2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to l,l-dichloroethane. Its purpose is to present levels of significant exposure for l,l-dichloroethane based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of l,l-dichloroethane and (2) a depiction of significant exposure levels associated with various adverse health effects.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure -- inhalation, oral, and dermal -- and then by health effect -- death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods -- acute, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies 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 on the tables and graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects (LOAEL) in humans or animals or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) are of interest to health professionals and citizens alike.

2. HEALTH EFFECTS

Estimates of exposure posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1986a; EPA 1989), uncertainties are associated with the techniques.

2.2.1 Inhalation Exposure

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

ATSDR, in consultation with EPA, is evaluating the inhalation exposure database for development of inhalation MRLs. The evaluation process will be completed following the public comment period for this document.

Table 2-l and Figure 2-l describe the health effects observed in laboratory animals associated with inhalation exposure levels at varying time and exposure durations.

2.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to l,l-dichloroethane. No deaths were observed in rats exposed to 4,000 ppm for 8 hours, but an 8-hour exposure to 16,000 ppm was lethal (Smyth 1956). It has been reported in the early literature that the lethal exposure level of l,l-dichloroethane in mice was 17,500 ppm (Browning 1965). These values were reported in a secondary source and it is therefore impossible to assess their validity. Subchronic intermittent exposure to 500 ppm of l,l-dichloroethane for 13 weeks followed by l,000 ppm of l,l,-dichloroethane for an additional 13 weeks was not lethal to rats, rabbits, guinea pigs, or cats (Hofmann et al. 1971). Based on these limited data in laboratory animals, it would appear that l,l-dichloroethane causes death in animals at high concentrations (16,000 ppm).

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

2.2.1.2 Systemic Effects

One study of the subchronic effects of inhaled l,l-dichloroethane in animals was located. No adverse clinical effects were noted in rats, rabbits,

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

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Developmental							
1	Rat	10 d Gd6-15 7hr/d		3800		6000[a] (skeletal anomalies)	Schwetz et al. 1974
INTERMEDIATE EXPOSURE							
Death							
2	Rat	13 wk 6hr/d 5d/wk		1000			Hofmann et al. 1971
3	Gn Pig	13 wk 5d/wk 6hr/d		1000			Hofmann et al. 1971
4	Rabbit	13 wk 5d/wk 6hr/d		1000			Hofmann et al. 1971
5	Cat	13 wk 6hr/d 5d/wk		1000			Hofmann et al. 1971
Systemic							
6	Rat	13 wk 6hr/d 5d/wk	Hemato Hepatic Other (body wt)	1000 1000 1000			Hofmann et al. 1971
7	Gn Pig	13 wk 5d/wk 6hr/d	Hemato Hepatic Renal Other (body wt)	1000 1000 1000 1000			Hofmann et al. 1971

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
8	Rabbit	13 wk 5d/wk 6hr/d	Hemato Hepatic Renal Other (body wt)	1000 1000 1000 1000			Hofmann et al. 1971
9	Cat	13 wk 6hr/d 5d/wk	Hemato Hepatic Renal Other (body wt)	500 500 500 500	1000 (decreased body wt)	1000 (enzyme changes, histopathology)	Hofmann et al. 1971

[a]Adjusted for intermittent exposure and presented in Table 1-2.

d = day; wk = week; min = minute; Gd = gestational day; hemato = hematological; wt = weight

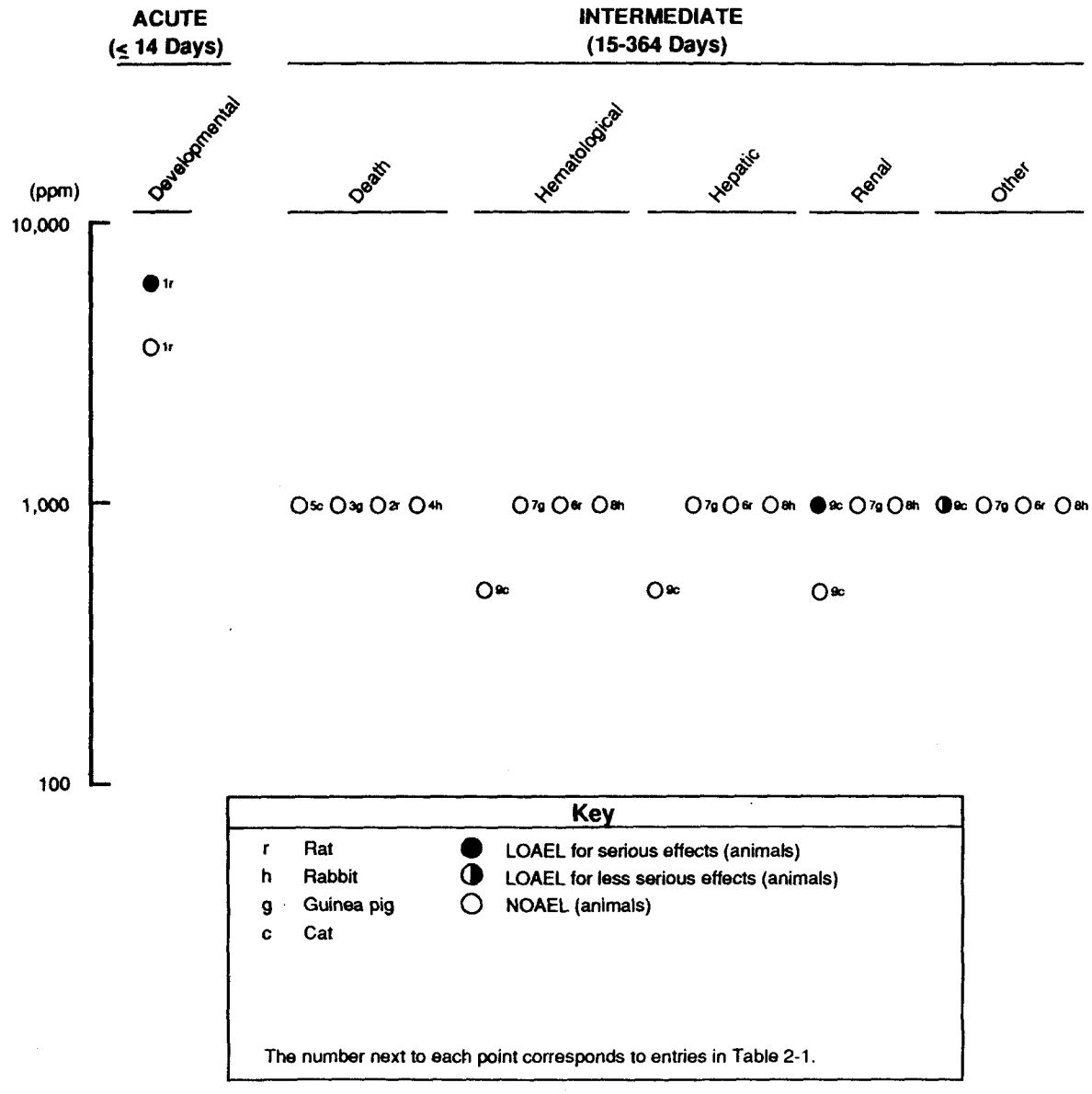

FIGURE 2-1. Levels of Significant Exposure to 1,1-Dichloroethane - Inhalation

or guinea pigs exposed to 1000 ppm l,l-dichloroethane for 13 weeks, which followed a prior 13 week exposure to 500 ppm of l,l-dichloroethane (Hofmann et al. 1971). Histological examination of the liver and kidneys after 26 weeks revealed no treatment-related lesions. These NOAELs are recorded in Table 2-l and plotted in Figure 2-l. However, this study is limited in that an inadequate number of animals was tested. Also, it is not clear how the lack of effects observed in these experiments relates to continuous exposure to 1000 ppm l,l-dichloroethane over a 26-week period. This is particularly relevant for humans living in the vicinity of hazardous waste sites since exposure to l,l-dichloroethane in this situation is expected to be continuous. No studies were located regarding respiratory, gastrointestinal, hematological, musculoskeletal, or dermal/ocular effects in humans or animals following inhalation exposure to l,l-dichloroethane.

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

Hepatic Effects. No studies were located regarding hepatic effects in humans following inhalation exposure to l,l-dichloroethane. Rats, rabbits, guinea pigs and cats experienced no change in serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) activity after intermittent 6-hour inhalation exposure to 500 ppm l,l-dichloroethane for 13 weeks followed by 13 weeks of exposure 6 hours per day to 1,000 ppm l,l-dichloroethane (Hofmann et al. 1971). Furthermore, no treatment-related histopathological lesions were noted in the livers of these animals after this 26 week exposure regimen. Six days after the tenth and last daily 7-hour exposure to 6,000 ppm l,l-dichloroethane, female rats exhibited a slight but statistically significant increase in relative liver weight (Schwetz et al. 1974). However, there was no increase in SGPT activity over control values and no changes in the gross appearance of the liver were noted at necropsy in these animals. These results indicate that under the conditions of these studies, l,l-dichloroethane is not hepatotoxic.

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to l,l-dichloroethane. Renal injury was apparent in cats intermittently exposed 6 hours daily to 1,000 ppm l,l-dichloroethane for 13 weeks following 13 weeks of intermittent exposure to 500 ppm l,l-dichloroethane (Hofmann et al. 1971). Serum urea and creatinine were increased in these animals. One cat was so severely affected that it had to be removed from the study. Histopathological lesions in the kidney tubules (including crystalline precipitates and dilation) were noted at necropsy. The ill health of these animals was also manifest by a progressive decrease in

body weight. Rats, rabbits, and guinea pigs similarly exposed to l,l-dichloroethane exhibited no adverse effects. Thus, based on the results of this study, cats appear to be uniquely sensitive to the nephrotoxic effects of l,l-dichloroethane. This study is limited in that only four cats were used and it is not clear how the effects observed in this experiment relate to continuous exposure to 1000 ppm l,l-dichloroethane over a 26-week period. A NOAEL of 500 ppm was identified for cats. However, the observation that all cats exhibited a high degree of renal toxicity suggests that these findings were toxicologically significant.

2.2.1.3 Immunological Effects

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

2.2.1.4 Neurological Effects

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

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

2.2.1.5 Developmental Effects

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

In the only animal study located, retarded fetal development without any significant toxic effects was observed following inhalation exposure 7 hours daily to l,l-dichloroethane in pregnant rats during days 6 through 15 of gestation (Schwetz et al. 1974). Except for a significant increase in the incidence gf fetuses with delayed ossification of sternebrae at an exposure level of 6,000 ppm, no other malformations were observed. The use of only two exposure levels precluded the assessment of a dose-dependent response. Maternal food consumption and body weight were significantly reduced in the treated animals during the exposure period but returned to normal by day 21 of gestation. No other adverse effects were noted in the dams. This study showed that l,l-dichloroethane is only slightly fetotoxic, though not teratogenic, in rats following inhalation exposure to high levels of the chemical, and it is not likely that humans would experience adverse developmental effects as a result of low-level exposure to l,l-dichloroethane. Based on the observed effects, the LOAEL value for the developmental toxicity of l,l-dichloroethane in rats was 6,000 ppm; the NOAEL was 3,800 ppm. These values are listed in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Reproductive Effects

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

2.2.1.7 Genotoxic Effects

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

2.2.1.8 Cancer

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

2.2.2 Oral Exposure

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

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

2.2.2.1 Death

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

Secondary sources report the following oral LD_{50} in rats: 725 mg/kg (RTECS 1988) and 14.1 g/kg (Grayson 1978). Since these values were obtained from secondary sources, no details were available to assess the quality of these data. Survival was poor in both treated and control rats and mice in the chronic bioassay conducted by NCI (1977), but a significant dose-related trend for mortality was noted in the male rats and mice. The deaths could not be attributed to cancer or any other non-neoplastic lesions, though pneumonia was observed in a large percentage of the rats, and this was thought to be related to the increased mortality (NCI 1977).

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

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

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
INTERMEDIATE EXPOSURE								
Death								
1	Rat	(G)	6 wk 5d/wk 1x/d		M:5620		F:3160	NCI 1977
2	Mouse	(G)	6 wk 5d/wk 1x/d		3160		5620	NCI 1977
Systemic								
3	Rat	(G)	6 wk 5d/wk 1x/d	Other		M:562 (decreased body weight) F:1780		NCI 1977
4	Mouse	(G)	6 wk 5d/wk 1x/d	Other (body weight)	10000			NCI 1977
CHRONIC EXPOSURE								
Death								
5	Rat	(G)	78 wk 5d/wk 1x/d				[a]M:382 F:475	NCI 1977
6	Mouse	(W)	52 wk ad lib		475			Klaunig et al. 1986
7	Mouse	(G)	78 wk 5d/wk 1x/d		M:1442 F:1665		M:2885 F:3331	NCI 1977

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
Systemic								
8	Rat	(G)	78 wk 5d/wk 1x/d	Resp	M:764 F:950			NCI 1977
				Cardio	M:764 M:950			
				Gastro	M:764 M:950			
				Hemato	M:764 M:950			
				Hepatic	M:764 M:950			
				Renal	M:764 M:950			
				Other (body weight)	M:764 F:950			
9	Mouse	(G)	78 wk 5d/wk 1x/d	Resp	M:2885 F:3331			NCI 1977
				Cardio	M:2885 M:3331			
				Gastro	M:2885 F:3331			
				Hemato	M:2885 F:3331			
				Hepatic	M:2885 F:3331			
				Renal	M:2885 F:3331			
				Other (body weight)	M:2885 F:3331			

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
10	Mouse	(W)	52 wk ad lib	Resp	475			Klaunig et al. 1986
				Hepatic	475			
				Renal	475			
				Other (body weight)	475			
Cancer								
11	Rat	(G)	78 wk 5d/wk 1x/d				[b]F:475 (CEL) (blood vessels, mammary glands)	NCI 1977
12	Mouse	(G)	78 wk 5d/wk 1x/d				F: (CEL) 3331 (uterus)	NCI 1977

[a]Converted to an equivalent concentration of 7,640 ppm in food for presentation in Table 1-4.

[b]Converted to an equivalent concentration of 9,500 ppm in food for presentation in Table 1-4.

d = day; wk = week; min = minute; M = male; F = female; G = gavage; W = water; ad lib = ad libitum; CEL = cancer effect level; Resp = respiratory; Cardio = cardiovascular; Gastro = gastrointestinal; Hemato = hematological.

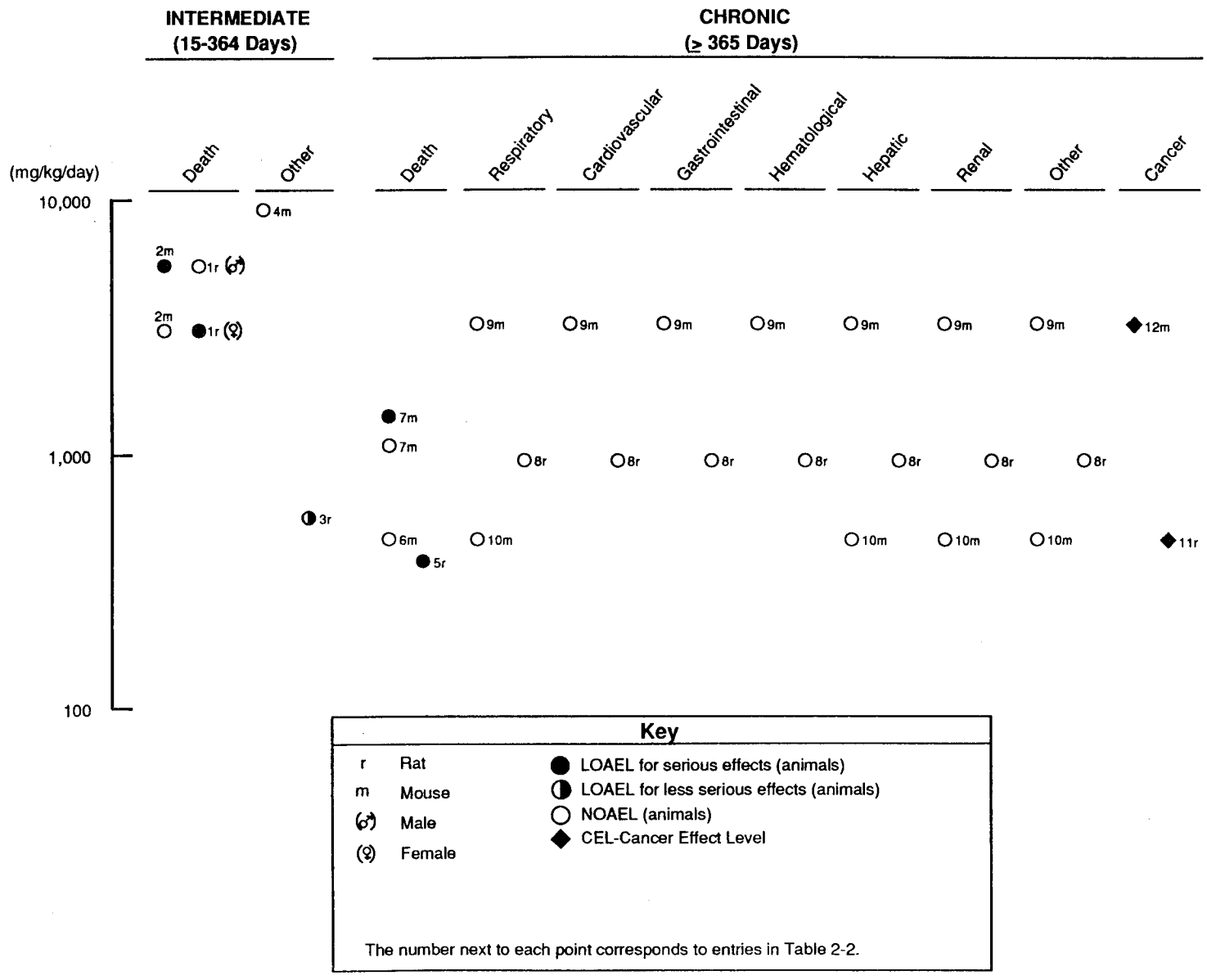

FIGURE 2-2. Levels of Significant Exposure to 1,1-Dichloroethane - Oral

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or dermal/ocular effects in humans or animals following oral exposure to l,l-dichloroethane. There were no treatment-related histopathological changes in the liver, kidneys, or other tissues of the rats examined in the NCI (1977) study. Similarly, no histopathological alterations were noted in the liver, kidneys, or lungs of male mice that ingested relatively high levels of l,l-dichloroethane in drinking water (up to 2500 mg/L) for 52 weeks (Klaunig et al. 1986).

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

2.2.2.3 Immunological Effects

2.2.2.4 Neurological Effects

2.2.2.5 Developmental Effects

2.2.2.6 Reproductive Effects

2.2.2.7 Genotoxic Effects

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to l,l-dichloroethane. The results of the bioassay conducted by NCI (1977) suggest carcinogenic effects induced by l,l-dichloroethane in rats and mice. A significant positive dose-related trend was observed for the incidence of hemangiosarcomas and mammary adenocarcinomas in female rats, hepatocellular carcinoma in male mice, and endometrial stromal polyps in female mice. However, only the incidence of endometrial stromal polyps in female mice was significantly increased over the corresponding control animals. There are several limitations to this study. Survival was poor in both treated and control animals, thereby limiting the validity of these results. Although it appears that the maximum tolerated dose (MTD) had been reached (475 mg/kg/day for rats; 3,331 mg/kg/day for mice), it is not clear that the increase in mortality was treatment-related. Furthermore, there were no other treatment-related effects on body weight, clinical signs, or the incidence of non-neoplastic lesions. Because of the high mortality in both the treated and control animals, the authors concluded that not enough animals survived to be at risk for late-developing tumors. Thus, though the results of this bioassay suggest that l,l-dichloroethane is carcinogenic to rats and mice, the evidence is not conclusive.

The carcinogenicity of l,l-dichloroethane was studied in mice chronically exposed to 475 mg/kg/day of the compound in the drinking water (Klaunig et al. 1986). A two-stage carcinogenesis protocol was also employed in this study to assess the ability of l,l-dichloroethane to act as a tumor promoter. Neither l,l-dichloroethane-treated animals initiated with diethylnitrosamine (DENA) or animals treated with l,l-dichloroethane without initiation showed a significant increase in the incidence of lung or liver tumors over their corresponding controls. The authors concluded that l,l-dichloroethane was not carcinogenic to mice and that it did not act as a tumor promoter following initiation with DENA under the conditions of this study. This was generally a well-conducted study: the MTD was used (as demonstrated in preliminary rangefinding studies), an adequate number of animals was used, and the appropriate clinical, gross, and microscopic observations were made. However, the conclusion that l,l-dichloroethane is not a tumor promoter may not be entirely justified since a maximal response was observed in terms of tumor incidence in the DENA-alone-treated mice (100% tumor incidence at 52 weeks). Therefore, an increase in the incidence of liver tumors due to l,l-dichloroethane following DENA initiation, if it existed, could not have been detected. Furthermore, since measurement of water consumption and replenishment were only done once a week, there was no way to determine the extent, if any, evaporation contributed to loss of the test chemical and affected the reported level of exposure. However, precautions were taken to minimize the loss of test chemical during the l-week period; amber bottles with Teflon stoppers and double sipper tubes were used. Since l,l-dichloroethane is a volatile chemical, this may present a limitation to the interpretation of results obtained from drinking water administration.

The difference in results (e.g., induction of liver tumors) between the NC1 (1977) and Klaunig et al. (1986) studies may be due to the method of administration, vehicle, and/or doses used. The pharmacokinetics of l,l-dichloroethane may vary considerably when administered in drinking water ad libitum over a week as compared to bolus doses given in corn oil. Evidence obtained with carbon tetrachloride indicates that corn oil likely acts as a reservoir in the gut to delay and diminish the systemic absorption of the lipophilic chemical, while such a chemical is probably rapidly absorbed when ingested in water (Kim et al. 1990a,b). Furthermore, the doses given to mice by gavage were approximately six times higher than the drinking water concentrations. Species differences in susceptibility may also have played a role, as rats used in the NC1 study showed adverse effects at a dose that was without effect in the Klaunig et al. (1986) study. Sufficient information is not available to assess the contributions of these factors to the apparently disparate responses; i.e., the finding of 475 mg/kg/day as a LOAEL in the NC1 study and the same dose as a NOAEL in the Klaunig study.

2.2.3 Dermal Exposure

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

2.2.3.1 Death

2.2.3.2 Systemic Effects

2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

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

It is known that an isomer of l,l-dichloroethane, 1,2-dichloroethane, is well-absorbed following inhalation exposure. However, the blood/air partition coefficient for 1,2-dichloroethane is approximately four times that of l,l-dichloroethane. This suggests that l,l-dichloroethane would not be absorbed into the blood from air as readily as 1,2-dichloroethane, but it will still be well absorbed from the lung (Sato and Nakajima 1987). However, the excretion of metabolites in the urine indicated that l,l-dichloroethane was absorbed following inhalation exposure, though the rate or extent of dichloroethane absorption is not known, since this represents theoretical estimates rather than actual data (Sato and Nakajima 1987).

2.3.1.2 Oral Exposure

No studies were located that quantitated the absorption of ingested l,l-dichloroethane in humans or animals. However, when 700 mg [^{14}C]- l,l-dichloroethane/kg was orally administered to rats and mice, absorption was evidenced by the presence of radiolabel in expired air and the presence of radiolabeled metabolites in urine, though there was no quantitative assessment made of the extent or rate of absorption (Mitoma et al. 1985).

2.3.1.3 Dermal Exposure

No studies were located regarding the absorption of l,l-dichloroethane in humans or animals following dermal exposure. However, Browning (1965) reported evidence that l,l-dichloroethane penetrates the skin. l,l-Dichloroethane was applied to the shaved abdominal skin of rabbits that were fitted with masks to prevent inhalation of the compound. Exhaled air from the rabbits was passed into pure alcohol, and the presence of halogen was tested by flaming a copper wire introduced into it. The green color observed after 1 hour indicated that the halogen ion was absorbed into the bloodstream, though no quantitative assessment of the extent or rate of absorption was possible.

2.3.1.4 Other Routes of Exposure

Binding of radiolabeled l,l-dichloroethane or its metabolites to macromolecules (e.g. DNA, RNA, and proteins) in the liver, stomach, lung, and kidney of rats and mice following intraperitoneal injection is evidence that absorption of l,l-dichloroethane occurs (Colacci et al. 1985).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

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

2.3.2.2 Oral Exposure

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

2.3.2.3 Dermal Exposure

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

2.3.2.4 Other Routes of Exposure

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

2.3.3 Metabolism

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

Large portions of orally administered l,l-dichloroethane are excreted unchanged by rats and mice in the expired air (Table 2-3). Forty-eight hours after oral administration of quite high doses of [^{14}C]-1,1-dichloroethane, 7.4% and 29.3% of the dose was metabolized by rats and mice, respectively. The predominant metabolite in both species was [^{14}C]-CO_2 (Mitoma et al. 1985). It is likely that the ingested radiolabeled l,l-dichloroethane underwent first-pass extraction by the liver. It has been suggested that high doses such as those used in this study exceed the capacity of the animals to metabolize l,l-dichloroethane (Bruckner 1989). The radiolabeled compound that was not excreted unchanged in the expired air was probably largely metabolized in the liver, followed by subsequent redistribution of labeled metabolites to other organs prior to their excretion.

l,l-Dichloroethane was added to phenobarbital-induced and uninduced hepatic microsomes from rats, and P-450 enzyme activity was monitored by measuring the production of metabolite spectrophotometrically. Induction with phenobarbital significantly stimulated the binding, as well as hepatic microsomal NADPH oxidation, demonstrating the involvement of the P-450 system. Increased P-450 levels resulted in an increased affinity of enzyme for l,l-dichloroethane, thus increasing the rate of metabolism. ,6-naphthaflavone, an agent that specifically induces P-448, had no effect on the extent of l,l-dichloroethane binding, suggesting that P-448 is not involved in

TABLE 2-3. Metabolic Disposition of Radiolabeled 1,1-Dichloroethane in Rats and Mice[a]

Dose	Rat (700 mg/kg)	Mouse (1,800 mg/kg)
Expired air	86.1	70.4
Carbon dioxide (a)	5.1	25.2
Excreta (b)	0.9	1.6
Carcass (c)	1.4	2.4
% Metabolized (a)+(b)+(c)	7.4	29.2
Recovery	93.5	99.6

[a]Reported as % of the administered dose.

Source: Mitoma et al. 1985.

l,l-dichloroethane metabolism (McCall et al. 1983). The rate and extent of l,l-dichloroethane metabolism was increased 6.3 times in the hepatic microsomes of rats that were induced by chronic ethanol consumption (Sato et al. 1980). Chronic ethanol consumption increased the levels of P-450, supporting the role of cytochrome P-450 in the metabolism of l,l-dichloroethane.

Colacci et al. (1985) reported that l,l-dichloroethane binds to nucleic acids and proteins in vivo and in vitro. This binding is also mediated by the liver cytochrome-P-450 system. Phenobarbital enhances the extent of covalent macromolecular binding. Hence, metabolites of l,l-dichloroethane bind to the DNA, RNA, and tissue proteins. The involvement of P-450 was confirmed by a reduction in binding when rats were pretreated with SKF-525-A, a P-450 inhibitor. Liver microsomes are the only tissue microsomes that are efficient in bioactivating l,l-dichloroethane. Therefore, binding to macromolecules of various organs in vivo could be due to an hepatic metabolite that is sufficiently stable to reach extrahepatic organs. Addition of GSH to the microsomal system suppresses the extent of binding and minimizes the potential for toxic effects.

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

Chloroethanes have been shown to undergo dechlorination by an enzyme system that is similar to the hepatic microsomal mixed function oxidase system (Van Dyke and Wineman 1971). Dechlorination was inducible by phenobarbital and required oxygen and NADPH. However, dechlorination also required a factor from the cytosolic fraction of the liver homogenate for optimal dechlorinating activity. In terms of structural requirements, dechlorination was enhanced if the carbon atom containing the chlorine had only one hydrogen. In a microsomal incubation, 13.5% of the ^{36}C1 of l,l-dichloroethane was enzymatically removed after 30 minutes, while less than 0.5% of the ^{36}C1 of 1,2-dichloroethane was removed (Van Dyke and Wineman 1971).

Under hypoxic conditions, l,l-dichloroethane gives rise to free radicals. However, its ability to develop free radicals is much less when compared to

TABLE 2-4. Production of Metabolites from l,l-Dichloroethane with Hepatic Microsomes from Phenobarbital-Induced Rats

Metabolites	Metabolite Production[a] (nmoles/mg microsomal proteion/20 min)
Acetic acid	179 (15)
2,2-Dichloroethane	0.12 (0.02)
Chloroacetic acid	0.22 (0.08)
Dichloroacetic acid	0.048 (0.005)
Chloroacetaldehyde	<0.07 (0.03)

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

Source: McCall et al. 1983.

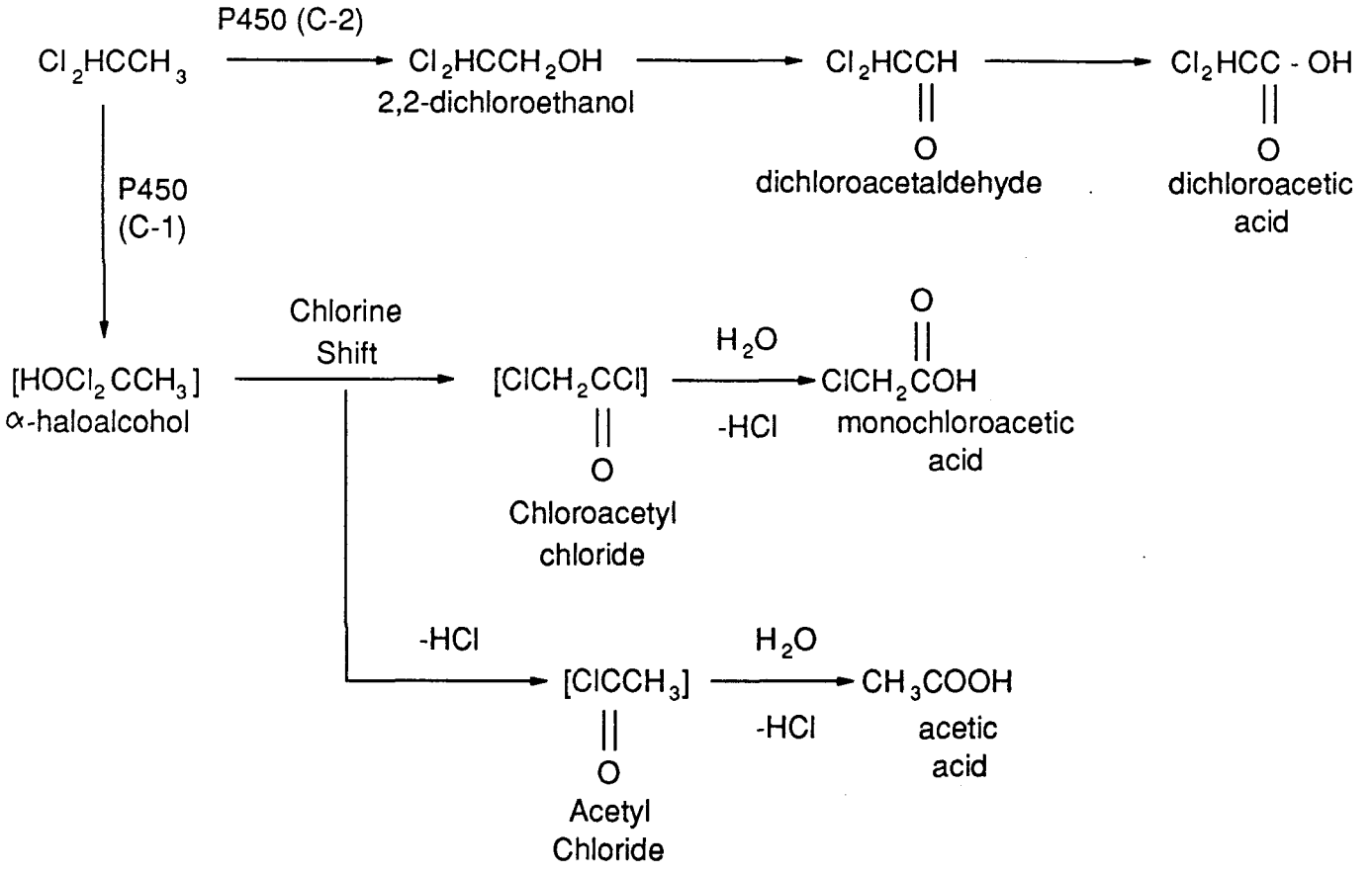

FIGURE 2-3. Proposed Metabolic Scheme for 1,1-Dichloroethane

Source: McCall et al. 1983

other chlorinated hydrocarbons like trichloroethane and carbon tetrachloride. It has been suggested that these free radicals possess the potential to induce toxic and carcinogenic effects. There is no correlation between the ease of free radical activation, covalent binding formation, or carcinogenic potency (Tomasi et al. 1984).

2.3.4 Excretion

One study was located regarding the extent or rate of l,l-dichloroethane excretion in humans (Sato and Nakajima 1987). They reported that 59% of the l,l-dichloroethane inhaled was metabolized and excreted in the urine and 41% was excreted in expired air. This amount of inhaled l,l-dichloroethane that was metabolized and excreted in the urine was considerably less than the 88% of inhaled 1,2-dichloroethane that was metabolized and excreted in the urine. However, these values are theoretical and not actual.

A study conducted by Mitoma et al. (1985) indicated that more than 90% of an oral dose in rats (700 mg/kg) and mice (1,800 mg/kg) was excreted unchanged or as carbon dioxide within 48 hours after administration. However, no blood, urine, or tissue concentrations were monitored over time to determine the elimination kinetic parameters. No studies were located in humans or animals regarding excretion of l,l-dichloroethane following dermal exposure.

2.4 RELEVANCE TO PUBLIC HEALTH

Relatively little information is available on the health effects of l,l-dichloroethane in humans or animals. However, the limited data available in animals indicate that it is less toxic than its isomer, 1,2-dichloroethane, and most other chlorinated aliphatics (Bruckner 1989). Chlorinated aliphatics as a class are known to cause central nervous system depression, and respiratory tract and dermal irritation when humans are exposed by inhalation to sufficiently high levels (Parker et al. 1979).

The available data in animals suggest that inhaled l,l-dichloroethane may be nephrotoxic. However, this finding is limited to one species (cat) and was not observed in three other species tested under the same conditions. Another effect observed in animals but not humans following inhalation exposure to l,l-dichloroethane exposure is fetotoxicity. Suggestive, but inconclusive, evidence of carcinogenicity was obtained in an oral chronic bioassay of l,l-dichloroethane in rats and mice.

Death. No reports of death in humans following exposure to l,l-dichloroethane were found. Death has been observed in laboratory animals following inhalation and oral exposure to l,l-dichloroethane. No reliable LC_{50} or LD_{50} data were found, but lethal doses of l,l-dichloroethane are perhaps 5 to 10 times higher than those required to produce death following exposure to 1,2-dichloroethane or tetrachlorocarbons (EPA 1985; Hofmann et

al. 1971; Smyth 1956). Thus, it is likely that l,l-dichloroethane can be fatal to humans, if exposure to high enough levels occurs.

The cause of death in animals following exposure to l,l-dichloroethane has not been well-defined, but Plaa and Larson (1965) reported that deaths observed following intraperitoneal injection of this compound appeared to be due to fatal central nervous system depression.

Systemic Effects. The use of l,l-dichloroethane as an anesthetic was discontinued when it was discovered that this compound induced cardiac arrhythmias in humans at anesthetic doses (approximately 105,000 mg/m^3, or 26,000 ppm). The mechanism of action for the induction of cardiac arrhythmias by l,l-dichloroethane is not known. However, when the cardiac muscle is markedly depressed, it is more susceptible to the effects of catecholamines. Secretion of catecholamines is increased in this situation by compensatory and other mechanisms, resulting in excessive spontaneous contractions of the heart. This is an effect common to exposure to other chlorinated aliphatics at high concentrations (Reinhardt et al. 1971). Cardiovascular toxicity has not been reported in animals following exposure to l,l-dichloroethane.

No reports of adverse renal effects in humans following exposure to l,l-dichloroethane were found. Nephrotoxicity has been observed in cats following subchronic inhalation exposure to l,l-dichloroethane. However, rats, rabbits, and guinea pigs exposed under the same conditions failed to exhibit any toxic effects on the kidney (Hofmann et al. 1971). Plaa and Larson (1965) tested renal function in mice following intraperitoneal injection of l,l-dichloroethane, and found that adverse effects on the kidney were only observed at lethal doses. These effects included increased glucose and protein in the urine and tubular swelling. Though data obtained following intraperitoneal injection provides information on potential health effects, data from oral, inhalation and dermal experiments are more relevant to possible exposures in humans. No histopathological changes in the kidney were noted after chronic ingestion of l,l-dichloroethane by rats and mice (Klaunig et al. 1986; NCI 1977). The toxicological significance of the nephrotoxicity observed in cats and the mice with regard to human health is not known given the small number of animals tested (cats), the lack of a nephrotoxic effect in other species and in other studies where l,l-dichloroethane was administered orally, and the fact that nephrotoxicity is not an effect commonly attributed to the halogenated hydrocarbons.

Immunological Effects. No studies were located regarding immunologic effects in humans or animals following exposure to l,l-dichloroethane, and it is not known if l,l-dichloroethane is immunotoxic in humans.

Neurological Effects. Chlorinated aliphatics as a class are known to cause central nervous system depression following high-level exposure in humans and animals. No reliable dose-response data were found on the central

nervous system depression induced by l,l-dichloroethane, though l,l-dichloroethane was once used as an anesthetic agent in humans. However, Plaa and Larson (1965) attributed deaths observed in mice following intraperitoneal injection to fatal central nervous system depression. Neurologic effects associated with long-term exposure to l,l-dichloroethane in humans or animals have not been reported.

Developmental Effects. Adverse developmental effects in humans associated with exposure to l,l-dichloroethane have not been reported. One study in rats indicated that inhalation exposure to l,l-dichloroethane resulted in retarded fetal development (delayed ossification of vertebrae) in the absence of significant maternal toxicity (Schwetz et al. 1974). The absence of maternal toxicity implies a direct effect on the fetus, rather than effects due to illness in the dam. The implications of the findings from one study with regard to potential developmental effects in humans are not known.

Reproductive Effects. No studies were located regarding reproductive effects in humans or animals following exposure to l,l-dichloroethane, and it is not known if l,l-dichloroethane has the potential to cause adverse reproductive effects in humans.

Genotoxic Effects. No studies were located regarding in vivo genotoxic effects in humans. The genotoxic potential of l,l-dichloroethane has been investigated in vitro in Salmonella tvphimurium (Riccio et al. 1983; Simmon et al. 1977), Saccharomyces cerevisiae (Bronzetti et al. 1987; Simmon et al. 1977), and Syrian hamster embryo cells (Hatch et al. 1983). In addition in vitro and in vivo assays have been conducted using rat and mouse organs (Colacci et al. 1985). Results of these studies are summarized in Table 2-5. Results from three studies conducted in S. typhimurium tester strains were conflicting. l,l-Dichloroethane was nonmutagenic in yeast cells even in the presence of metabolic activation system. However, because of insufficient reporting of data by Bronzetti et al. (1987) and Simmon et al. (1977), no assessment of the genotoxic potential of l,l-dichloroethane in S. cerevisiae can be made. The available data from the remaining studies indicate that, although l,l-dichloroethane did not induce cell transformation in BALB/c-3T3 cells (Tu et al. 1985), it increased the frequency of transformations induced by Simian adenovirus (SA7) in hamster embryo cells (Hatch et al. 1983).

In the Ames assay, l,l-dichloroethane was nonmutagenic in Salmonella strains TA97, TA98, Ta100, and TA102 (Nohmi et al. 1985). The compound was tested with and without metabolic activation. The highest dose was toxic to all strains of bacteria. In contrast, l,l-dichloroethane was mutagenic to strains TA1537, TA98, TA100, and TA1535 exposed to its vapor in a desiccator in the presence and absence of S9 mix (Riccio et al. 1983). Although the tests were conducted using three dose levels, the authors did not report the actual doses tested, and therefore the presence of a dose-dependent response could not be assessed. Simmon et al. (1977) on the other hand obtained

TABLE 2-5. Genotoxicity of 1,1-Dichloroethane In Vitro

End Point	Species (Test System)	Results: With Activation	Results: Without Activation	Reference
Prokaryotic organisms:				
Gene mutation	Salmonella typhimurium (Ames assay)	-	-	Nohmi et al. 1986
	S. typhimurium (Dessicator assay; vapor exposure)	+	+	Riccio et al. 1983
	S. typhimurium (Dessicator assay; vapor exposure)	-	No data	Simmon et al. 1977
Eukaryotic organisms:				
Gene mutation	Saccharomyces cerevisiae D7	-	-	Bronzetti et al. 1987
	S. cerevisiae D3 (Suspension assay)	-	No data	Simmon et al. 1977
Mammalian cells:				
DNA viral transformation	Syrian hamster embryo (cell transformation assay; vapor exposure)	No data	+	Hatch et al. 1983
Cell transformation	BALB/C-3T3 (cell transformation assay; exposure in sealed chamber)	No data	-	Tu et al. 1985
Macromolecular binding	Rat and mouse organs	+[a]	No data	Colacci et al. 1985

- = negative result; + = positive result;

[a]Pretreatment with phenobarbitone enhanced the extent of binding to DNA, microsomal RNA and proteins while addition of GSH suppressed the binding.

negative results using the same strains of Salmonella and a similar protocol. The concentrations of l,l-dichloroethane tested were not reported. Because the reporting of data was insufficient in studies by Riccio et al. (1983) and Simmon et al. (1977), the discrepancies in their reported results cannot be explained at this time.

l,l-Dichloroethane was nonmutagenic in yeast strains D3 and D7, even in the presence of S9 mix (Bronzetti et al. 1987; Simmon et al. 1977). Bronzetti et al. (1987) conducted an assay using strain D7 of Saccharomvces cerevisiae from the stationary and logarithmic growth phase. The cells harvested from the log phase cultures contained cytochrome P-450 and were capable of metabolizing promutagens to genetically active products. Both studies lacked details regarding doses of l,l-dichloroethane tested, though conflicting results may also be due to impurities in the chemicals used.

Tu et al. (1985) exposed BALB/c-3T3 cells to l,l-dichloroethane in a sealed chamber for 24 hours. No cell transformation was detected. This lack of effect may be due to the short period of exposure. However, l,l-dichloroethane increased the frequency of transformation induced by SA-7 virus in Syrian hamster embryo cells (Hatch et al. 1983). Embryo cell cultures were exposed in a sealed treatment chamber to volatilized l,l-dichloroethane for 20 hours and then treated with SA7 virus for 3 hours. l,l-Dichloroethane treatment significantly increased the viral transformation frequency in cells in a dose-dependent manner. The highest concentration (1,000 μg/mL) was cytotoxic. These results reflect the capacity of l,l-dichloroethane to interact with cellular DNA in hamster embryo cells.

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

that binding is enhanced with induction of P-450 suggests that it represents the metabolite(s). Thus, GSH appears to play a detoxification role in the metabolism of l,l-dichloroethane. The fact that l,l-dichloroethane binds to nucleic acid suggests that it may have a potential to produce mutation in a mammalian system.

Cancer. There is inconclusive evidence that l,l-dichloroethane may be carcinogenic in humans. A significant positive dose-related trend was observed for the incidence of hemangiosarcomas and mammary adenocarcinomas in female rats, hepatocellular carcinoma in male mice, and endometrial stromal polyps in female mice. However, only the incidence of endometrial stromal polyps in female mice was significantly increased over the corresponding control animals. Limitations in this study (e.g., poor survival in both treated and control animals) preclude the consideration of these results as conclusive evidence of carcinogenicity (NCI 1977).

Results of a recently reported drinking water bioassay in mice indicated that l,l-dichloroethane is not carcinogenic (Klaunig et al. 1986). Possible differences in the pharmacokinetics of l,l-dichloroethane between the NCI (1977) and Klaunig et al. (1986) studies because of the different methods of administration and different vehicle and/or differences in dose levels employed may account for the disparate results. An in vitro assay of carcinogenicity initiation also yielded negative results for l,l-dichloroethane (Herren-Freund and Pereira 1986).

The induction of γ-glutamyltranspeptidase (GTP) foci, which are putative preneoplastic lesions, in isolated rat liver hepatocytes correlates well with carcinogenicity. l,l-Dichloroethane failed to induce GTP foci in liver hepatocytes obtained from rats and mice treated with l,l-dichloroethane for 7 days followed by promotion with phenobarbital (Herren-Freund and Pereira 1986). This suggests that l,l-dichloroethane is not carcinogenic, though these results are not conclusive.

There is limited evidence that neither confirms or dispels the carcinogenic potential of l,l-dichloroethane. Thus, these results are inconclusive as to whether it poses a cancer threat for humans. The EPA has classified l,l-dichloroethane as a Class C chemical which is defined as a possible human carcinogen (IRIS 1990).

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 or cell 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 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 (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds), Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc and selenium). Biomarkers of exposure to l,l-dichloroethane 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 often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by l,l-dichloroethane 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. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to l,l-Dichloroethane

Although analytical methods are available to determine levels of l,l-dichloroethane in blood, urine, and expired breath, no information was located on levels of l,l-dichloroethane found in human tissues following exposure to measured quantities of this chemical.

2.5.2 Biomarkers Used to Characterize Effects Caused by l,l-Dichloroethane

l,l-Dichloroethane was used as an anesthetic in the early part of this century (Browning 1965; Konietzko 1984). However, no information was

available on blood levels associated with anesthesia or the occurrence of anesthesia-induced cardiac arrhythmias.

2.6 INTERACTIONS WITH OTHER CHEMICALS

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

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No populations unusually susceptible to l,l-dichloroethane or chlorinated ethanes in general have been identified. NIOSH (1978) has identified the following individuals as possibly being at increased risk from exposure to l,l-dichloroethane: (1) Individuals with skin disease because of the purported dermal irritant effects induced by l,l-dichloroethane. (2) Individuals with liver disease because of the role of this organ in the biotransformation and detoxification of xenobiotics such as l,l-dichloroethane. (3) Individuals with impaired renal function because of the limited evidence that l,l-dichloroethane is nephrotoxic in animals. (4) Individuals with chronic respiratory disease because of the purported respiratory irritant effects induced by l,l-dichloroethane. Although there are no data to substantiate this, additional populations that may be unusually susceptible to l,l-dichloroethane include children and the elderly because of immature or compromised metabolic capabilities, and phenobarbital or alcohol consumers because of the ability of these substances to alter the activity of the cytochrome P-450 system.

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

2.8 ADEQUACY OF THE DATABASE

Section 104(i)5 of CERCLA 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 l,l-dichloroethane is available. Where adequate information is not available, ATSDR, in conjunction with 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 l,l-dichloroethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.8.1 Existing Information on the Health Effects of l,l-Dichloroethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to l,l-dichloroethane are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of l,l-dichloroethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

Figure 2-4 graphically depicts the information that currently exists on the health effects of l,l-dichloroethane. The literature reviewed concerning the health effects of l,l-dichloroethane in humans consisted solely of an anecdotal report describing the occurrence of cardiac arrhythmias when this compound was used as a gaseous anesthetic. Chlorinated aliphatics as a class are known to cause central nervous system depression. Respiratory tract and dermal irritation also result when humans are exposed by inhalation to sufficiently high levels. It has been inferred that l,l-dichloroethane causes these latter effects, but no reliable data were found that verified this activity.

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

2.8.2 Identification of Data Needs

Acute-Duration Exposure. No reliable information is available on the effects of single-dose exposures in humans and animals. LD_{50} values are available in secondary sources, but no details are available to assess the

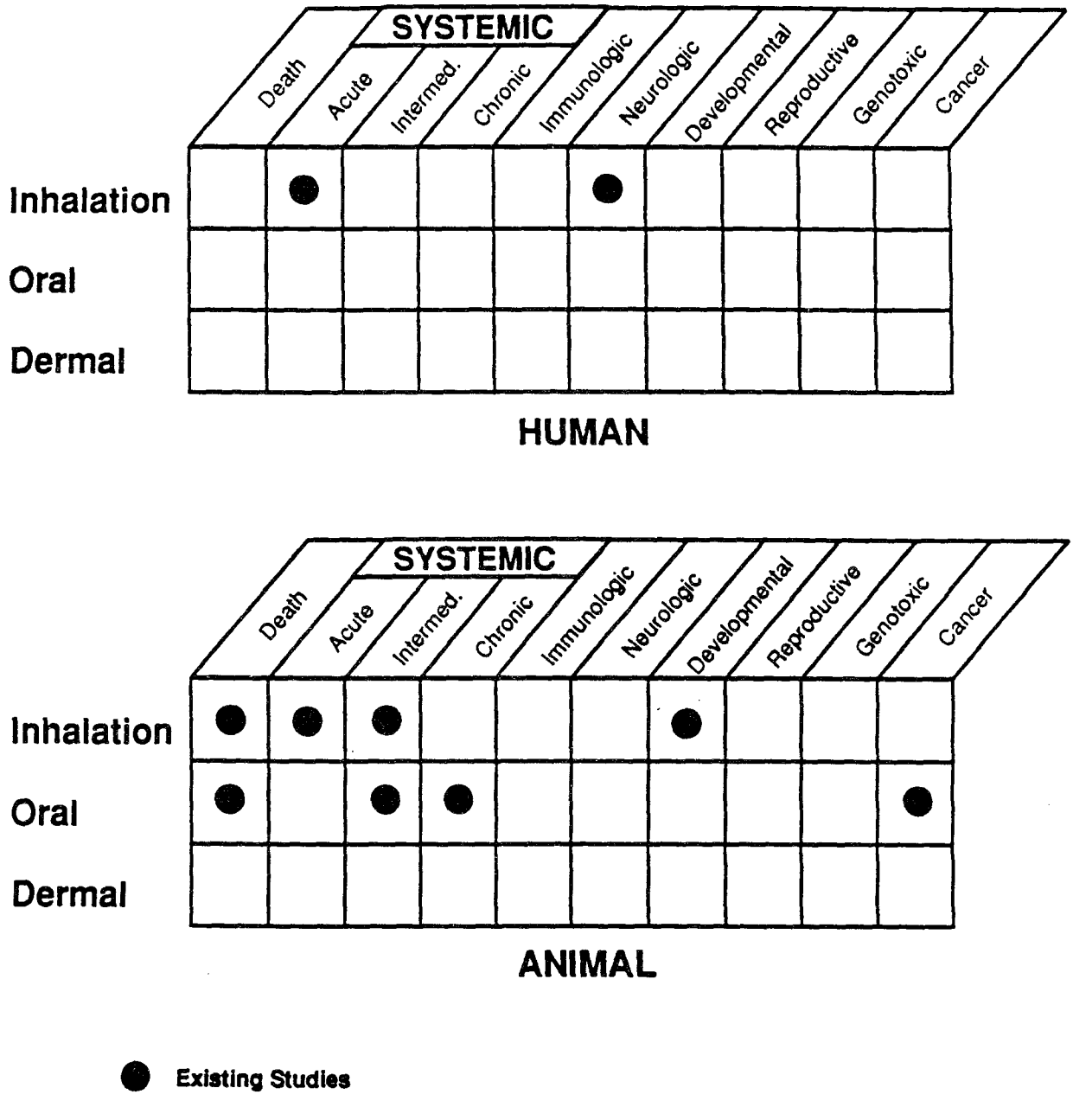

FIGURE 2-3. Existing Information on Health Effects of 1, 1-Dichloroethane

quality of these data. Therefore, an acute MRL for systemic effects can not be derived because of insufficient data. Since the chlorinated aliphatics in general are known to cause central nervous system depression and irritation of respiratory and ocular mucosal epithelium following single high-level exposures, more information on the effects of single-dose exposures to 1,1-dichloroethane by all routes would be useful to assess more fully the acute hazards of this chemical. Single-dose inhalation studies are of a higher priority, since inhalation is the most likely exposure pathway for this chemical although disposal may be by buried storage drums so soil and groundwater contamination from leakage is also possible. Though the relative potential for a high level of exposure via contaminated air is probably remote, there is a need to determine the threshold exposure level for effects caused by acute inhalation exposure.

Intermediate-Duration Exposure. No reliable information is available on the effects of repeated-dose exposure in humans. Limited information is available on the effects of repeated inhalation and oral exposures to 1,1-dichloroethane in animals. The studies reviewed indicate that 1,1-dichloroethane is possibly nephrotoxic, but this effect has only been demonstrated at high doses in one of several species tested. No other toxic effects have been attributed to 1,1-dichloroethane following repeated-dose exposures in animals. An intermediate MRL could not be derived for any routes of exposure. More information on the systemic effects of repeated-dose exposures in animals, particularly by the inhalation route since this is the most likely route of human exposure, would be useful to determine whether nephrotoxic effects observed in one study are an actual result of exposure to 1,1-dichloroethane, to determine if 1,1-dichloroethane reacts like other chlorinated aliphatics (e.g., causes neuro- and liver toxicity), and to more fully assess potential human health hazards from repeated exposure to 1,1-dichloroethane. This latter justification is particularly important since repeated exposure to low levels of 1,1-dichloroethane may be of more concern than short-term exposure to very high levels based on the current use and/or disposal of this chemical.

Chronic-Duration Exposure and Cancer. No information is available on the effects of chronic exposure to 1,1-dichloroethane in humans. The NCI study reported histopathological examinations for endpoints of systemic toxicity in addition to the neoplastic effects in rats and mice. No MRL can be derived for long-term exposure. Additional chronic toxicity studies particularly by the inhalation route would be useful to fully assess potential human health hazard from long-term exposure to 1,1-dichloroethane. This justification is important since chronic exposure to low levels of 1,1-dichloroethane may be of more concern than short-term exposure to very high levels based on the current use and/or disposal of this chemical.

Two bioassays were reviewed that investigated the potential carcinogenic effect of 1,1-dichloroethane by the oral route of exposure in animals. One

study provided suggestive evidence of carcinogenicity, but because there was poor survival in this study and the statistical significance of the cancer incidence is uncertain, the results could not be considered conclusive. The other bioassay yielded negative results for l,l-dichloroethane. No chronic toxic effects other than lethality were noted in either bioassay. The possibility that significant differences between the two studies could be due to administering l,l-dichloroethane in drinking water as compared to bolus doses in corn oil needs to be evaluated. Given the limitations present in the one study, the fact that 1,2-dichloroethane and certain other chlorinated aliphatics are carcinogenic and hepatotoxic, and the observations that l,l-dichloroethane possibly forms DNA adducts and metabolizes to free radicals, more information obtained from well-conducted carcinogenicity studies would be useful to assess more fully the carcinogenic potential of l,l-dichloroethane in humans and animals. Studies conducted by the inhalation route would be useful.

Genotoxicity. With one exception, the genotoxic potential of l,l-dichloroethane has been investigated almost exclusively using in vitro assays. Though the available data are conflicting, l,l-dichloroethane is generally considered to be nongenotoxic. l,l-Dichloroethane has been observed to enhance cell transformation in Syrian hamster embryo cells and results suggest that l,l-dichloroethane or a metabolite can bind to cellular macromolecules such as DNA. More information on the genotoxic effects of l,l-dichloroethane in animals both in vitro and in vivo would be useful to resolve the discrepancies in the present data and to assess the genotoxic hazard of this chemical in humans.

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

Developmental Toxicity. No information on the developmental effects of l,l-dichloroethane in humans Is available. One study was located that investigated the developmental effects of inhaled l,l-dichloroethane in animals. The results from this study indicated that l,l-dichloroethane is fetotoxic in rats, causing retarded fetal development (i.e., delayed ossification of the vertebrae) in the absence of significant maternal toxicity. Additionally, well-conducted developmental toxicity studies on l,l-dichloroethane, particularly by the inhalation route since this is the most likely route of human exposure, would be useful to verify the data from the single study that suggest this compound may cause adverse developmental effects. Data that compared the effects caused from different routes of exposure in mammalian species would also be useful to determine the likeliness of effects in humans.

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

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

Epidemiological and Human Dosimetry Studies. No epidemiological studies were located on l,l-dichloroethane. Well-controlled epidemiological studies of people living in close proximity to areas where l,l-dichloroethane contamination of surface water and groundwater or air is known to have occurred, people living near hazardous waste sites, and of occupationally exposed people could add to the limited database and clarify health effects in humans induced by l,l-dichloroethane. However, while this information would be useful, it is unlikely that it could be easily obtained from occupational studies. Other short-chain halogenated hydrocarbons are usually encountered in the same facilities where l,l-dichloroethane is manufactured or used, thus confounding the results obtained in such a study.

Biomarkers of Exposure and Effect. For high exposure to l,l-dichloroethane, the levels of this compound in the blood, urine, and breath may be used for biomarkers of exposure. However, these methods should be more sensitive and quantitative. The development of methods for detecting metabolites in the fluids and tissue of humans is needed to indicate l,l-dichloroethane exposure.

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

Absorption, Distribution, Metabolism, and Excretion. Studies of the pharmacokinetics of l,l-dichloroethane are very limited. Much of the

information regarding the disposition of l,l-dichloroethane is based on indirect evidence. Pharmacokinetic data are useful for providing information on mechanisms of toxicity and can often support findings of toxicity studies.

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

Studies in humans and animals regarding tissue distribution of l,l-dichloroethane are not available. Its lipophilicity suggests that the compound would be well absorbed and distributed to tissues according to their lipid content. Binding studies conducted in rats following intraperitoneal injection indicate that l,l-dichloroethane localizes in the liver, kidney, lung, and stomach. However, analysis has been limited to these tissues. Distribution studies using routes of administration relevant to human exposure (inhalation, oral) would provide useful information on potential target organs of l,l-dichloroethane-induced toxicity in humans.

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

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

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

2.8.3 On-going Studies

No on-going studies were identified that explored the health effects or toxicokinetics of l,l-dichloroethane or attempted to associate l,l-dichloroethane levels in human tissues with effects.