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 1,1,2-trichloroethane. Its purpose is to present levels of significant exposure for 1,1,2-trichloroethane 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 1,1,2-trichloroethane 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 in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (minimal risk levels, MRLs) are of interest to health professionals and citizens alike.

For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited. Because cancer effects could occur at lower exposure levels, the figures also show estimated excess risks, ranging from a risk of one in 10,000 to one in l0,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer endpoint 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 1980c), uncertainties are associated with the techniques.

2.2.1 Inhalation Exposure

Much of the data on the health effects of 1,1,2-trichloroethane following inhalation exposure were taken from a limited, unpublished study conducted by Dow Chemical Company. The original study was not available for review, but a brief description of the results was reported by Torkelson and Rowe (1981). This study is discussed below because in some cases, comparable information was not available from other reports, and in other cases, the levels of exposure associated with effects were noticeably different from those reported in other studies. These data indicate that the health effects of 1,1,2-trichloroethane might occur over a broader range of exposure levels than data from other studies would suggest. Although these results are discussed below, they are not included in Table 2-1 or plotted in Figure 2-1 as levels of significant exposure because the details of experimental methods and results were not provided.

2.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to 1,1,2-trichloroethane.

Mortality produced by inhalation of 1,1,2-trichloroethane has been studied in animals. Three of 5 rats exposed to 2080 ppm of 1,1,2-trichloroethane for 2 hours died within about 24 hours, but 5 rats exposed to 890 ppm for 2 hours survived (Carlson 1973). Carpenter et al. (1949) exposed rats to 1,1,2-trichloroethane vapor for 4 hours. They reported that 2-4/6 rats died within 14 days following exposure to 2000 ppm and 0-1/6 died following exposure to 1000 ppm. The exact number of rats killed in each treatment group was not reported. Because it was not explicitly stated that no rats died following exposure to 1000 ppm, this concentration was not used as a NOAEL. The LC_{50} of 1,1,2-trichloroethane in rats exposed for 6 hours was 1654 ppm (Bonnet et al. 1980). During exposure, animals are first excited and then somnolent. Most mortality occurred within 24 hours of exposure, but some deaths were reported up to 8 days later. No macroscopic

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

Graph Key	Species	Exposure Frequency/ Duration	Effect	NOAEL[b] (ppm)	LOAEL[a] (Effect)		Reference
					Less Serious (ppm)	Serious (ppm)	
ACUTE EXPOSURE							
Lethality							
1, 2	rat	2 h		890		2080 (3/5 dead)	Carlson 1973
3	rat	4 h				2000 (2-4/6 dead)	Carpenter et al. 1949
4	rat	6 h				1654 (LC_{50})	Bonnet et al. 1980
5	rat	8 h				999 (LC_{50})	Pozzani et al. 1959
6	rat	8 h				500 (4/6 dead)	Smyth et al. 1969
7	mouse	2 h				12,934 (death)	Lazarew 1929
8	mouse	6 h				416 (LC_{50})	Gradiski et al. 1978
9	mouse	15 h				3750 (death)	Gehring 1968
Systemic							
10, 11	rat	2 h	Hepatic	890	2080 (incr SGPT)		Carlson 1973
12	mouse	3 h	Hepatic		800 (incr SGPT)		Takahara 1986a
13	mouse	15 h	Hepatic		3750 (incr SGPT)		Gehring 1968
Neurological							
14	rat	6 h				1654 (somnolent)	Bonnet et al. 1980
15, 16	mouse	2 h			1833 (lie down on side)	2749 (loss of reflex control)	Lazarew 1929
17	mouse	4 h				418 (CNS depression)	De Ceaurriz et al. 1981
18	mouse	15 h				3750 (anesthesia)	Gehring 1968

[a]LOAEL - Lowest Observed Adverse Effect Level
[b]NOAEL - No Observed Adverse Effect Level

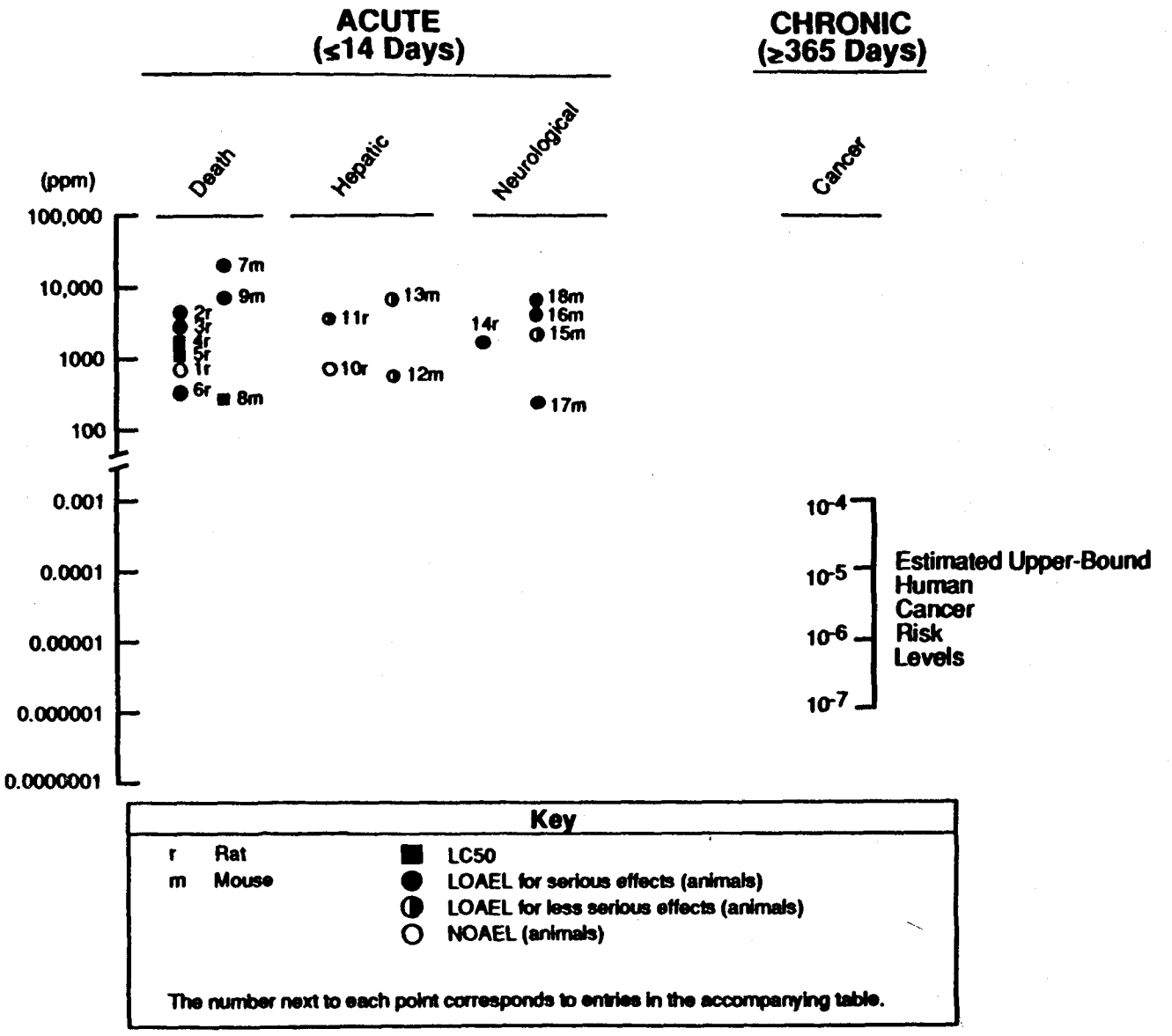

FIGURE 2-1. Levels of Significant Exposure to 1,1,2-Trichloroethane - Inhalation

lesions in the lungs, liver, or kidneys were found at autopsy. More than half of the test rats died following 7-hour exposure to 250 or 500 ppm of 1,1,2-trichloroethane, but no rats died following exposure to 100 ppm [Unpublished data, Dow Chemical Co. (cited in Torkelson and Rowe 198l)]. The results of this study were not used as levels of significant exposure because experimental methods and results were not described in sufficient detail. In rats exposed to 1,1,2-trichloroethane for 8 hours, the LC_{50} was 999 ppm (Pozzani et al. 1959). These authors reported, in a later study, that exposure to 500 ppm for 8 hours produced death in 4 out of 6 rats within 14 days (Smyth et al. 1969).

In mice, 12,934 ppm of 1,1,2-trichloroethane was found to be the minimum lethal concentration in a 2-hour exposure test (Lazarew 1929). The animals lay down on their sides and lost control of their reflexes prior to death. An LC_{50} value of 416 ppm was calculated in mice exposed for 6 hours and observed for 14 days (Gradiski et al. 1978). In mice exposed to 3750 ppm of 1,1,2-trichloroethane, the LT_{50}, or exposure duration that produced mortality in one-half of the mice tested, was calculated to be 600 minutes (Gehring 1968).

Only one study investigated the health effects of long-term inhalation exposure to 1,1,2-trichloroethane. Exposure to 15 ppm of 1,1,2-trichloroethane for 6 months did not increase mortality in rats, guinea pigs, or rabbits [Unpublished data, Dow Chemical Co. (cited in Torkelson and Rowe 1981)]. Values reported by this study are not included as levels of significant exposure because experimental methods and results were not described in sufficient detail.

The highest NOAEL values and all reliable LOAEL values for death in each species are recorded in Table 2-1 and plotted in Figure 2-1. The concentrations of 416 ppm (Gradiski et al. 1978) and 500 ppm (Smyth et al. 1969) in air are presented in Table 1-2.

2.2.1.2 Systemic Effects

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

Only one study investigated the respiratory effects of 1,1,2-trichloroethane inhalation in animals. Bonnet et al. (1980) macroscopically examined the lungs of rats that survived a 6-hour exposure test from which an LC_{50} of 1654 ppm was calculated. No lesions were found. This study was not used as the basis of a NOAEL because histological examinations were not performed, and gross observations alone are not sufficient to detect subtle health effects.

Hepatic Effects. No studies were located regarding hepatic effects in humans following inhalation exposure to 1,1,2-trichloroethane.

Several studies examined the hepatotoxicity of inhaled 1,1,2-trichloroethane vapor in animals. In rats, inhalation of 2080 ppm of 1,1,2-trichloroethane for 2 hours resulted in a small, but significant, increase in serum glutamic-pyruvic transaminase (SGPT) levels measured 22 hours after exposure ended (Carlson 1973). This treatment did not affect serum glutamic-oxaloacetic transaminase (SGOT), glucose-6-phosphatase, or liver weight. There were no hepatic effects after exposure to 890 ppm in this study. Macroscopic examination of rats that survived exposure to 250 ppm of 1,1,2-trichloroethane for 4 hours, and 250-500 ppm for 7 hours, revealed necrosis and tissue damage in the liver [Unpublished data, Dow Chemical Co. (cited in Torkelson and Rowe 1981)]. No macroscopic lesions were found in the livers of rats that survived a 6-hour exposure test from which an LC_{50} of 1654 ppm was calculated (Bonnet et al. 1980). This study was not used as the basis of a NOAEL because histological examinations were not performed, and gross observations alone are not sufficient to detect subtle health effects. The occurrence of hepatic effects at lower concentrations in the Dow Chemical study than in other studies may be due to differences in duration of exposure, endpoint examined, strain of rat used, or other differences in experimental protocols.

Mice exposed to 800 ppm of 1,1,2-trichloroethane for 3 hours had decreased adenosine triphosphate (ATP), increased liver triglycerides, decreased plasma triglycerides, and increased SGPT (Takahara 1986c). Recovery occurred within 20 hours for all parameters except SGPT, which remained elevated. The ET_{50} for increased SGPT levels in mice exposed to 3750 ppm of 1,1,2-trichloroethane (duration of exposure that produced increased SGPT levels in one-half of the exposed mice) was 17.5 minutes (Gehring 1968). This was substantially shorter than the LT_{50} of 600 minutes for lethality.

Minor fatty changes and cloudy swelling were found in the livers of female rats exposed to 30 ppm of 1,1,2-trichloroethane for 16 days. However, 6-month exposure to 15 ppm 1,1,2-trichloroethane did not have histopathological effects on the liver in rats, guinea pigs, or rabbits [Unpublished data, Dow Chemical Co. (cited in Torkelson and Rowe 1981)].

The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species are recorded in Table 2-1 and plotted in Figure 2-l. Although increased SGPT is reported as a less serious effect, it is suggestive of cell damage that can range from less serious to serious. The study by Dow Chemical was not used as the basis of a NOAEL or LOAEL because experimental details were not reported. The concentration of 800 ppm in air (Takahara 1986c) is presented in Table 1-2.

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

The renal effects of 1,1,2-trichloroethane have been studied in animals. In the rat, inhalation of 250 ppm of 1,1,2-trichloroethane for 4

hours produced kidney necrosis [Unpublished data, Dow Chemical Co. (cited in Torkelson and Rowe 1981)]. Exposure to 250 or 500 ppm for 7 hours produced marked kidney damage. This study was not used as the basis of a LOAEL because experimental details were not reported. No macroscopic lesions were found in the kidneys of rats that survived a 6-hour exposure test from which an LC_{50} of 1654 ppm was calculated (Bonnet et al. 1980). This study was not used as the basis of a NOAEL because histological examinations were not performed, and gross observations alone are not sufficient to detect subtle health effects.

In the only long-term study available, 6-month exposure to 15 ppm of 1,1,2-trichloroethane did not produce renal histopathological effects in rats, guinea pigs, or rabbits [Unpublished data, Dow Chemical Co. (cited in Torkelson and Rowe 1981)]. This study was not used as the basis of a NOAEL because experimental details were not reported.

Other Systemic Effects. No studies were located regarding other systemic effects in humans following inhalation exposure to 1,1,2-trichloroethane.

One study examined the relationship between inhalation of 1,1,2-trichloroethane and body weight in animals. Reduced body weight gain was reported in rats following a 6-hour exposure test from which an LC_{50} of 1654 ppm was calculated (Bonnet et al. 1980). No level of significant exposure was taken from this study because no data were presented in the paper.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following inhalation exposure to 1,1,2-trichloroethane.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans following inhalation exposure to 1,1,2-trichloroethane.

Studies in animals indicate that inhalation of 1,1,2-trichloroethane may produce neurological effects. Exposure to 1654 ppm of 1,1,2-trichloroethane for 6 hours produced excitation, followed by sleepiness, in rats (Bonnet et al. 1980). Mice exposed to 1,1,2-trichloroethane vapor for 2 hours laid down on their sides at 1833 ppm, and lost control of their reflexes at 2749 ppm. These concentrations are substantially lower than the minimum lethal concentration of 12,934 ppm that was reported in this study, which suggests that 1,1,2-trichloroethane exhibited increased central nervous system depression in this study (Lazarew 1929). The ET_{50} for anesthesia in mice exposed to 3750 ppm (duration of exposure that produced anesthesia in one-half of the exposed mice) was 18 minutes (Gehring 1968). This was substantially shorter than the LT_{50} of 600 minutes for lethality, indicating significant CNS-depressant potency in this study. A 50%

elevation in the threshold for pentylenetetrazol-induced seizures of CNS function, occurred in mice after exposure to 418 ppm of 1,1,2-trichloroethane for 4 hours (De Ceaurriz et al. 1981). This effect may indicate depression of CNS function.

All reliable LOAEL values for neurological effects in each species are recorded in Table 2-1 and plotted in Figure 2-1. The concentration of 418 ppm in air (De Ceaurriz et al. 1981) is presented in Table 2-2.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals following inhalation exposure to 1,1,2-trichloroethane.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following inhalation exposure to 1,1,2-trichloroethane.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following inhalation exposure to 1,1,2-trichloroethane.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals following inhalation exposure to 1,1,2-trichloroethane. Because 1,1,2-trichloroethane was carcinogenic to mice by the oral route in the NCI (1978) bioassay (Section 2.2.2.8), it is assumed that it is carcinogenic by inhalation, and the q_1^* for oral exposure was adopted as the q_1^* for inhalation (EPA 1988a). The q_1^* was converted to a unit risk for inhalation of 1.6×10^{-5} $(\mu/m^3)^{-1}$, which is equivalent to 8.7×10^{-2} $(ppm)^{-1}$. This unit risk corresponds to upper bound individual lifetime cancer risks at 10^{-4} to 10^{-7} of 1×10^{-3} to 1×10^{-6} ppm, which are plotted in Figure 2-1.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans following oral exposure to 1,1,2-trichloroethane.

Several reports indicate that 1,1,2-trichloroethane may be lethal to animals. An LD_{50} of 837 mg/kg (0.58 mL/kg) was calculated for orally administered, undiluted 1,1,2-trichloroethane in rats (Smyth et al. 1969). Moody et al. (1981) reported no mortality among fasted rats given single oral doses of 1,1,2-trichloroethane in mineral oil at 1080 mg/kg, but this value was not used as a NOAEL because only deaths during the first 18 hours

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

Graph Key	Species	Route[c]	Exposure Frequency/ Duration	Effect	NOAEL[b] (mg/kg/day)	LOAEL[a] (Effect) Less Serious (mg/kg/day)	LOAEL[a] (Effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Lethality								
1	rat	(G)	1x				837 (LD_{50})	Smyth et al. 1969
2	mouse	(G)	1x				378 (LD_{50})	White et al. 1985
3, 4	mouse	(G)	1x/d 7 d		100		300 (7/7 dead)	Kallman et al. 1983
5, 6	dog		1x		433		722 (1/1 dead)	Wright and Schaffer 1932
Systemic								
7	rat	(G)	1x	Hepatic		1080 (biochemical changes)		Moody and Smuckler Smuckler 1986
8	rat	(G)	1x	Hepatic		1080 (biochemical changes)		Moody et al. 1981 1981
9	rat	(G)	1x	Hepatic		60 (incr SGOT and SGPT)		Tyson et al. 1983
10	rat	(G)	1x/d	Hepatic		180 (biochemical changes)		Platt and Cockrill 1969
11			7 d	Other		180 (body wt changes)		
12	mouse	(G)	1x/d	Hemato	38			White et al. 1985
13			14 d	Hepatic	38			
14				Renal	38			
15				Other	38			
16, 17	dog		1x	Gastro		144 (mild effect)	433 (hemorrhage)	Wright and Schaffer 1932
18, 19				Hepatic		144 (mild effect)	433 (necrosis)	
20				Renal		144 (mild effect)		

TABLE 2-2 (continued)

Graph Key	Species	Route[c]	Exposure Frequency/ Duration	Effect	NOAEL[b] (mg/kg/day)	LOAEL[a] (Effect)		Reference
						Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Immunological								
21	mouse	(G)	1x/d 14 d		38			Sanders et al. 1985
Neurological								
22	mouse	(G)	1x				450 (sedation)	White et al. 1985
23	mouse	(G)	1x				128 (motor impairment)	Borzelleca 1983
24,25	mouse	(G)	1x/d 7 d		30[d]	100 (taste aversion)		Kallman et al. 1983
26	mouse	(W)	4d		46			Kallman and Kaempf 1984
27, 28	dog		1x		144		289 (drowsiness)	Wright and Schaffer 1932
Reproductive								
29	mouse	(G)	5d (days 8-12 of gestation)		350			Seidenberg et al. 1986
INTERMEDIATE EXPOSURE								
Systemic								
30	rat	(G)	5 d/wk 7 wk	Other		69 (body wt changes)		Story et al. 1986
31	mouse	(W)	90 d	Hemato	305			White et al. 1985
32, 33				Hepatic	4.4[e]	46 (liver effects)		
34				Renal	305			
35, 36				Other	46	305 (body wt changes)		

TABLE 2-2 (continued)

Graph Key	Species	Route[c]	Exposure Frequency/ Duration	Effect	NOAEL[b] (mg/kg/day)	LOAEL[a] (Effect) Less Serious (mg/kg/day)	LOAEL[a] (Effect) Serious (mg/kg/day)	Reference
Immunological								
37,38	mouse	(W)	90 d		4.4	44 (immune effects)		Sanders et al. 1985
CHRONIC EXPOSURE								
Lethality								
39	rat	(G)	5 d/wk 78 wk		92			NCI 1978
40	mouse	(G)	5 d/wk 78 wk				195 (increased mortality)	NCI 1978
Systemic								
41	rat	(G)	5 d/wk 78 wk	Resp	92			NCI 1978
				Cardio	92			
				Gastro	92			
				Hemato	92			
				Musc/skel	92			
				Hepatic	92			
				Renal	92			
				Derm/Oc	92			
				Other	92			
42	mouse	(G)	5 d/wk 78 wk	Resp	390			NCI 1978
				Cardio	390			
				Gastro	390			
				Hemato	390			
				Musc/skel	390			
				Hepatic	390			
				Renal	390			
				Derm/Oc	390			
				Other	390			

TABLE 2-2 (continued)

Graph Key	Species	Route[c]	Exposure Frequency/ Duration	Effect	NOAEL[b] (mg/kg/day)	LOAEL[a] (Effect)		Reference
						Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Carcinogenic								
43	mouse	(G)	5 d/wk 78 wk				195 (CEL[f]-liver, adrenals)	NCI 1978

[a]LOAEL - Lowest Observed Adverse Effect Level
[b]NOAEL - No Observed Adverse Effect Level
[c]G - gavage, W - drinking water
[d]Used to derive acute oral MRL; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) resulting in an MRL of 0.3 mg/kg/day. The MRL was converted to an equivalent concentration in water (10.5 ppm) for presentation in Table 1-3.
[e]Used to derive intermediate oral MRL; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) resulting in an MRL of 0.04 mg/kg/day. The MRL was converted to an equivalent concentration in water (1.4 ppm) for presentation in Table 1-3.
[f]CEL - Cancer Effect Level

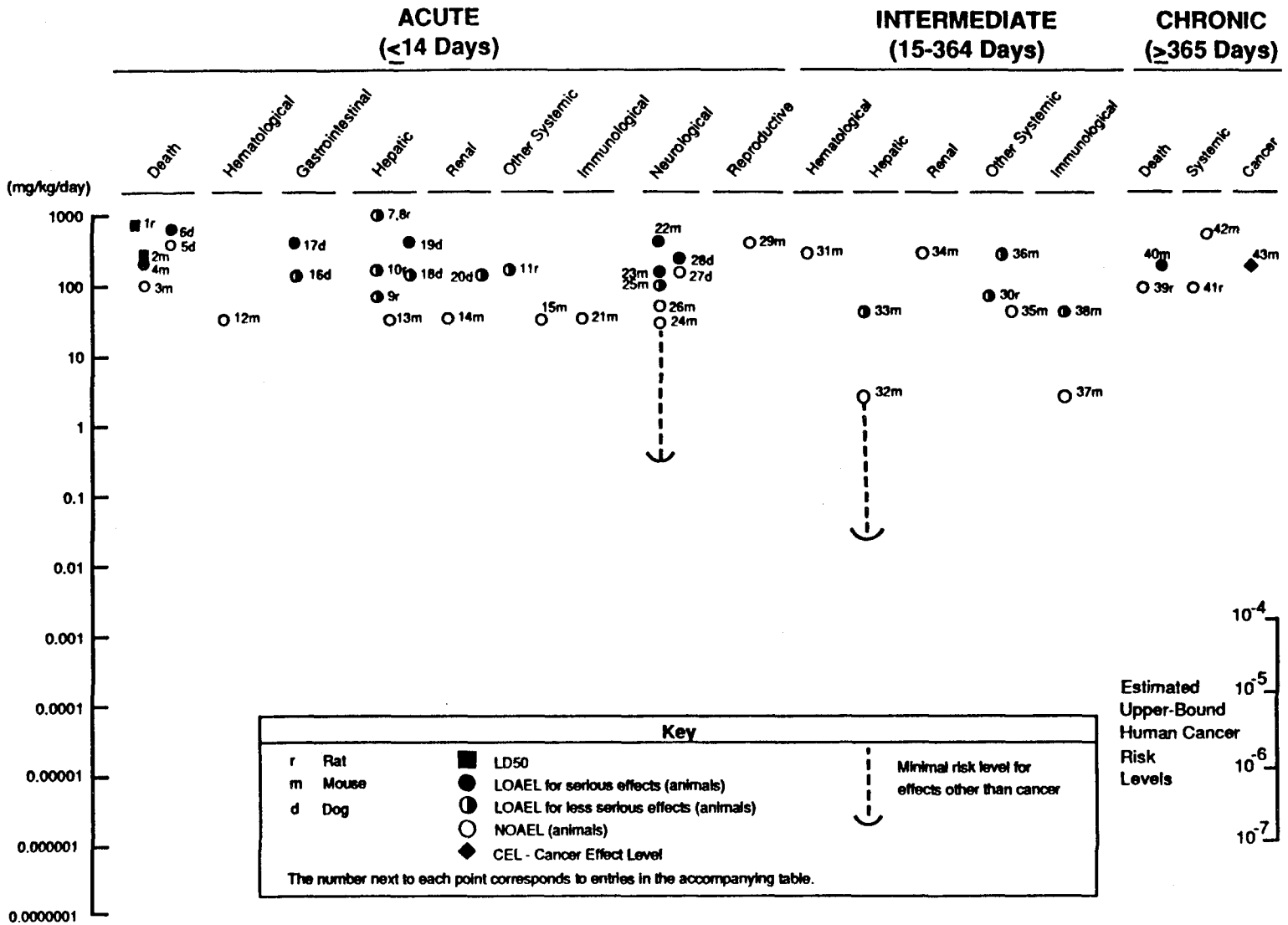

FIGURE 2-2. Levels of Significant Exposure to 1,1,2-Trichloroethane - Oral

after administration were recorded, and only 3 rats were tested. In mice, the oral LD_{50} of 1,1,2-trichloroethane administered by gavage in water was reported to be 378 mg/kg for males and 491 mg/kg for females (White et al. 1985). The lower value of 378 mg/kg, which was obtained in the males, was used in Table 2-2 and Figure 2-2. Necropsy of mice that died in this study revealed hemorrhagic areas in the lungs and pale coloration of the liver, which may also have been caused by hemorrhage. These effects may have contributed to the death of these animals. The only dog given 1,1,2-trichloroethane (vehicle not specified) at 722 mg/kg died, but all 5 that received doses ranging from 144 to 433 mg/kg survived (Wright and Schaffer 1932).

Lethality was investigated in two short-term repeated-dose studies. Oral doses of 1,1,2-trichloroethane given by gavage in water at 300 mg/kg, repeated daily for 7 days, resulted in the death of all 7 mice tested (Kallman et al. 1983). Doses up to 100 mg/kg/day did not produce death in this study. Oral administration by gavage of 38 mg/kg/day in 10% Emulphor for 14 days did not produce mortality in mice (White et al. 1985).

One long-term study investigated the effect of 1,1,2-trichloroethane on animal survival. Mice were given daily oral doses of 1,1,2-trichloroethane at 195 or 390 mg/kg in corn oil for 78 weeks (NCI 1978). Although male survival was not affected, female survival was reduced in a dose-dependent manner. A large number of the deaths in the female low dose group occurred early in the experiment; these were not tumor-related and did not appear to have a common cause. In rats, survival was not affected by oral administration of doses of 1,1,2-trichloroethane at either 46 or 92 mg/kg/day for 78 weeks (NCI 1978). However, rat vehicle controls had unusually high mortality in this study.

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. No short-term studies of 1,1,2-trichloroethane administered in drinking water were located; therefore the dose level of 837 mg/kg/day, which was administered by gavage undiluted (Smyth et al. 1969), and the dose level of 378 mg/kg/day, which was administered by gavage in water (White et al. 1985), were converted to equivalent concentrations, respectively, of 5980 and 1990 ppm in water for presentation in Table l-4. No long-term studies of 1,1,2-trichloroethane administered in food were located; therefore the dose level of 195 mg/kg/day, which was administered by gavage in corn oil (NCI 1978), was converted to an equivalent concentration of 1500 ppm in food for presentation in Table l-4.

2.2.2.2 Systemic Effects

Respiratory Effects. No studies were located regarding respiratory effects in humans following oral exposure to 1,1,2-trichloroethane.

Respiratory effects have been studied in animals. Hemorrhagic areas were found in the lungs of mice that died following gavage administration of 1,1,2-trichloroethane in water at 200 to 600 mg/kg (White et al. 1985). This study was not used as the basis of a LOAEL because the effect was reported only in mice that died as a result of exposure. Daily administration of 1,1,2-trichloroethane by gavage in 10% Emulphor at 38 mg/kg for 14 days did not affect lung weight in the mouse (White et al. 1985). Consumption of 305 mg/kg/day by males and 384 mg/kg/day by females in the drinking water for 90 days was also without effect on mouse lung weight (White et al. 1985). These dose levels were not used as NOAEL values because lung weight alone may not be an adequate endpoint to assess possible tissue damage. However, organ weight changes, when they occur in conjunction with other subtle effects, may indicate tissue damage. Histopathological examination of respiratory organs and tissues using light microscopy found no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral 1,1,2-trichloroethane administration in corn oil at doses of 46 or 92 mg/kg/day in rats and 195 or 390 mg/kg/day in mice (NCI 1978). NOAEL values for respiratory effects derived from this study are recorded in Table 2-2 and plotted in Figure 2-2.

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

One study of cardiovascular effects in animals was located. Histopathological examination of cardiovascular tissues using light microscopy found no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral 1,1,2-trichloroethane administration in corn oil at doses of 46 or 92 mg/kg/day in rats and 195 or 390 mg/kg/day in mice (NCI 1978). NOAEL values for cardiovascular effects in each species are recorded in Table 2-2 and plotted in Figure 2-2.

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

There is some evidence for adverse gastrointestinal effects in animals. Mice that died following administration by gavage in water of single oral doses of 1,1,2-trichloroethane above 200 mg/kg displayed a dose-related increase in the incidence of gastric irritation until all animals were affected at 500 mg/kg (White et al. 1985). This study was not used as the basis of a LOAEL because the effect was reported only in mice that died as a result of exposure. Mild inflammation and congestion of the gastrointestinal tract, as well as nausea, were noted in a dog given oral administration (vehicle not specified) of 144 mg/kg (Wright and Schaffer 1932). Severe irritation and hemorrhage were found in 2 of the 3 dogs given doses of 433 or 722 mg/kg. Histopathological examination of gastrointestinal organs and tissues by light microscopy revealed no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral

1,1,2-trichloroethane administration by gavage in corn oil at doses of 46 or 92 mg/kg/day in rats and 195 or 390 mg/kg/day in mice (NCI 1978). The highest NOAEL values and all reliable LOAEL values for gastrointestinal effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

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

In animals, hematological effects were the subject of several studies. No hematological effects were found after daily administration to mice of 1,1,2-trichloroethane by gavage in Emulphor at 38 mg/kg for 14 days (White et al. 1985). No hematological effects were found in male mice exposed to ≤305 mg/kg/day in the drinking water for 90 days, but changes in hematological parameters were recorded in females that received doses as low as 3.9 mg/kg/day (White et al. 1985). These included mild decreases in hematocrit and hemoglobin at 384 mg/kg/day, increases in platelets and fibrinogen that were found in all groups, but were not dose-related, and leukocytes that were elevated, compared to controls, in the high-dose group, but which were only slightly higher than the historical control value in this laboratory. There was also a decrease in prothrombin time that appeared to be dose-related and became significant at 44 mg/kg/day. These changes were not clearly adverse to the mice, so only a NOAEL was derived from this study. Histopathological examination of spleen and bone marrow using light microscopy found no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral 1,1,2-trichloroethane administration in corn oil at doses of 46 or 92 mg/kg/day in rats and 195 or 390 mg/kg/day in mice (NCI 1978). The NOAEL values for hematological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

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

Only one study investigated musculoskeletal effects in animals. Histopathological examination of musculoskeletal tissues by light microscopy revealed no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral 1,1,2-trichloroethane administration in corn oil at doses of 46 or 92 mg/kg/day in rats and 195 or 390 mg/kg/day in mice (NCI 1978). NOAEL values for musculoskeletal effects in each species are recorded in Table 2-2 and plotted in Figure 2-2.

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

Necropsy of mice that died following single oral doses of 1,1,2-trichloroethane by gavage in water at 200 to 600 mg/kg revealed pale coloration of the liver (White et al. 1985). This study was not used as the basis of a LOAEL because the effect was reported only in mice that died as a

result of exposure. Dogs given 144 mg/kg or more had congestion, fatty degeneration, edema, and the onset of necrosis in the liver (Wright and Schaffer 1932). Massive liver necrosis occurred in 1 of the 3 dogs given 433 mg/kg or above. Tyson et al. (1983) found significant increases in SGOT and SGPT following oral administration of 1,1,2-trichloroethane in corn oil to rats. The ED_{50} for this effect was 60 mg/kg. Decreases in cytochrome P-450, ALA-dehydratase, and glutathione levels occurred after administration of 1080 mg/kg by gavage in mineral oil in rats (Moody et al. 1981, Moody and Smuckler 1986). Increased relative liver weight and alterations in fatty acid content of liver microsomes (increased oleic acid and decreased arachidonic acid content) were also seen in this study, which was limited by small sample size (Moody et al. 1981). Glucose-6-phosphate dehydrogenase levels increased 195%, and $NADH_2$-cytochrome c reductase levels decreased 33%, in rats administered 1,1,2-trichloroethane orally in liquid paraffin at 180 mg/kg/day for 7 days (Platt and Cockrill 1969). Liver weight, microsomal and cell-sap protein concentrations, and levels of $NADPH_2$-cytochrome c reductase, aminopyrine demethylase, glucose-6-phosphatase, lactate dehydrogenase, glutamate dehydrogenase, and 6-phosphogluconate dehydrogenase were not significantly changed in this study. SGPT levels were not affected by 14-day administration of 1,1,2-trichloroethane by gavage in an aqueous Emulphor emulsion at 38 mg/kg/day in mice (White et al. 1985). In male mice exposed to 1,1,2-trichloroethane for 90 days in the drinking water, liver glutathione decreased 16% following exposure to 46 mg/kg/day and 28% following exposure to 305 mg/kg/day; serum transaminase levels were not significantly increased at either dose (White et al. 1985). In the same study, female mice that received 384 mg/kg/day had a 13% increase in liver glutathione and significantly elevated SGPT levels. SGOT levels were increased in females exposed to 3.9 mg/kg/day and above, but this was not considered to be a compound-related effect because no dosedependency was established. The NOAEL for liver effects in this study was taken to be 4.4 mg/kg/day. Based on this value, which was rounded off to 4mg/kg/day, an intermediate oral MRL of 0.04 mg/kg/day was calculated, as described in the footnote in Table 2-2. This MRL has been converted to an equivalent concentration in water (1.4 ppm) for presentation in Table 1-3. No increase in the occurrence of non-neoplastic lesions in the liver was found by light microscopic histopathological examination following 78 weeks of oral 1,1,2-trichloroethane administration by gavage in corn oil at doses of 92 mg/kg/day in rats and 390 mg/kg/day in mice (NCI 1978).

The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. No short-term studies of 1,1,2-trichloroethane administered in food were located; therefore, the dose level of 60 mg/kg/day, which was administered by gavage in corn oil (Tyson et al. 1983), was converted to an equivalent concentration of 1200 ppm in food for presentation in Table 1-4. The dose of 46 mg/kg/day was calculated from an administered concentration of 200 ppm in water (White et al. 1985). This concentration is presented in Table 1-4.

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

There are some reports of renal toxicity in animals, although most studies reported negative results. Cloudy swelling and congestion of the kidney were found by histopathological examination in dogs given 1,1,2-trichloroethane orally (vehicle not specified) at doses of 144 mg/kg or above (Wright and Schaffer 1932). There was a significant, low-level depression of in vitro organic ion uptake in renal cortical slices taken from rats given single oral doses of 1,1,2-trichloroethane in corn oil at 72 to 505 mg/kg (Watrous and Plaa 1972a). There was no clear dose-response relationship in this study, however. In mice administered 1,1,2-trichloroethane at up to 2886 mg/kg, the results were more inconsistent, with significant increases and decreases reported at various doses in different trials (Watrous and Plaa 1972a). Consequently, this study was not used as the source of a level of significant exposure in either species. There were no significant changes in kidney weight or blood urea nitrogen, an indicator of kidney function, in mice given 1,1,2-trichloroethane by gavage in 10% Emulphor for 14 days at a dose of 38 mg/kg/day or in the drinking water for 90 days at a dose of 305 mg/kg/day in males and 384 mg/kg/day in females (White et al. 1985). No increase in the occurrence of non-neoplastic lesions was found in the kidney by light microscopic histopathological examination following 78 weeks of oral 1,1,2-trichloroethane administration in corn oil at doses of 92 mg/kg/day in rats and 390 mg/kg/day in mice (NCI 1978). The highest NOAEL values and all reliable LOAEL values for renal effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Dermal/Ocular Effects. No studies were located regarding dermal or ocular effects in humans following oral exposure to 1,1,2-trichloroethane.

Only one study evaluated dermal or ocular effects in animals. Histopathological examination of the skin and eye using light microscopy found no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral 1,1,2-trichloroethane administration in *corn oil at* doses of 46 or 92 mg/kg/day in rats and 195 or 390 mg/kg/day in mice (NCI 1978). NOAEL values for dermal/ocular effects in each species are recorded in Table 2-2 and plotted in Figure 2-2.

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

The effect of 1,1,2-trichloroethane on body weight was investigated in several reports. Moody et al. (1981) reported reduced body weight gain in rats orally exposed to 1,1,2-trichloroethane in mineral oil at 1080 mg/kg, but a LOAEL was not derived because no data were presented. Rats given 180 mg/kg/day in liquid paraffin for 7 days grew only 8% over the course of the experiment, whereas control rats grew 34% (Platt and Cockrill 1969). Growth was reduced approximately 60% in rats given 69 mg/kg/day by gavage in corn

oil for 7 weeks (Story et al. 1986). In mice, body weight gain was not significantly affected by gavage administration of 1,1,2-trichloroethane in 10% Emulphor at 38 mg/kg/day for 14 days (White et al. 1985). Kallman and Kaempf (1984) reported that body growth in male mice was unchanged by go-day exposure to 46 mg/kg/day in the drinking water. Exposure to 1,1,2-trichloroethane in the drinking water for 90 days produced a concentration-dependent reduction in weight gain in male mice that was significant at 305 mg/kg/day (White et al. 1985). Weight gain in female mice was not affected in this study. When administered by gavage in corn oil, doses of 92 mg/kg/day in rats and 390 mg/kg/day in mice for 78 weeks (NCI 1978) did not inhibit body growth. The highest NOAEL and all reliable LOAEL values for reduced growth in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. Some of the variability in these results may be explained by differences in the vehicles and animal strains used.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans following oral exposure to 1,1,2-trichloroethane.

Immunological effects in mice were studied by Sanders and co-workers (Sanders et al. 1985, White et al. 1985). Oral administration of 1,1,2-trichloroethane to male mice at gavage doses in 10% Emulphor up to 38 mg/kg once a day for 14 days had no effect on humoral or cell-mediated immune response to sheep red blood cells (Sanders et al. 1985). Humoral immune response was measured by the number of IgM antibody forming cells produced against sheep red blood cells in the spleen. Spleen and thymus weight were not affected by treatment (White et al. 1985). A NOAEL of 38 mg/kg/day for immunological effects in mice following acute oral exposure was derived from this study.

In a longer-term study, mice were exposed to 1,1,2-trichloroethane in the drinking water for 90 days (Sanders et al. 1985, White et al. 1985). Males received doses of 4.4, 46, and 305 mg/kg/day and females received doses of 3.9, 44, and 384 mg/kg/day. Humoral immune response was measured by the number of IgM antibody forming cells produced against sheep red blood cells in the spleen, hemagglutination titers, and spleen lymphocyte response to lipopolysaccharide (Sanders et al. 1985). The number of antibody forming cells in the spleen was not consistently affected by treatment. A significant increase was obtained in females that received 384 mg/kg/day, but only on day 4 following immunization and only when counted on a 10^6 cell basis. Significant increases were also found by some measurements in low-dose males, but high-dose males were not affected. Hemaglutination titers exhibited a dose-dependent depression that was significant at 46 mg/kg/day in males

Cell-mediated immune response to sheep red blood cells was not affected in any group tested by Sanders et al. (1985). Both delayed-type hypersensitivity and popliteal lymph node proliferation responses were examined. Other immune responses were also evaluated. Peritoneal macrophages from males exposed to 305 mg/kg/day had a significantly depressed ability to phagocytize sheep red blood cells. This effect was not found in females. The functional activity of the fixed macrophages of the reticuloendothelial system was altered in females exposed to 384 mg/kg/day, which had a 17% increase in vascular clearance of sheep red blood cells, but not males. Spleen weight was unchanged in most groups, but was increased in females exposed to 384 mg/kg/day (White et al. 1985). Thymus weight was not affected in any group.

On the basis of this study, 44 mg/kg was chosen as the LOAEL and 4.4 mg/kg/day as the NOAEL for immunological effects in oral studies of intermediate duration. The dose of 44 mg/kg/day was calculated from an administered concentration of 200 ppm in water by Sanders et al. (1985). This concentration is presented in Table l-4.

No increase in the occurrence of non-neoplastic lesions was found in organs and tissues of the immune system following 78 weeks of oral 1,1,2-trichloroethane administration in corn oil at doses of 46 or 92 mg/kg/day in rats and 195 or 390 mg/kg/day in mice (NCI 1978). This study involved histopathological examination of the spleen, thymus, and lymph nodes using light microscopy, but because specific tests for immunotoxicity were not performed, NOAEL values were not derived.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to 1,1,2-trichloroethane.

1,1,2-Trichloroethane has neurological effects in acutely exposed animals. All mice given single oral doses of 1,1,2-trichloroethane at 450 mg/kg or more in water were sedated within 1 hour of administration (White et al. 1985). The ED_{50} for motor impairment (dose that produced motor impairment in one half of the test animals) in mice was 128 mg/kg administered by gavage in water (Borzelleca 1983). The peak effect occurred within 5 minutes of exposure. In dogs, doses of 1,1,2-trichloroethane at 289 to 722 mg/kg (vehicle not specified) produced drowsiness, incoordination, and partial narcosis after 12 to 50 minutes (Wright and Schaffer 1932).

Kallman et al. (1983) reported that 1,1,2-trichloroethane administered by gavage in water produced a significant dose-related taste aversion to saccharin in the drinking water. The NOAEL for this effect was 30 mg/kg and the LOAEL was 100 mg/kg. An ED_{50} of 32 mg/kg was calculated. Mice did not

display a taste aversion to 1,1,2-trichloroethane itself when 46 mg/kg/day was added to the drinking water for 4 days (Kallman and Kaempf 1984).

Longer-term studies did not report neurological effects following oral administration of 1,1,2-trichloroethane. Administration of 38 mg/kg/day in 10% Emulphor for 14 days did not affect brain weight in mice (White et al. 1985). Mouse brain weight was also unaffected by exposure to 305-384 mg/kg/day in the drinking water for 90 days (White et al. 1985). NOAEL values were not derived from these studies because brain weight alone is not an adequate endpoint to assess neurotoxicity. No effect on the occurrence of non-neoplastic lesions in nervous system organs and tissues was found by histopathological examination using light microscopy following 78 weeks of oral 1,1,2-trichloroethane administration in corn oil at doses of 46 or 92 mg/kg/day in rats and 195 or 390 mg/kg/day in mice (NCI 1978). NOAEL values were not derived from this study because tests of nervous system function were not included, and histopathology alone may not be an adequate endpoint to assess neurotoxicity.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species are recorded in Table 2-2 and plotted in Figure 2-2. Effects were not reported by short-term studies of 1,1,2-trichloroethane in drinking water; therefore, the dose levels of 100 mg/kg/day, resulting in taste aversion (Kallman et al. 1983), and 128 mg/kg/day, resulting in motor impairment (Borzelleca 1983), which were administered by gavage in water, were converted to equivalent concentrations of 525 and 670 ppm, respectively, for presentation in Table 1-4. Based on the NOAEL of 30mg/kg/day, an acute oral MRL of 0.3 mg/kg/day was calculated as described in the footnote in Table 2-2. This MRL has been converted to an equivalent NOAEL of 30 concentration in water (10.5 ppm) for presentation in Table l-3.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to 1,1,2-trichloroethane.

One study of the developmental effects of 1,1,2-trichloroethane in animals was found. Pregnant female mice were orally administered 1,1,2-trichloroethane in corn oil at 350 mg/kg/day on days 8 through 12 of gestation (Seidenberg et al. 1986). The percent survival of neonates from day 1 through day 3 was not affected by treatment, and neither was average neonatal weight measured on days 1 and 3 post partum. A NOAEL for developmental effects was not derived from this study because more explicit developmental endpoints (eg the incidence of malformations) were not investigated.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to 1,1,2-trichloroethane.

Studies of orally administered 1,1,2-trichloroethane did not report significant reproductive effects in animals. Seidenberg et al. (1986) found no effect on number of litters resorbed or average number of neonates per litter in mice following oral administration of 350 mg/kg/day in corn oil on days 8 through 12 of gestation. This was a minimally toxic dose expected to produce significant maternal weight reduction and up to 10% maternal mortality. Maternal body weight was not affected in this study, but some maternal mortality did occur. A NOAEL of 350 mg/kg/day derived from this study is recorded in Table 2-2 and plotted in Figure 2-2. Testis weight in mice was not affected when 1,1,2-trichloroethane was administered by gavage in 10% Emulphor for 14 days at a dose of 38 mg/kg/day (White et al. 1985). Exposure to 46 mg/kg/day or above in the drinking water for 90 days produced a significant increase in relative, but not absolute, testis weight in mice (White et al. 1985). NOAEL and LOAEL values were not derived from these studies, however, because testes weight alone may not be an adequate endpoint to assess reproductive toxicity. Also, changes in testis weight are not necessarily associated with reproductive dysfunction. No effect on the occurrence of non-neoplastic lesions in structures of the reproductive system was found by histopathological examination using light microscopy following 78 weeks of oral 1,1,2-trichloroethane administration in corn oil at doses of 46 or 92 mg/kg/day in rats and 195 or 390 mg/kg/day in mice (NCI 1978). NOAEL values were not derived from this study because tests of reproductive function were not included and histopathology alone may not be an adequate endpoint to assess reproductive toxicity.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following oral exposure to 1,1,2-trichloroethane.

2.2.2.8 Cancer

No studies were located regarding cancer in humans following oral exposure to 1,1,2-trichloroethane.

One study of cancer in animals orally exposed to 1,1,2-trichloroethane was located. There was no significant increase in the occurrence of neoplasms in Osbourne-Mendel rats of either sex following 78 weeks of oral 1,1,2-trichloroethane administration in corn oil at doses of 46 or 92 mg/kg/day (NCI 1978). In B6C3Fl mice, there was a highly significant dose-related increase in the incidence of hepatocellular carcinomas in both males and females following 78 weeks of oral administration in corn oil at doses of 195 or 390 mg/kg/day (NCI 1978). These carcinomas were found in 10 percent of untreated control males, 12 percent of vehicle control males, 37 percent of low-dose males, and 76 percent of high-dose males; they were found in 10 percent of untreated control females, 0% of vehicle control females, 33% of low-dose females, and 89% of high-dose females. In addition, there was a significant increase in the occurrence of adrenal

pheochromocytomas in mice of both sexes at 390 mg/kg/day. These lesions, not found in the control or low-dose groups, had an incidence of 17 percent in high-dose males and 28 percent in high-dose females. The value of this study is limited by its relatively short duration of 78 weeks and its conduct before the implementation of Good Laboratory Practices (GLP). A Cancer Effect Level (CEL) of 195 mg/kg/day is recorded in Table 2-2 and plotted in Figure 2-2. A ql* of 5.73×10^{-2} $(mg/kg/day)^{-1}$ was calculated for 1,1,2-trichloroethane based on the incidence of hepatocellular carcinoma in male mice (EPA 1980, 1988a). This q_1* was used to calculate upper bound individual lifetime cancer risks at 10^{-4} to 10^{-7} risk levels of 1.8×10^{-3} to $1.8 \times l0^{-6}$ mg/kg/day, which are plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans following dermal exposure to 1,1,2-trichloroethane.

Dermally applied 1,1,2-trichloroethane has been reported to cause death in animals. A single dermal application of 116 mg/cm^2 (0.25 mL applied to a 3.1 cm2 area of the back) was allowed to remain on the skin of guinea pigs until it disappeared (5 to 7 days). This treatment resulted in the death of 25% of the guinea pigs tested within 28 days (Wahlberg 1976). Doses of 233 and 931 mg/cm^2 killed all tested animals within 3 days in this study. A dose of 116 mg/cm^2 is, therefore, indicated as a LOAEL in Table 2-3 and Figure 2-3 for acute dermal exposure to 1,1,2-trichloroethane in guinea pigs. A dermal LD_{50} of 3.73 mL/kg (see Table 2-3) was reported for rabbits (Smyth et al. 1969). This value could not be plotted in Figure 2-3 because it was not reported in per-area units.

2.2.3.2 Systemic Effects

Hepatic Effects. No studies were located regarding hepatic effects in humans following dermal exposure to 1,1,2-trichloroethane.

One study investigated the hepatotoxicity of dermally applied 1,1,2-trichloroethane in animals. Guinea pig liver glycogen content was reduced within 2 hours following dermal application of 1 mL of 1,1,2-trichloroethane to a 3.1 cm^2 area of the back (465 mg/cm^2) (Kronevi et al. 1977). Hydropic changes in the liver were also found. These effects may not have been compound-related, however, since they were found in animals killed under anesthesia produced by pentobarbital, but not unanesthetized animals. Untreated controls were not used in this study. The authors suggest that these liver effects may be due to an interaction between 1,1,2-trichloroethane and pentobarbital. This possibility is discussed further in Section 2.7.

TABLE 2-3. Levels of Significant Exposure to 1,1,2-Trichloroethane - Dermal

Graph Key	Species	Exposure Frequency/ Duration	Effect	NOAEL	LOAEL[a] (Effect)		Reference
					Less Serious	Serious	
ACUTE EXPOSURE							
Lethality							
1	guinea pig	5-7 d				116 mg/cm^2/day (5/20 dead)	Wahlberg 1976
	rabbit	1x				3.73 mL/kg (LD_{50})	Smyth et al. 1969
Systemic							
2	human	5 min	Derm/Oc		698 mg/cm^2 (stinging pain)		Wahlberg 1984a
	human	5 min	Derm/OC	0.1 mL			Wahlberg 1984a
3	guinea pig	12 h	Derm/Oc		465 mg/cm^2 (skin damage)		Kronevi et al. 1977
4			Renal	465 mg/cm^2			
	rabbit	24 h	Derm/Oc	0.01 mL			Smyth et al. 1969
	rabbit	10 d 1x/d	Derm/Oc		0.1 mL (irritation)		Wahlberg 1984b
INTERMEDIATE EXPOSURE							
Systemic							
	human	15 d 1x/d	Derm/Oc	0.1 ML			Wahlberg 1984b

[a]LOAEL - Lowest Observed Adverse Effect Level
[b]NOAEL - No Observed Adverse Effect Level

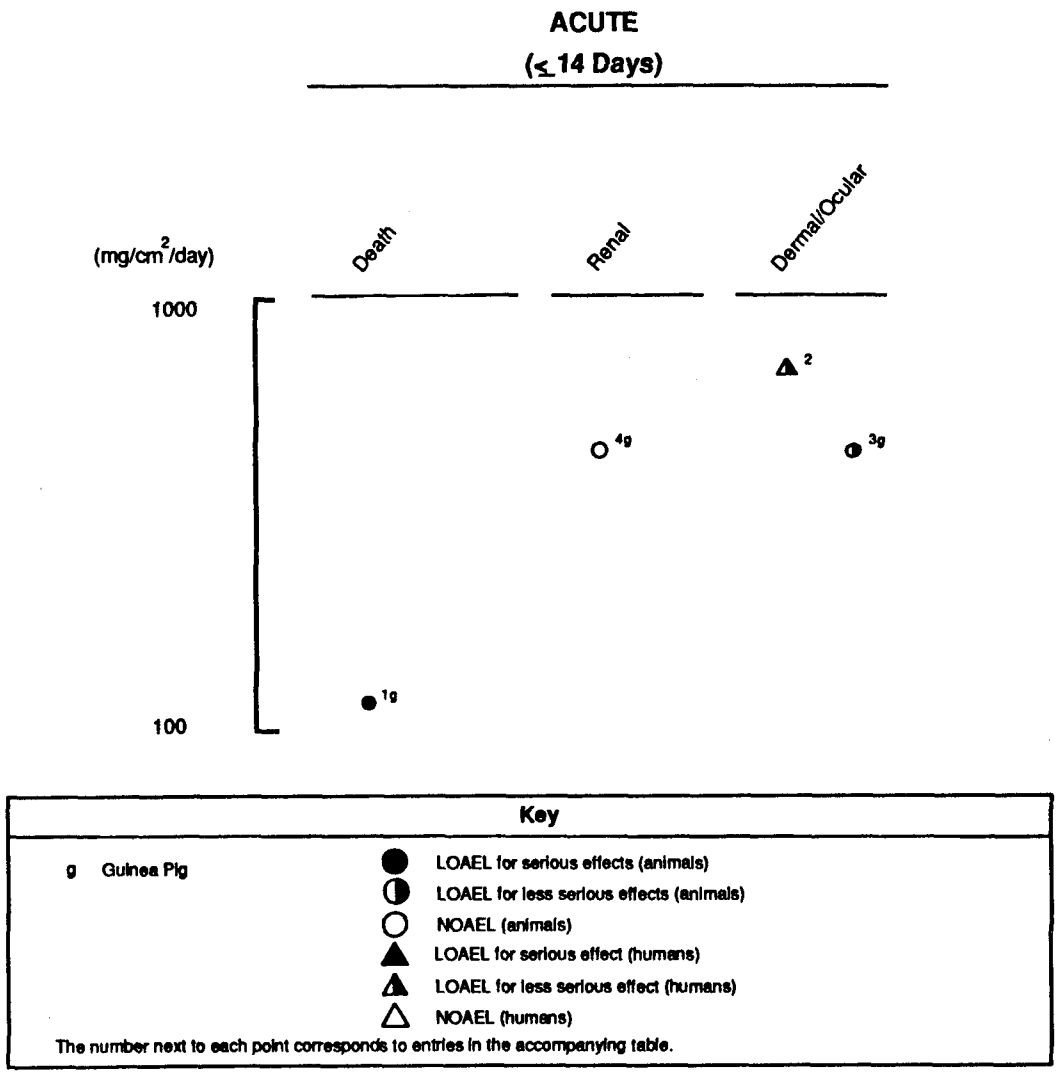

FIGURE 2-3. Levels of Significant Exposure to 1,1,2-Trichloroethane - Dermal

Renal Effects. No studies were located regarding renal effects in humans following dermal exposure to 1,1,2-trichloroethane.

The renal effects of dermally applied 1,1,2-trichloroethane in animals were examined in one study. No histopathological changes were found in the kidneys of guinea pigs 2, 6, or 12 hours after dermal application of 1,1,2-trichloroethane at 465 mg/cm^2 (Kronevi et al.mg/cm^{2}1977). The NOAEL of 465 is presented in Table 2-3 and plotted in Figure 2-3.

Dermal/Ocular Effects. The effect of 1,1,2-trichloroethane on the human skin was the subject of several reports. A human subject given 5 minute dermal exposure to 1,1,2-trichloroethane under occlusion at 698 mg/cm^2 (1.5 mL on 3.1 cm^2 of the forearm) reported stinging and burning sensations and displayed transient whitening of the skin (Wahlberg 1984a). A small, immediate increase in blood flow was measured by laser Doppler flowmetry, but no visible erythema was present. The acute human LOAEL was taken to be 698 mg/cm^2 on the basis of this report (see Table 2-3 and Figure 2-3). In general, use of a cover disk markedly enhances the percutaneous absorption and dermal irritant properties of volatile organic chemicals, which would usually evaporate from the skin's surface. In an open test on the same subject, in which 0.1 mL of 1,1,2-trichloroethane was applied to the skin without a cover disc, there was no effect on blood flow and no visible erythema was found (Wahlberg 1984a). A volunteer given daily open application of 0.1 mL of 1,1,2-trichloroethane for 15 days did not have any visible skin reactions, nor was there any increase in skin-fold thickness, which was measured using calipers (Wahlberg 1984b). These doses are presented in Table 2-3, but could not be converted to per-area units in the open tests because the area of application was not limited to the 3.1 cm^2 of the cover disc, so they are not plotted in Figure 2-3.

The dermal effects of 1,1,2-trichloroethane have also been studied in animals. Dermal application of 1,1,2-trichloroethane at 465 mg/cm^2 produced pyknotic nuclei in epidermal cells within 15 minutes in guinea pigs (Kronevi et al. 1977). As the duration of exposure increased, damage progressed to vesicle formation and separation of skin layers (Kronevi et al. 1977). A LOAEL of 465 mg/cm^2 for acute dermal effects in guinea pigs is reported in Table 2-3 and plotted in Figure 2-3. Rabbits given a single application of 0.01 mL of 1,1,2-trichloroethane had no effects other than slight capillary congestion (Smyth et al. 1969) (see Table 2-3). This study was not plotted on Figure 2-3 because the dose was not reported in per-area units. Duprat et al. (1976) compared the dermal irritancy of chlorinated aliphatic solvents in rabbits and determined that 1,1,2-trichloroethane was a severe skin irritant compared to other compounds in this group, producing serious erythema, serious edema, and necrosis. The results of this study were not used for a LOAEL because no dose was reported. In a repeated-dose study, daily open application of 0.1 mL for 10 days increased skin-fold thickness 170% in guinea pigs and 218% in rabbits (Wahlberg 1984b). All animals in this study displayed marked erythema and edema, and fissuring and scaling

were also seen. The LOAEL is presented in Table 2-3 but not in Figure 2-3 because the dose was not reported in per-area units.

1,1,2-Trichloroethane applied directly to the eye did not produce significant cornea1 necrosis in rabbits (Smyth et al. 1969). It was classified as a slight eye irritant by Duprat et al. (1976), who found moderate catarrhal conjunctivitis and epithelial abrasion following application in rabbits. Neither study reported the dose of 1,1,2-trichloroethane applied, so neither was used as the basis for a level of significant exposure.

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following dermal exposure to 1,1,2-trichloroethane.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans following dermal exposure to 1,1,2-trichloroethane.

One study of neurological effects in animals was located. No histopathological changes were found in the brains of guinea pigs 2, 6, or 12 hours after dermal application of 1,1,2-trichloroethane at 465 mg/cm^2 (Kronevi et al. 1977). A NOAEL was not derived from this study because tests of nervous system function were not included, and histopathology alone may not be an adequate endpoint to assess neurotoxicity.

2.2.3.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals following dermal exposure to 1,1,2-trichloroethane.

2.2.3.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following dermal exposure to 1,1,2-trichloroethane.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following dermal exposure to 1,1,2-trichloroethane.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals following dermal exposure to 1,1,2-trichloroethane.

2.3 RELEVANCE TO PUBLIC HEALTH

Other than studies on dermal irritation, no studies were located regarding health effects in humans following inhalation, oral, or dermal exposure to 1,1,2-trichloroethane; therefore, all implications for public health are derived from animal studies.

Lethality. 1,1,2-Trichloroethane produced mortality in animals by all routes of exposure tested, including inhalation, oral, dermal, intraperitoneal injection, and subcutaneous injection. Death was produced in rats, mice, guinea pigs, rabbits, and dogs, although not every species was tested by every route of exposure.

There is some evidence that mice were more susceptible than rats to 1,1,2-trichloroethane-induced mortality following acute inhalation, oral and intraperitoneal exposure. Inhalation LC_{50} values for rats and mice were 1654 and 416 ppm, respectively, in two studies done in the same laboratory (Bonnet et al. 1980, Gradiski et al. 1978). Oral LD_{50} values for rats and mice were 837 mg/kg (administered by gavage undiluted) and 378 mg/kg (administered by gavage as an aqueous emulsion), respectively, but only studies by different groups of investigators were available for comparison (Smyth et al. 1969, White et al. 1985). Rat and mouse intraperitoneal LD_{50} values were 938 and 505 mg/kg, respectively, in two tests performed by the same investigators (Klaassen and Plaa 1966, 1969). In each of these cases, mice proved to be more susceptible to death produced by 1,1,2-trichloroethane than rats. However, the maximum tolerated oral dose was higher in mice (300 mg/kg/day) than rats (70 mg/kg/day) in a 6-week study in which 1,1,2-trichloroethane was administered by gavage in corn oil (NCI 1978). Differences in duration of exposure, vehicle, and strain of animal used may account for the discrepancy between this study and the others. Metabolism of 1,1,2-trichloroethane occurs at a faster rate in mice than in rats (Mitoma et al. 1985), and it is possible that greater amounts of reactive metabolites in mice are responsible for the species difference in susceptibility to this chemical.

In addition, there may be sex differences in sensitivity to 1,1,2-trichloroethane. This compound was more toxic to male mice (LD_{50} = 378 mg/kg) than female mice (LD_{50} = 491 mg/kg) following acute oral administration (White et al. 1985). However, survival was reduced in female mice given chronic oral administration of 1,1,2-trichloroethane, but not in males (NCI 1978). No sex difference was noted in LD_{50} values determined after intraperitoneal administration in a different strain of mice (Klaassen and Plaa 1969).

Levels of 1,1,2-trichloroethane that produce mortality have been identified in a number of species, and by several routes of exposure. Exposure to high levels of 1,1,2-trichloroethane may also be fatal to humans. Species and sex variation in susceptibility make it difficult to estimate the level at which this compound might produce death in humans.

Hepatic Effects. 1,1,2-Trichloroethane had adverse effects on the livers of rats, mice, guinea pigs, and dogs when administered orally or by inhalation. These effects included necrosis, elevated SGPT and SGOT levels, and reduced liver glycogen content (Gehring 1968, Tyson et al. 1983, White et al. 1985, Wright and Schaffer 1932). Intraperitoneal studies in these same four species revealed similar hepatic effects, including centrilobular necrosis, elevated SGPT levels, increased serum ornithine carbamyl transferase activity, and fatty changes (Klaassen and Plaa 1966, Klaassen and Plaa 1967a, Traiger and Plaa 1974, Divincenzo and Krasavage 1974, Harms et al. 1976, MacDonald et al. 1982). 1,1,2-Trichloroethane was also toxic to isolated rat hepatocytes in vitro (Tyson et al. 1980, Jernigan et al. 1983, Chang et al. 1985). A sex difference in susceptibility was noted by White et al. (1985), who reported that female mice exposed to 384 mg/kg/day in the drinking water for 90 days had significantly elevated SGPT levels, but males exposed to 304 mg/kg/day did not. These investigators also found that liver glutathione decreased in males and increased in females. Although there is no information available to suggest that 1,1,2-trichloroethane is a liver toxin in humans, it is considered a potential human hepatotoxin because experiments in animals indicate hepatotoxic potential in all species tested.

One mechanism that has been proposed to explain the hepatotoxicity of 1,1,2-trichloroethane is the generation of free radical intermediates from reactive metabolites of 1,1,2-trichloroethane (acyl chlorides). Free radicals may stimulate lipid peroxidation which, in turn, may induce liver injury (Albano et al. 1985). However, Klaassen and Plaa (1969) found no evidence of lipid peroxidation in rats given near-lethal doses of 1,1,2-trichloroethane by intraperitoneal injection. Takano and Miyazaki (1982) determined that 1,1,2-trichloroethane inhibits intracellular respiration by blocking the electron transport system from reduced nicotinamide adenine dinucleotide (NADH) to coenzyme Q (CoQ), which would deprive the cell of energy required to phosphorylate adenosine diphosphate (ADP) and thereby lead to depletion of energy stores.

Renal Effects. There was only one reliable report of kidney damage following oral exposure to 1,1,2trichloroethane. Wright and Schaffer (1932) found cloudy swelling and congestion in the kidneys of treated dogs. No kidney pathology was found after dermal application in guinea pigs (Kronevi et al. 1977) or inhalation exposure in rats (Bonnet et al. 1980). One unpublished study reported kidney damage following inhalation exposure in rats [Dow Chemical Co. (cited in Torkelson and Rowe 1981)].

Renal effects in mice and dogs given intraperitoneal or subcutaneous injections of 1,1,2-trichloroethane were studied in a series of experiments by Plaa and co-workers. Although no gross effects were visible, tubular lesions with necrosis were seen microscopically in the cortex of the kidneys of mice injected subcutaneously with 173 mg/kg 1,1,2-trichloroethane (Plaa et al. 1958). The ED_{50} for necrosis, swelling of the kidney, and renal dysfunction in mice, as indicated by increased protein and glucose in the

urine, was 216 mg/kg by intraperitoneal injection (Plaa and Larson 1965). Klaassen and Plaa (1966, 1967a) found necrosis and reduced ability to excrete intravenously-administered PSP (phenolsulfonphthalein) in the kidneys of male mice and dogs given 1,1,2-trichloroethane intraperitoneally. Female mice did not show this effect, even at lethal doses (Klaassen and Plaa 1967b). This evidence strongly suggests a sex difference in susceptibility to the renal effects of 1,1,2-trichloroethane in mice, but the reason for this difference is not known.

There is good evidence that 1,1,2-trichloroethane is nephrotoxic when parenterally administered in mice and dogs. There is also some evidence for kidney effects in animals following inhalation and oral exposure. These results suggest that 1,1,2-trichloroethane may be nephrotoxic in humans.

Immunological Effects. A detailed study of the effects of 1,1,2-trichloroethane on the immune system was performed by Sanders et al. (1985). They reported that significant effects on mouse immune function were found at doses as low as 44 to 46 mg/kg/day in a 90-day study. Humoral immune function, functional activity of the fixed macrophages of the reticuloendothelial system, and macrophage phagocytic activity were all affected (although the latter two were only altered in high-dose mice). These data suggest that 1,1,2-trichloroethane may interfere with immune function in animals. It is possible that these effects could also be produced in humans exposed to 1,1,2-trichloroethane, although there are no data currently available indicating immune system effects in humans.

There was a distinct sex difference in immune response to 1,1,2-trichloroethane exposure in mice. Some effects, such as reduced spleen lymphocyte response to lipopolysaccharide and increased vascular clearance by the fixed macrophages of the reticuloendothelial system, were found only in females. Others, such as depressed ability to phagocytize sheep red blood cells, occurred only in males. The reason for these differences is not known and their significance for human health is unclear.

Neurological Effects. Anesthesia has been produced in animals by oral intake, inhalation, and intraperitoneal injection of 1,1,2-trichloroethane. This effect has been studied in both mice and dogs. The ED_{50} for motor impairment in mice reported by Borzelleca (1983) was approximately one third the LD_{50} value for mice reported by White et al. (1985). At an inhalation concentration of 3750 ppm, the ET_{50} (time required to produce anesthesia in one-half of the treated animals) was 18 minutes, which is much less than the LT_{50} of 10 hours in this study (Gehring 1968). The occurrence of anesthetic effects at doses well below those that produce death indicates that 1,1,2-trichloroethane is a potent CNS depressant.

Central nervous system depression was reported by De Ceaurriz et al. (1981) following inhalation exposure in mice. Tham et al. (1984) found that intravenous infusion of 28 mg/kg 1,1,2-trichloroethane had a depressive effect on the vestibulo-oculomotor reflex in rats. Taste aversion, which

represents a conditioned avoidance response, was another neurological effect produced by 1,1,2-trichloroethane. Kallman et al. (1983) suggest that taste aversion may be sensitive to the acute health effects of 1,1,2-trichloroethane, but that it may not be useful in assessing delayed or cumulative toxicity. No data on neurological effects of 1,1,2-trichloroethane in humans were located, but the evidence in animals suggests that this compound may have central nervous depressant effects in humans as well.

Genotoxic Effects. Data on the genotoxic effects of 1,1,2-trichloroethane are presented in Tables 2-4 and 2-5. In vitro mutagenicity assays were negative in Salmonella typhimurium and positive in Saccharomvces cerevisiae. A cell transformation assay performed in the absence of activation on mouse BALB/c-3T3 cells was negative. A test of DNA repair in cultured rat hepatocytes was positive, but one in mouse hepatocytes was not (Williams 1983). Adduct formation with calf thymus DNA occurred in vitro at a significant rate (DiRenzo et al. 1982a). DNA adduct formation in vivo occurred to a greater extent in mouse liver than in rat liver (Mazzullo et al. 1986). The authors point out that there is a correlation between these adduct formation results and species susceptibility to cancer, as the incidence of hepatocellular carcinomas was increased in mice, but not rats, given 1,1,2-trichloroethane for 78 weeks. Finally, DNA synthesis was inhibited by intratesticular injection of 1,1,2-trichloroethane in the mouse (Borzelleca 1983). Although there are negative as well as positive results, it is evident that this compound does have some genetic effects both in vitro and in vivo. The significance of these effects for humans is not clear, especially since results of in vivo mammalian assays showed species variability.

Cancer. There is no evidence for carcinogenicity of 1,1,2-trichloroethane in humans. Among animals, 1,1,2-trichloroethane was carcinogenic in $B6C3F_1$ mice, but not Osbourne-Mendel rats. In a gavage study by NCI (1978), this compound produced significant increases in the incidence of hepatocellular carcinomas and adrenal pheochromocytomas in mice. Based on this study, Gold et al. (1987) calculated the carcinogenic potency (TD50) of 1,1,2-trichloroethane in mice to be 47.6 mg/kg/day, which is similar to the value for chloroform and about one third the value for carbon tetrachloride. No increase in the incidence of neoplasms was observed in rats under the conditions of the NCI bioassay. Carcinogenicity in rats was also studied by Norpoth et al. (1988), who found that subcutaneous injection of 15.4 or 46.8 μmol of 1,1,2-trichloroethane in DMSO once a week for 2 years had no effect on the incidence of benign mesenchymal and epithelial tumors in Sprague-Dawley rats. The incidence of sarcomas (mostly localized on the extremities) increased with dose in both sexes and was significantly elevated in high-dose rats compared to untreated controls. However, the lack of any sarcomas in the untreated controls was unusual for this strain, and when compared to the spontaneous incidence of sarcomas reported in the literature, this effect was no longer significant. In addition, sarcoma incidence was not elevated when compared to vehicle controls. From the

TABLE 2-4. Genotoxicity of 1,1,2-Trichloroethane In Vitro

Endpoint	Species/Test System	Result (Activation) With	Result (Activation) Without	References
Gene mutation	Salmonella typhimurium	-	-	Simmon et al. 1977 Rannug et al. 1978 Barber and Donish 1982 Mitoma et al. 1984 Zeiger et al. 1988
Gene conversion	Saccharomyces cerevisiae	+	+	Bronzetti et al. 1987
Cell transformation	mouse BALB/c-3T3 cells	NT	-	Tu et al. 1985
DNA repair	mouse hepatocytes	NA	-	Williams 1983
	rat hepatocytes	NA	+	Williams 1983
DNA adduct formation	calf thymus	NA	+	DiRenzo et al. 1982

NT = Not tested
NA = Not applicable

Table 2-5. Genotoxicity of 1,1,2-Trichloroethane In Vivo

Endpoint	Species (Test System)	Result	Reference
DNA adduct formation	mouse liver	+	Mazzullo et al. 1986
	rat liver	+	Mazzullo et al. 1986
Inhibition of DNA synthesis	mouse testis	+	Borzelleca 1983

limited evidence in mice, 1,1,2-trichloroethane has been classified in Group C as "a possible carcinogen" (EPA 1988a).

The mechanism of 1,1,2-trichloroethane carcinogenicity in mice is not known. Metabolism of this compound involves formation of acyl chlorides and free radicals, which may play a role in cancer formation. Although 1,1,2-trichloroethane has not been shown to be carcinogenic in rats, a study of cancer initiation and promotion in this species was located. Story et al. (1986) gave a single oral dose of 1,1,2-trichloroethane at 69 mg/kg in corn oil to rats and followed this treatment with 8 weeks administration of phenobarbital, a promoter of hepatocellular carcinomas. Using liver foci with altered enzyme levels as pre-neoplastic markers, they found no evidence that 1,1,2-trichloroethane acted as an initiator. The reciprocal experiment, using diethylnitrosamine (DEN) as the initiator and 1,1,2-trichloroethane as the possible promoter, gave similar results whether or not DEN initiation was given. In either case, there was a large increase in the total number of liver foci. However, when examined more closely, it was found that these increases occurred solely in the number of Type II foci, which do not appear to be preneoplastic. Therefore, no evidence of cancer promotion by 1,1,2-trichloroethane was found in this study.

2.4 LEVELS IN HUMAN TISSUES AND FLUIDS ASSOCIATED WITH HEALTH EFFECTS

No studies were located regarding the levels of 1,1,2-trichloroethane in human tissues and fluids associated with effects.

2.5 LEVELS IN THE ENVIRONMENT ASSOCIATED WITH LEVELS IN HUMAN TISSUES AND/OR HEALTH EFFECTS

The levels of 1,1,2-trichloroethane were studied in 230 personal air samples, 170 drinking water samples, 66 breath samples and 16 food samples from 9 volunteers in New Jersey and 3 in North Carolina (Wallace et al. 1984). In 99% of the cases, no 1,1,2-trichloroethane or only trace amounts were found in the environment, or in the exhaled breath of the people. Specifically, the personal air concentrations of 1,1,2-trichloroethane were below the detection limit in 151/161 samples, 7 contained trace levels, and the others had a very low median value of 0.35 $\mu g/m^3$ (0.063 ppb). Breath samples were negative in 44/49 samples, value of 0.2 $\mu g/m^3$ (0.036 ppb). and the others had a very low median

The levels of halogenated organic compounds were studied in the Ruhr region of West Germany from 1976-1978 (Bauer 1981a,b). The concentration of 1,1,2-trichloroethane in the Rhine river at this time averaged 0.2 $\mu g/L$ (ppb), and the concentration in the drinking water in 100 German cities had a maximum of 5.8 $\mu g/L$ (ppb). Air concentrations rarely were over 1 $\mu g/m^3$ (0.18 ppb) and 1,1,2-trichloroethane was not detected in the foods or cosmetic products available locally. The average concentrations in humans tissues studied in 15 people who were exposed primarily via the air (94% of the exposure) were 6 $\mu g/kg$ in adrenal capsule adipose tissue, 14 $\mu g/kg$ in

subdermal adipose tissue, 2 μg/kg in the lungs, 3 μg/kg in the liver, and 17 μg/kg in the muscle tissue. This study does not establish levels in human tissue associated with health effects.

2.6 TOXICOKINETICS

2.6.1 Absorption

2.6.1.1 Inhalation Exposure

Studies in humans indicate that 1,1,2-trichloroethane is absorbed rapidly after inhalation exposure (Morgan et al, 1970, 1972). A volunteer took one breath of radiolabeled 1,1,2-trichloroethane and expired 10% of the inspired dose in the alveolar air after 12 seconds and about 0.5% after 40 seconds of breath-holding. More than 90% of the administered dose was retained in the body after 50 minutes. These data indicate that 1,1,2-trichloroethane was extensively absorbed into the bloodstream.

The only data on absorption of 1,1,2-trichloroethane following inhalation exposure in animals comes from the assumption that an administered chemical has been absorbed by the body if it can be shown to affect physiological processes. 1,1,2-Trichloroethane has been shown to affect the exhalation of acetone in rats (Filser et al. 1982), so it can be assumed that the 1,1,2-trichloroethane was absorbed.

2.6.1.2 Oral Exposure

No studies were located regarding absorption in humans following oral exposure to 1,1,2-trichloroethane. The only data available in animals showed that oral doses near the MTD (maximum tolerated dose) in mice (300 mg/kg) or rats (70 mg/kg) were 81% metabolized, indicating that at least this amount was absorbed (Mitoma et al. 1985). This suggests that 1,1,2-trichloroethane, like other structurally related halocarbons, is well absorbed from the gastrointestinal tract of animals, and probably humans as well.

2.6.1.3 Dermal Exposure

No studies were located regarding absorption in humans following dermal exposure to 1,1,2-trichloroethane. Two studies in animals indicate that 1,1,2-trichloroethane is easily absorbed through the skin. In the guinea pig, blood concentration of 1,1,2-trichloroethane peaked at ≈3.7 μg/mL within a half-hour following 1,1,2-trichloroethane application to the skin (Jakobson et al. 1977). Following the peak, the blood level declined to ≅2.5 μg/L at 1 hour, remained at this level until ≅4 hours, and then rose to ≅3.7 μg/L at 6 hours. The authors suggested that this complex dermal absorption of 1,1,2-trichloroethane may be due to an initial increased barrier function of the skin after 1. hour, which led to decreased absorption. Subsequent absorption during the next few hours may represent

an overcoming of the barrier. In mice, 15 minutes after application of 0.5 ml of 1,1,2-trichloroethane, 99.7% was retained in the body and 0.3% was expired in the breath (Tsuruta 1975). The absorption rate was calculated to be 130 nmoles/min/cm^2 of skin. The rapid absorption through the skin may well be due to the highly lipid soluble character of 1,1,2-trichloroethane (Kronevi et al. 1977).

2.6.2 Distribution

2.6.2.1 Inhalation Exposure

No studies were located regarding distribution in humans following inhalation of 1,1,2-trichloroethane. After an inhalation exposure of 1000 ppm for 1 hour, 1,1,2-trichloroethane was distributed in mice organs in the following manner: approximately 600 μg/g in fats, 80 μg/g in the kidney and liver, 45-60 μg/g in the blood and brain, and 20-35 μg/g in the heart, spleen and lung (Takahara 1986a). Examination of partition coefficients showed that 1,1,2-trichloroethane had a moderate degree of lipid solubility compared to other hydrocarbons, but was still quite lipid soluble (Gargas et al. 1989, Imbriani et al. 1985, Morgan et al. 1972, Sato and Nakajima 1979). This indicates that 1,1,2-trichloroethane could be easily distributed and retained in fat, liver, and brain in both animals and humans.

2.6.2.2 Oral Exposure

No studies were located regarding distribution in humans or animals following oral exposure to 1,1,2-trichloroethane. One study showed that 1,1,2-trichloroethane was distributed to the liver following oral exposure in animals (Mitoma et al. 1985). In this study, 1,1,2-trichloroethane was extensively metabolized (presumably by the liver), and was also found to bind hepatic protein. It is likely that 1,1,2-trichloroethane is also distributed to the liver in humans.

2.6.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals following dermal exposure to 1,1,2-trichloroethane.

2.6.3 Metabolism

No studies were located regarding metabolism in humans following exposure to 1,1,2-trichloroethane.

The primary metabolites identified by high-performance liquid chromatography in rats and mice given 1,1,2-trichloroethane by gavage were chloroacetic acid, S-carboxymethylcysteine, and thiodiacetic acid (Mitoma et al. 1985). An earlier study reported these three compounds to be the primary metabolites of 1,1,2-trichloroethane following intraperitneal injection (Yllner 1971). S-carboxymethycysteine and thiodiacetic acid are

formed from 1,1,2-trichloroethane following conjugation with glutathione (Yllner 1971). Chloroacetic acid is formed by hepatic cytochrome P-450 (Ivanetich and Van Den Honert 1981). This reaction is thought to proceed via the acyl chloride. Cytochrome P-450 can also produce free radicals from 1,1,2-trichloroethane (Mazzullo et al. 1986). These proposed pathways are shown in Figure 2-4. Acyl chlorides and free radicals are reactive metabolites that can bind to proteins and nucleic acids, and are suspected of being cytotoxic, mutagenic, and carginogenic (Ivanetich and Van Den Honert 1981, Mazzullo et al. 1986). Other metabolites, found only in trace amounts in mice and rats following exposure to 1,1,2-trichloroethane, included trichloroacetic acid and trichloroethanol (Ikeda and Ohtsuji 1972, Takahara 1986b, Yllner 1971). It is not clear how these compounds were formed; it was suggested by Yllner (1971) that they might be derived from impurities in the 1,1,2-trichloroethane samples used.

Although percent of the orally-administered dose metabolized was identical in rats and mice (81%), the actual amount of 1,1,2-trichloroethane metabolized was much higher in mice (Mitoma et al. 1985). The chemical was given to each species at the MTD, which was 4.3 times greater in mice; mice experienced a higher body burden than rats, but were able to metabolize the same percentage of it. The inherent ability of mice to metabolize 1,1,2-trichloroethane at a higher rate than rats may contribute to the greater susceptibility of mice to 1,1,2-trichloroethance cytotoxicity and carcinogenity. It is not known how the rate of 1,1,2-trichloroethane metabolism *in* humans compares to that in mice and rats. Metabolism in humans is likely to be qualitatively similar to that in animals, however.

2.6.4 Excretion

2.6.4.1 Inhalation Exposure

The excretion rate of inhaled 1,1,2-trichloroethane in humans was measured in the breath and urine of humans (Morgan et al. 1970). Excretion in the breath after 1 hour was 2.9% of the administered dose; the slope of the retention curve was 0.006. The excretion rate in the urine was less than 0.0l%/min of administered radioactivity. From these data, the half-life for urinary excretion was estimated to be about 70 minutes.

The half-life following l-hour inhalation exposure to 1005 ppm of 1,1,2-trichloroethane in mice was determined to be 625 minutes in the heart, 203 minutes in the fat, 147 minutes in the brain, 127 minutes in the spleen, 122 minutes in the lungs, 43 minutes in the kidney, 39 minutes in the blood, and 19 minutes in the liver (Takahara 1986a). The half-life in the whole body was calculated to be 49.3 minutes. The presence of 1,1,2-trichloroethane in tissue samples was determined by gas chromatography,

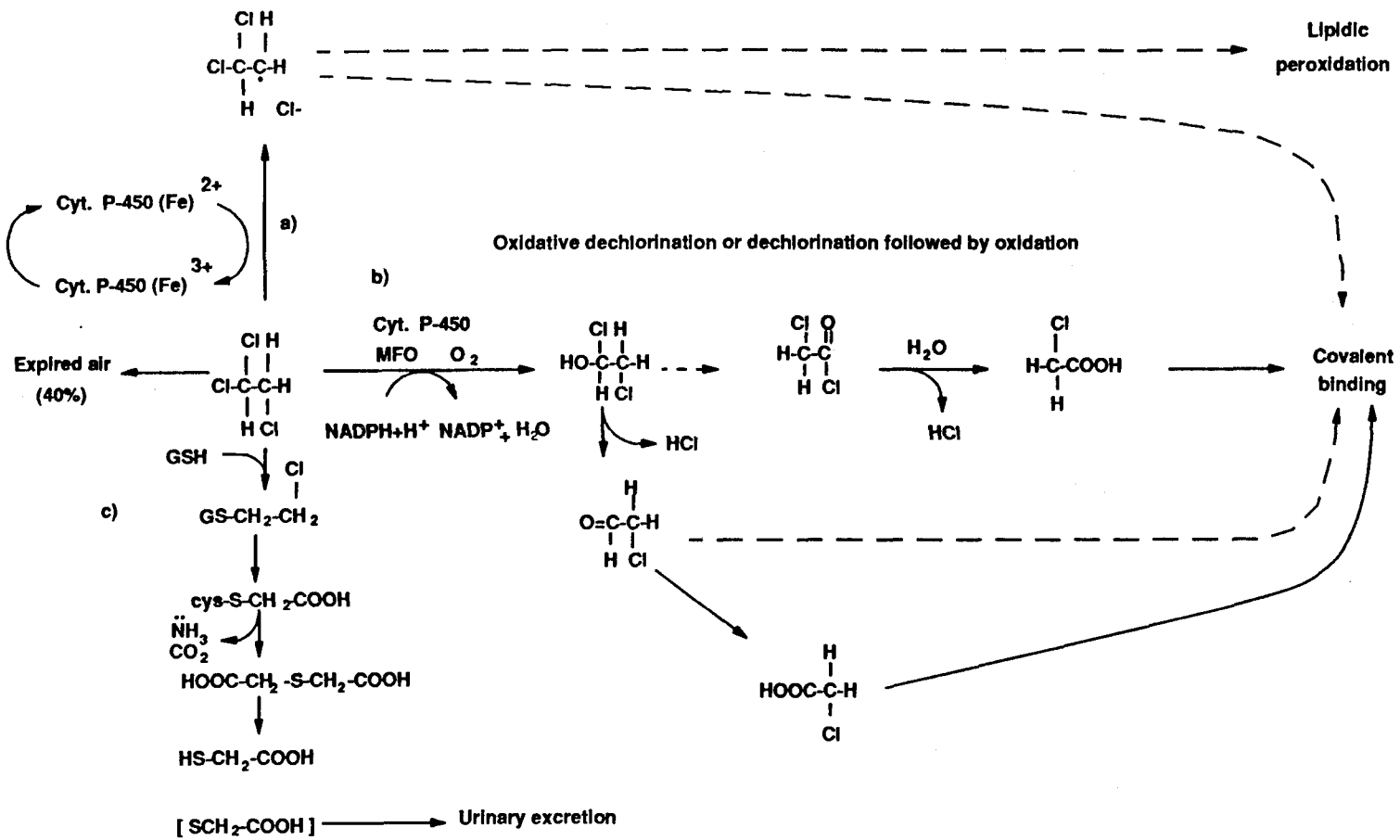

FIGURE 2-4. Proposed Metabolic Pathway of 1,1,2-Trichloroethane. a) one-electron oxidation; b) two-electron oxidation; c) detoxification step. - - - supposed pathway; —proven pathway.

(from Mazzullo et al. 1986)

2.6.4.2 Oral Exposure

No studies were located regarding excretion in humans following oral exposure to 1,1,2-trichloroethane.

The excretion routes were shown to be similar in rats and mice, regardless of whether the chemical was given orally (Mitoma et al. 1985) or intraperitoneally (Yllner et al. 1971). Following a dose of radiolabeled compound, about 7-10% of 1,1,2-trichloroethane was exhaled unchanged in the breath, 3-7% was exhaled as $C0_2$, 72%-87% was found as metabolites in the urine, about 1% was in the feces, and l-3% remained in the carcasses of rats and mice after 48 hours. The excretion from humans is also likely to be primarily via metabolites in the urine.

2.6.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals following dermal exposure to 1,1,2-trichloroethane.

2.7 INTERACTIONS WITH OTHER CHEMICALS

Polybrominated biphenyls (PBBs) were shown to increase the renal toxicity of 1,1,2-trichloroethane as measured by decreases in paminohippurate accumulation in renal cortical slices (Kluwe et al. 1978). PBBs are known to increase the activities of microsomal mixed-function oxygenases in the kidney and liver, so increased metabolism of 1,1,2-trichloroethane and the increased presence of metabolites more toxic than the parent compound itself may be responsible for the increased toxicity of 1,1,2-trichloroethane in the kidney. However, the study also showed that PBBs did not increase the hepatotoxic effects of 1,1,2-trichloroethane, as indicated by relative liver weight or SGOT levels.

Phenobarbital, another microsomal enzyme inducing agent, was found to potentiate liver toxicity, as indicated by increases in SGOT and SGPT in rats that were exposed to 1,1,2-trichloroethane vapor (Carlson 1973). Guinea pigs treated with pentobarbital as an anesthetic following dermal application of 1,1,2-trichloroethane were shown to have reduced glycogen levels and hydropic changes in the liver (Kronevi et al. 1977). Liver effects were not found in anesthetized "control" animals or animals that were treated with 1,1,2-trichloroethane, but not anesthetized. The authors suggest that the liver effects they observed were produced by the interaction of pentobarbital and 1,1,2-trichloroethane. The lack of untreated controls makes this claim difficult to evaluate, however. Potentiation is usually seen only after pretreatment with the inducer, since time is required for enzyme induction. It may be that dermal absorption of 1,1,2-trichloroethane was slow enough, compared to intraperitoneal absorption of pentobarbital, for this to occur.

Pretreatment with low, but not high doses of acetone (MacDonald et al. 1982) potentiated the hepatotoxicity of 1,1,2-trichloroethane in rats as indicated by a rise in SGPT and a decrease in hepatic GSH levels. Acetone also potentiated the 1,1,2-trichloroethane-induced elevation of SGPT in mice (Traiger and Plaa 1974).

Pretreatment with isopropyl alcohol (Traiger and Plaa 1974) or ethanol (Klaassen and Plaa 1966) potentiated the 1,1,2-trichloroethane-induced elevation of SGPT activity in mice. Pretreatment with ethanol did not alter BSP retention (Klaassen and Plaa 1966).

Pretreatment with alloxan, which induces a hyperglycemic state similar to that found in diabetic humans, also enhanced the hepatotoxic effects of 1,1,2-trichloroethane in rats as indicated by increased SGPT activity and increased hepatic triglyceride concentration (Hanasono et al. 1975). The mechanism of this interaction is unknown.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Persons with diabetes (Hanasono et al. 1975), or with prior exposure to PBBs (polybrominated biphenyls) (Kluwe et al. 1978), or with prior exposure to isopropyl or ethyl alcohol or acetone (Traiger and Plaa 1974) may be more susceptible to the hepatotoxic effects of 1,1,2-trichloroethane. Prior exposure to other enzyme-inducing drugs or chemicals could potentially have the same effect.

2.9 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 DCE is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

2.9.1 Existing Information on Health Effects of Trichloroethane

Existing studies on the health effects of 1,1,2-trichloroethane are shown in Figure 2-5. Almost no data exist for the health effects of this compound in humans; a single study on the dermal irritation of 1,1,2-trichloroethane in man was located in the literature.

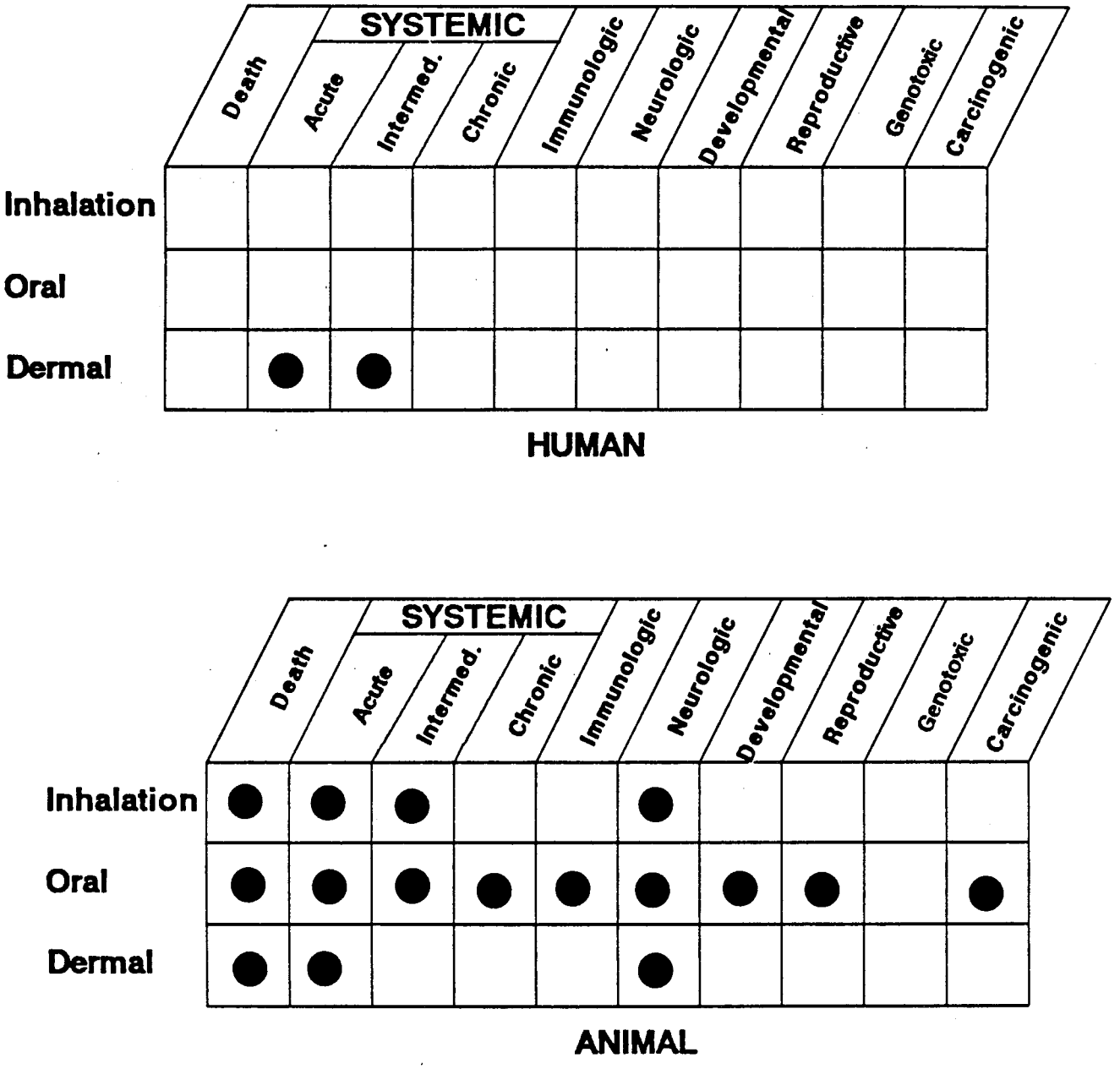

FIGURE 2-5. Existing Information on the Health Effects of 1,1,2-Trichloroethane

The health effects of 1,1,2-trichloroethane in animals have been fairly well studied. A number of inhalation studies investigated lethality in rats and mice, and several made LC_{50} determinations. The systemic effects that have been studied following inhalation exposure are liver and kidney effects. Liver effects were investigated in several studies that measured serum transaminase levels and other biochemical endpoints; only one unpublished study included histopathological examination of the liver. The same study included histopathological examination of the kidney. This study was also the only one in which animals were repeatedly exposed to 1,1,2-trichloroethane vapor; all other studies by this route were single exposure tests. Neurological effects following inhalation were studied by behavioral observations in rats and mice and tests of neurological function in mice.

Following oral exposure, lethality in rats, mice, and dogs has been reported. LD_{50} values were calculated for the first two species. Systemic effects were studied in rats, mice, and dogs using biochemical and histopathological measures. Most studies were of single exposures, but there was one study of intermediate duration (which did not include histopathological examination) and one of chronic duration (which included only histopathologic examination). Immunological effects were reported in a study that included tests of humoral and cell-mediated immune function. Neurological effects were studied by behavioral observation and, in longerterm studies, examination of tissues. Developmental toxicity was the subject of one study that did not include examination of fetuses for malformations. Data on reproductive effects come from this study and longer-term studies that examined reproductive tissues, but did not perform tests of reproductive function. Carcinogenicity was studied in one 78-week bioassay in rats and mice and one 2-year study in rats that was not, however, performed by a relevant route of exposure.

There is one study of lethality in guinea pigs following dermal exposure to 1,1,2-trichloroethane. There are also several studies of skin and eye irritation in dermally-exposed animals. One poorly-designed study investigated the effect of dermally applied 1,1,2-trichloroethane on liver, kidney, and brian histopathology.

2.9.2 Data Needs

Single Dose Exposure. Tests of the acute toxicity of 1,1,2-trichloroethane administered orally and by inhalation have provided information on 1,1,2-trichloroethane exposure levels that produce liver and kidney damage, neurological effects, and death in animals. Several of these studies included analyses for subtle liver effects, but few included histopathological examinations. More studies which carefully examine liver and other tissues histologically and look for subtle effects on other organs may be beneficial. They might provide information on mechanisms by which 1,1,2-trichloroethane produces lethality and neurological effects and provide further information on other toxic effects. Knowledge of mechanisms

is helpful to understanding the health effects of a chemical. Dermal studies of 1,1,2-trichloroethane have provided information on exposure levels that produce skin irritation in humans and animals and death in animals. One poorly-designed study attempted to investigate systemic effects in dermally exposed animals. A study of systemic toxicity following dermal application of 1,1,2-trichloroethane might provide useful information.

Repeated Dose Exposure. Only one study examined the health effects of 14- and 90-day ingestion of 1,1,2-trichloroethane in drinking water of animals, and it did not include histopathological examinations. A subchronic oral study with complete histological examination would be useful. Repeated dose exposure by inhalation was examined only in an unpublished report that could not be obtained for review. A published report of this study or a replacement would provide useful information. Repeated dermal application of 1,1,2-trichloroethane to humans was done in one study. No effects were found, but the irritancy of 1,1,2-trichloroethane in single-dose exposure tests suggests that repeated-exposure dermal tests in animals would provide meaningful information.

Chronic Exposure and Carcinogenicity. A 78-week bioassay on orally administered 1,1,2-trichloroethane was performed in rats and mice by the National Cancer Institute. 1,1,2-Trichloroethane was found to be cancerous in mice, but not rats. The 78-week dosing period is no longer considered adequate for rats. Current studies of this type use exposure durations of approximately 2 years. A 2-year study was conducted by Norpoth et al. (1988), but exposure was by subcutaneous injection, which is not a relevant route. Two-year studies by the oral and inhalation routes on rats and mice using several doses, examining endpoints of hematology, clinical chemistry, urinalysis, and performing microscopic examination of tissues may provide valuable dose-response data and identify more subtle indicators of toxicity. Studies of chronic toxicity and carcinogenicity do not exist for other routes of exposure.

Genotoxicity. The available genotoxicity studies indicate that *1,1,2*-trichloroethane is not mutagenic in bacteria, but may interact with mammalian DNA in vivo. Chromosomal aberration and micronucleus tests on 1,1,2-trichloroethane were not located. Additional genotoxicity tests would help to determine whether 1,1,2-trichloroethane is genotoxic in humans.

Reproductive Toxicity. Several studies included examination of reproductive organs and tissues following exposure to 1,1,2-trichloroethane, but found no effects. One study designed to look at developmental toxicity reported no effect on reproductive endpoints. Studies in which animals exposed to 1,1,2-trichloroethane are mated and their offspring observed would provide more information regarding the reproductive toxicity of 1,1,2-trichloroethane.

Developmental Toxicity. A study on the developmental toxicity of 1,1,2-trichloroethane in mice found no effect, but it did not include examination of the fetuses for malformations. A complete teratology study in two species would provide better information on the developmental toxicity of 1,1,2-trichloroethane in animals and help to determine whether it is possible that 1,1,2-trichloroethane has developmental effects in humans.

Immunotoxicity. The immunological effects of 1,1,2-trichloroethane have been studied following 14-day and 90-day oral exposure. Several measures of both humoral and cell-mediated immune response were investigated in this study, and some positive results were found. The fact that effects were found in some tests, but not others intended to measure the same response, indicates that more studies of this type could provide worthwhile information. In addition, immune responses were different in male and female mice, and investigation of these differences might provide meaningful information. No studies were located regarding dermal sensitization by 1,1,2-trichloroethane.

Neurotoxicity. Studies of 1,1,2-trichloroethane in animals have provided information on the neurological effects produced by acute exposure to 1,1,2-trichloroethane, and the levels at which they occur. The results of one study suggested that taste aversion may be a sensitive indicator of the acute neurological effects of 1,1,2trichloroethane. Additional neurobehavioral tests may reveal still more sensitive neurologic endpoints or provide support for use of taste aversion as an indicator of neurologic effects. Repeated exposure studies involved examination of neurological organs and tissues, but no tests of neurological function. Reliable studies of neurotoxicity by dermal exposure do not exist.

Epidemiological and Human Dosimetry Studies. No human studies were found in the literature which relate exposure to 1,1,2-trichloroethane with health effects. The evidence in animals, however, indicates that 1,1,2-trichloroethane can have effects on the nervous system, immune system, and liver and kidney function, and can be lethal. It is also carcinogenic in mice. These effects may also occur in humans, if they are exposed to appropriate levels of 1,1,2-trichloroethane. Epidemiological and human dosimetry studies might reveal whether humans are indeed susceptible to adverse health effects due to exposure to 1,1,2-trichloroethane.

Biomarkers of Disease. No studies were located that identified biomarkers specific for 1,1,2-trichloroethane-induced disease states. If epidemiological studies are performed that associate effects with exposure, it may be possible to identify alterations in blood chemistry indices or other pathological endpoints that would be useful to identify the disease state. Biomarkers for diagnosis of target organ toxicity (e.g., SGOT for liver damage) can provide useful information in conjunction with specific knowledge of 1,1,2-trichloroethane exposure,

Disease Registries. Currently, no human disease states are associated with exposure to 1,1,2-trichloroethane. If future studies identify particular diseases produced by 1,1,2-trichloroethane, it may be possible to determine the number of people affected and the factors associated with the development of the disease, such as involvement of populations in certain occupations or living in certain areas.

Bioavailability from Environmental Media. Since 1,1,2-trichloroethane is expected to exist in the atmosphere as the vapor rather than adsorb toparticulate matter, there would not be a competing adsorption that would impede its bioavailability via the lungs. Limited data showing the presence of 1,1,2-trichloroethane in adipose and other tissue of exposed subjects indicate that 1,1,2-trichloroethane is taken up via the lungs, GI tract or both. A pilot study demonstrated that similar low molecular weight chlorinated alkanes are found in human milk (Pellizzari et al. 1982). The source of these pollutants was probably ambient air, and this is the most probable route of intake for the general population.

Food Chain Bioaccumulation. 1,1,2-Trichloroethane has not been reported in food or biota, nor were any studies located in which the levels of this chemical in plants or animals were reported. The bioaccumulation potential for a chemical is most conveniently studied by measuring the bioconcentration factor (BCF) or the concentration of a chemical in fish divided by the concentration in water from which the chemical is taken up. The BCF of 1,1,2-trichloroethane in fish is reported to be <10 (Kawasaki 1980), indicating a very low potential for bioaccumulation in the food chain. Experimental verification of the lack of food chain bioaccumulation is not available. Such information can be obtained by studying the accumulation of 1,1,2-trichloroethane in organisms from different trophic levels that have been exposed to the chemical.

Absorption, Distribution, Metabolism, Excretion. Little information is available regarding the toxicokinetics of 1,1,2-trichloroethane in humans or animals. Information on absorption in humans comes from a brief study using two volunteers; the only information from animals is inferred from the fact that administration of 1,1,2-trichloroethane via the inhalation or oral routes causes toxic effects. Animal studies which specifically test the amount and rate of absorption of 1,1,2-trichloroethane would provide information as to how much 1,1,2-trichloroethane humans might be likely to absorb from various routes of exposure. For distribution, the only human data are from one briefly reported study, and the only animal data are from one acute study. More extensive and longer-term animal studies using the inhalation, oral or dermal routes would help determine 1,1,2-trichloroethane distribution in the body. For metabolism, more animal studies would be helpful in, showing what kind of metabolites might be expected to be found in the blood or urine of humans; if these could be measured, they might give an indication of amount of exposure to 1,1,2-trichloroethane. Additional metabolism studies may also reveal more

definitive information on mechanfsms of 1,1,2-trichloroethane toxicity and carcinogenicity. Data on excretion are fairly complete.

Comparative Toxicokinetics. No studies were located which compared human and animal toxicokinetics. Two comparative toxicokinetics studies were performed which examined the differences between rats and mice in the types of metabolites formed, and the excretion rates from various routes. Although percent of administered dose metabolized was similar in both species, the overall rate of metabolism of 1,1,2-trichloroethane was greater in mice (Mitoma et al. 1985). The same metabolites were formed in the same proportions in both species. The difference in metabolic rate may be related to species differences in susceptibility to the toxic effects of 1,1,2-trichloroethane. More studies of this type could corroborate this theory or identify other factors that may be responsible for the species difference in toxicity.

2.9.3 On-going Studies

No on-going studies were located regarding health effects or toxicokinetics in humans or animals following exposure to 1,1,2-trichloroethane.