggest route-specific target organs. Dermal exposure data are lacking. Studies with well-designed experiments and complete dose and time protocols, and measuring all sensitive toxicological end points, would provide valuable information on the health effects associated with long-term exposure to 1,l-dichloroethene. These chronic studies could provide information on subtle toxicological changes in organs associated with prolonged exposure to low levels of 1,l-dichloroethene. This information may be relevant for populations surrounding hazardous waste sites that might be exposed to 1,1-dichloroethene for long periods.

Available data are insufficient to permit an evaluation of the carcinogenic risk of 1,1-dichloroethene in humans. The data from animal studies are limited in their usefulness because of flaws in the experimental design (e.g., doses that are too low) (Maltoni et al. 1985; NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983; Rampy et al. 1977). An inhalation study in mice described a positive carcinogenic response in the kidney (Maltoni et al. 1985). This study, however, has been regarded as inconclusive since it appears that tumors were not observed in the absence of nephrotoxicity. Swiss mice, in fact, are much more susceptible to the nephrotoxic effects of 1,1-dichloroethene than other species, or even other strains of mice. Additional information of the carcinogenicity of 1,1-dichloroethene from well conducted animal bioassays and epidemiological studies using various routes of exposure would be useful in predicting the likelihood that such a response occurs in humans.

Genotoxicity. No studies were identified that evaluated genotoxic effects of 1,1-dichloroethene in humans following any route of exposure, or in animals following oral or dermal exposure. Studies by the oral and dermal routes could help develop dose-response relationships for these

routes. Several *in vitro* studies (Table 2-3 in Section 2.3.1.1) suggest that 1,1-dichloroethene, only in the presence of activating systems, is mutagenic in both prokarydc and eukatydc organisms. These results are consistent with the idea that a reactive metabolic intermediate(s), and not the parent compound, is (are) responsible for the genotoxic properties of 1,1-dichloroethene. With the exception of a weakly positive response in mouse kidney cells (Reitz et al. 1981), 1,1-dichloroethene tested negative in *in vivo* rodent assays following acute and intermediate inhalation or acute oral exposure to 1,1-dichloroethene (Anderson et al. 1977; Sawada et al. 1987; Short et al. 1977b). Cytogenetic analysis of human populations exposed to 1,1-dichloroethene in occupational settings would provide an opportunity to assess the genotoxic potential of this chemical in humans.

Reproductive Toxicity. The only study reported in humans regarding reproductive effects following oral exposure to 1,1-dichloroethene provides evidence of neural tube defects in children (NJDH 1992a, 1992b). However, these data are only suggestive and therefore, should be interpreted with caution. No information is available regarding reproductive effects of I,l-dichloroethene in humans following inhalation or dermal routes of exposure or in animals following dermal exposure. Only one multigeneration study was identified in rats (Nitschke et al. 1993). This study was conducted by the oral route, and the results were negative. Studies were identified that examined the reproductive effects of 1,1-dichloroethene after acute inhalation exposure in rats (Short et al. 1977b) and mice (Anderson et al. 1977). No adverse reproductive effects were observed in either one of these studies. Available pharmacokinetic data do not suggest route-specific target organs. Multigeneration studies by the inhalation and dermal routes would add information that could be relevant to humans.

Developmental Toxicity. The only study available in humans following oral exposure to 1,1-dichloroethene provides evidence of neural tube defects in children (NJDH 1992a, 1992b). However, these data are only suggestive and therefore, should be interpreted with caution. No relevant information is available indicating that 1,1-dichloroethene affects development in humans by any route of exposure or in animals following dermal exposure. Numerous studies have been conducted in rats by the inhalation route (Murray et al. 1979; Short et al. 1977a, 1977b). Based on the results of these studies no-observed-effect level could not be identified because the study authors did not use concentrations below those that produced adverse effects. Therefore, studies using lower exposure concentrations of 1,1-dichloroethene would provide useful information.

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Only one oral exposure study in rats was located (Murray et al. 1979), and this study used only one exposure level. No pharmacokinetic data are available that would indicate the transplacental transfer of 1, l-dichloroethane. However, the available developmental toxicity studies suggest that l,l-dichloroethane can be potentially toxic to the developing fetus. Therefore, additional oral studies using a range of doses would provide useful information.

Immunotoxicity. No information is available indicating that the immune system is a target f& 1,1-dichloroethene in humans or animals. Batteries of immune function tests have not been performed in the available acute-, intermediate-, and chronic-duration studies. Studies conducti tests for immunocompetence and histopathological observations of organs and tissues involved il immunological response would provide valuable information. Dermal sensitization studies in animals might provide information on whether 1,1-dichloroethene is likely to cause an allergic response. Available toxicokinetic data do not suggest route-specific target organs.

Neurotoxicity. Neurobehavioral toxicity studies of acute inhalation exposures to 1,1-dichloroethene in both humans (EPA 1979b) and animals (Henschler 1979; Klimisch and Freisberg 1979a, 1979b; Zeller et al. 1979a, 1979b) are inadequate. This limited information suggests that the nervous system can be affected by exposure to rather high concentrations of 1,1-dichloroethene. Information by other routes of exposure is lacking. Available toxicokinetics data do not suggest route-specific target organs. Studies by the inhalation, oral, and dermal routes, as well as tests for neurological impairment in animals, might provide information that could be relevant to humans.

Epidemiological and Human Dosimetry Studies. Most of the available information on the adverse effects of 1,1-dichloroethene in humans comes from cases of acute poisoning occurring primarily in the workplace. Limitations inherent in these studies include unquantified exposures, concentrations and durations, as well as concomitant exposure to other toxic substances. The few available industrial surveys and epidemiological studies are limited in their usefulness because of small sample size, short follow-up periods, and/or brief exposure periods. Despite their inadequacies, studies in humans indicate that 1,1-dichloroethene can cause central nervous system toxicity and irritation of the mucous membranes (EPA 1979b; Quast et al. 1986). There is also some evidence to suggest that repeated exposure to 1,1-dichloroethene is associated with liver damage in humans (EPA 1976). Well-controlled epidemiological studies of people living near areas where 1,1-dichloroethene has been detected in surface water and groundwater, in the

vicinity of industries releasing 1,1-dichloroethene, near hazardous waste sites, and of people occupationally exposed could add to and clarify the existing database on 1,l-dichloroethene-induced human health effects. However, such studies would probably be very difficult to conduct since the majority of exposed workers are carpenters, warehousemen, and machine operators for whom exposure information and health follow-up is difficult to obtain, and the exposed population is either decreasing or difficult to define. Furthermore, a study of human populations residing near hazardous waste sites or production sites would also be difficult to conduct because of the difficulty in obtaining meaningful historical estimates of exposure, historical medical data, and comprehensive follow-ups.

Biomarkers of Exposure and Effect

Exposure. Information regarding populations exposed specifically to 1,1-dichloroethene is not available; therefore, no known biomarker of exposure to 1,1-dichloroethene has been identified in humans. However, if 1,1-dichloroethene is metabolically disposed of by humans in a way similar to that observed in animals, 1,1-dichloroethene in expired air could be a biomarker of recent exposure to relatively high concentrations of 1,1-dichloroethene.Similarly, urinary excretion of metabolites such as thioglycollic acid could also be considered a biomarker of recent exposure. It must be mentioned, however, that the urinary metabolites would not be specific biomarkers for 1,1-dichloroethene exposure since other chemicals have similar urinary metabolites. Hence, the development of methods to detect alternative biomarkers, specific to 1,l -dichloroethene exposure would be useful.

Effect. Information regarding populations exposed specifically to 1,1-dichloroethene is not available. Limited information indicate that serum levels of certain enzymes indicative of liver damage may be elevated in humans exposed to 1,1-dichloroethene (EPA 1976). However, the elevation of liver enzymes is triggered by exposure to many other chemicals; hence, elevation of these enzymes cannot be considered a specific biomarker for 1,1-dichloroethene. Research leading to the identification of specific DNA adducts formed after 1,1-dichloroethene exposure would be valuable. This would facilitate medical surveillance leading to early detection of potentially adverse health effects and possible treatment.

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Absorption, Distribution, Metabolism, and Excretion. There are no quantitative data regarding absorption in humans by the inhalation, oral, or dermal route. The animal data indicate that 1,1-dichloroethene is efficiently absorbed by the inhalation (Dallas et al. 1983; McKenna et al. 1978b) and oral routes (Jones and Hathway 1978a; McKenna et al. 1978a; Putcha et al. 1986). These studies have been conducted mostly in rats and mice. Dermal absorption data are lacking, but absorption by this route should be suspected based on the physical and chemical properties of 1,1-dichloroethene and the fact that the fact that the Sencor mouse test was positive for initiation of papillomas.

No data were located regarding distribution of 1,1-dichloroethene or its metabolites in humans. Animal data regarding inhalation exposure (Jaeger et al. 1977a) and oral exposure (Jones and Hathway 1978b) to 1,1-dichloroethene indicate that 1,1-dichloroethene (or metabolites) distributes preferentially to the liver, kidney, and lung and that in general 1,1-dichloroethene does not accumulate in tissues. Additional data on the distribution of 1,1-dichloroethene following dermal exposure would be useful since humans can be exposed via this route as well. Studies regarding distribution through the placenta were not available.

Data regarding biotransformation of 1,1-dichloroethene in humans are not available. The use of human cell systems in culture might be considered a useful alternative to studying the metabolic fate of 1,l dichloroethene in individuals. The metabolism of 1,l -dichloroethene has been extensively studied in rats and mice following inhalation and oral exposure (Jones and Hathway 1978a, 1978b; McKenna et al. 1977, 1978a; Reichert et al. 1979). Experimental evidence indicates that the metabolism of 1,1-dichloroethene is a saturable process. Although information regarding metabolism following dermal exposure is lacking, there is no reason to believe that other pathways would operate after exposure by this route.

Data regarding excretion of 1,1-dichloroethene in humans are not available. Urinary excretion of metabolites is the main route of elimination of 1,1-dichloroethene metabolites in animals after inhalation (McKenna et al. 1978b) and oral exposure (McKenna et al. 1978a; Reichert et al. 1979). After exposure to high concentrations of 1,l -dichloroethene, however, elimination of unchanged 1, 1-dichloroethene in expired air was observed (Jones and Hathway 1978b; McKenna et al. 1978a, 1978b; Reichert et al. 1979). No studies were located regarding excretion following dermal exposure to 1,l -dichloroethene.

Comparative Toxicokinetics. No direct information exists to assess whether humans handle 1,1-dichloroethene in a way similar to that observed in animals. Toxicokinetics studies have been performed mainly in rats and mice, and the results suggest that no qualitative differences exist between these two species, although mice seem to metabolize 1,1-dichloroethene to a greater extent than rats (Jones and Hathway 1978a, 1978b; McKenna et al. 1977, 1978a; Reichert et al. 1979). Experiments in animals (mostly rats and mice) indicate that the liver, kidney, and lungs are common target organs across species. Data from occupationally exposed humans suggest that the liver is a target organ in humans (EPA 1976). Once reliable end points are determined in species other than rats and mice, it would be important to verify that primates are affected in a similar manner, in order to ensure that no unforeseen health effects might occur in humans.

Methods for Reducing Toxic Effects. There are no specific established methods or treatment for reducing absorption of 1,l -dichloroethene. Studies aimed at elucidating this mechanism would provide useful information. No information is available regarding the mechanism by which 1,1-dichloroethene distributes to tissues in the body. There are no well-established methods or treatment for reducing the body burden of 1,1-dichloroethene or metabolites or for prevention of toxicity following long-term exposure. The mechanism of toxicity of 1,1-dichloroethene in humans is not known, but there is evidence that 1,1-dichloroethene toxicity in animals is due to a reactive intermediate and not the parent compound (Dekant et al. 1989; Vamvakas and Anders 1990). Experimental methods exist that can prevent the toxic action of 1,1-dichloroethene in animals (i.e., administration of precursors of GHS) (Moslen et al. 1989b), but it is not known whether these methods are relevant to humans. Studies in primates could provide information regarding the mechanism of action of 1,1-dichloroethene that may be more relevant to humans than data obtained in rats and mice. Methods for mitigation of the adverse health effects induced by 1,1-dichloroethene in animals have involved administering the substance prior to exposure (Anderson et al. 1978).

2.9.3 On-going Studies

Studies being conducted by C.H. Tamburro and coworkers at the University of Louisville School of Medicine will continue medical surveillance of chemical industry workers exposed to vinylidene chloride with regard to gastrointestinal, pulmonary, brain, and hematopoietic cancers (IARC lW2).

2. HEALTH EFFECTS

Studies by Mary T. Moslen and coworkers at the University of Texas Medical Branch at Galveston are using 1,1-dichloroethene to selectively damage bile canaliculi to study liver function (Moslen 1993).