3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,1,2,2-tetrachloroethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between

"less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of 1,1,2,2-tetrachloroethane are indicated in Table 3-2 and Figure 3-2. Because cancer effects could occur at lower exposure levels, Figure 3-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

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

As discussed below, the database on health effects of 1,1,2,2-tetrachloroethane is limited by a paucity of studies in humans. The information in humans is generally very dated, incomplete, and unsuitable for determination of reliable effect levels.

3.2.1 Inhalation Exposure

3.2.1.1 Death

A few human deaths have been reported following excessive inhalation exposure to 1,1,2,2-tetrachloroethane. Immediately after World War I, gastrointestinal and neurological distress were reported following occupational exposure to a varnish containing 1,1,2,2-tetrachloroethane that was used to cover fabric airplane wings. Although workers generally recovered, at least 4 of 14 workers later became confused, delirious, comatose, and finally died (Willcox et al. 1915). Autopsies revealed extreme liver

destruction and fatty degeneration of the liver. The levels of 1,1,2,2-tetrachloroethane in the air were not measured, so inhaled concentrations that may cause death in humans are not known.

Inhalation of 1,1,2,2-tetrachloroethane has also been shown to cause death in animals. Mortality resulted from exposure to concentrations of 1,000–1,253 ppm for 4–6 hours in rats (Carpenter et al. 1949; Deguchi 1972; Schmidt et al. 1980b; Smyth et al. 1969), 1,168–5,900 ppm for 1.5–3 hours in mice (Horiuchi et al. 1962; Pantelitsch 1933), and 5,050–6,310 ppm for 30 minutes in rats and guinea pigs (NIOSH 1978). Mortality was reported in rats and mice repeatedly exposed to 1,1,2,2-tetrachloroethane vapors (Horiuchi et al. 1962). For example, exposure of six male rats at a concentration of 9,000 ppm (2 hours/day, once/week for a total of five exposures) resulted in 100% mortality; three of the six rats died following the first exposure period. All nine male mice exposed to 1,1,2,2-tetrachloroethane vapors at a concentration of 7,000 ppm for 2 hours once a week died during a 29-day study. All exposures from reliable studies that caused death in rats, mice, and guinea pigs are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal or dermal effects in humans or animals following inhalation exposure to 1,1,2,2-tetrachloroethane. The systemic effects observed in humans and animals after inhalation exposure to 1,1,2,2-tetrachloroethane are discussed below. The highest NOAEL and all LOAEL values from each reliable study for systemic end points in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Minor effects on the respiratory system are caused by 1,1,2,2-tetrachloroethane in humans. At a concentration of 13 ppm, but not 2.9 ppm, mucosal irritation occurred in two humans exposed for 10–30 minutes. Odor was noticed at the lowest concentration tested (2.9 ppm) (Lehmann and Schmidt-Kehl 1936).

Labored respiration was observed in rats and guinea pigs exposed to 1,1,2,2-tetrachloroethane vapors at lethal concentrations (5,050 or 6,310 ppm) for 30 minutes; histological examinations showed no treatment-related lesions in the lungs (NIOSH 1978). There was no histopathological evidence of exposure-related effects on the respiratory system of a monkey exposed to a time-weighted average (TWA) concentration of 1,974 ppm for 2 hours/day, 6 days/week for 9 months (Horiuchi et al. 1962), although the monkey study is limited by only one test animal and no control.

Table 3-1 Levels of Significant Exposure to 1,1,2,2-tetrachloroethane - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sherman)	4 hr				1000 (2/6 died)	Carpenter et al. 1949	
2	Rat (Sprague-Dawley)	30 min				5050 (3/10 died)	NIOSH 1978	
3	Rat (Wistar)	4 hr				1253 M (LC50)	Schmidt et al. 1980b	
4	Mouse (NS)	3 hr				5900 M (3/10 died)	Horiuchi et al. 1962	
5	Mouse (NS)	1.5-2 hr				1168 (3/3 died)	Pantelitsch 1933	
6	Gn Pig (Hartley)	30 min				6310 (3/10 died)	NIOSH 1978	

Table 3-1 Levels of Significant Exposure to 1,1,2,2-tetrachloroethane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Systemic								
7	Rat (Sprague-Dawley)	30 min	Resp	576		5050 (labored respiration)	NIOSH 1978	Labored respiration occurred at lethal exposure levels.
			Cardio	6310				
			Hepatic	6310				
			Renal	6310				
			Endocr	6310				
			Ocular	576	5050 (lacrimation)			
			Bd Wt	6310				
8	Mouse (NS)	3 hr	Hepatic		5900 M (congestion and fatty degeneration of the liver)		Horiuchi et al. 1962	
9	Mouse (Cb)	3 hr	Hepatic		600 F (increased triglycerides and total lipids and decreased ATP in liver)		Tomokuni 1969	
10	Mouse (Cb)	3 hr	Hepatic		800 F (increased triglycerides and decreased phospholipids in liver)		Tomokuni 1970	

Table 3-1 Levels of Significant Exposure to 1,1,2,2-tetrachloroethane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
11	Gn Pig (Hartley)	30 min	Resp	576			5050	(labored respiration)	NIOSH 1978	Labored respiration occurred at lethal exposure levels.
			Cardio	6310						
			Hepatic	6310						
			Renal	6310						
			Endocr	6310						
			Ocular		576	(lacrimation, squinting, eye closure)				
			Bd Wt	6310						
Neurological										
12	Rat (NS)	6 hr					360	(50% decreased motor activity)	Horvath and Frantik 1973	
13	Rat (Sprague-Dawley)	30 min			576	(reduced activity and alertness)	5050	(narcosis)	NIOSH 1978	
14	Mouse (NS)	1.5-2 hr					1022	(prostration, loss of reflexes)	Pantelitsch 1933	
15	Gn Pig (Hartley)	30 min			576	(reduced activity)	5050	(narcosis and tremors)	NIOSH 1978	

Table 3-1 Levels of Significant Exposure to 1,1,2,2-tetrachloroethane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Death								
16	Rat (NS)	29 d 2-3 d/wk 2 hr/d				9000 M (6/6 died)	Horiuchi et al. 1962	3/6 Deaths occurred prior to the second exposure period.
17	Mouse (NS)	29 d 1 d/wk 2 h/d				7000 M (9/9 died)	Horiuchi et al. 1962	5/9 Deaths occurred within 5 days following the first exposure period.
Systemic								
18	Monkey (Macaca cynomolga)	9 mo 6 d/wk 2 hr/d	Hepatic		1974 M (fatty degeneration)		Horiuchi et al. 1962	
19	Rat (NS)	29 d 2-3 d/wk 2 hr/d	Hemato		9000 M (decreases red cell count and hemoglobin content)		Horiuchi et al. 1962	
			Hepatic		9000 M (congestion and fatty degeneration)			
			Bd Wt	9000 M				
20	Mouse (NS)	29 d 1 d/wk 2 h/d	Hepatic		7000 M (congestion and fatty degeneration)		Horiuchi et al. 1962	
Neurological								
21	Monkey (Macaca cynomolga)	9 mo 6 d/wk 2 hr/d				1974 M (near unconsciousness)	Horiuchi et al. 1962	Near unconsciousness noted as early as the 15th exposure period.

Table 3-1 Levels of Significant Exposure to 1,1,2,2-tetrachloroethane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
22	Rat (NS)	29 d 2-3 d/wk 2 hr/d				9000 M (ataxia and loss of consciousness)	Horiuchi et al. 1962	
Reproductive								
23	Rat (NS)	9 mo 4 hr/d		1.9 M			Schmidt et al. 1972	Reproductive endpoints were adequately reported.

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

ATP = adenosine tri-phosphate; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno = immunological; LC50 = lethal concentration, 50% kill, LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; Resp = respiratory; wk = week(s)

Figure 3-1 Levels of Significant Exposure to 1,1,2,2-tetrachloroethane - Inhalation

Acute (≤14 days)

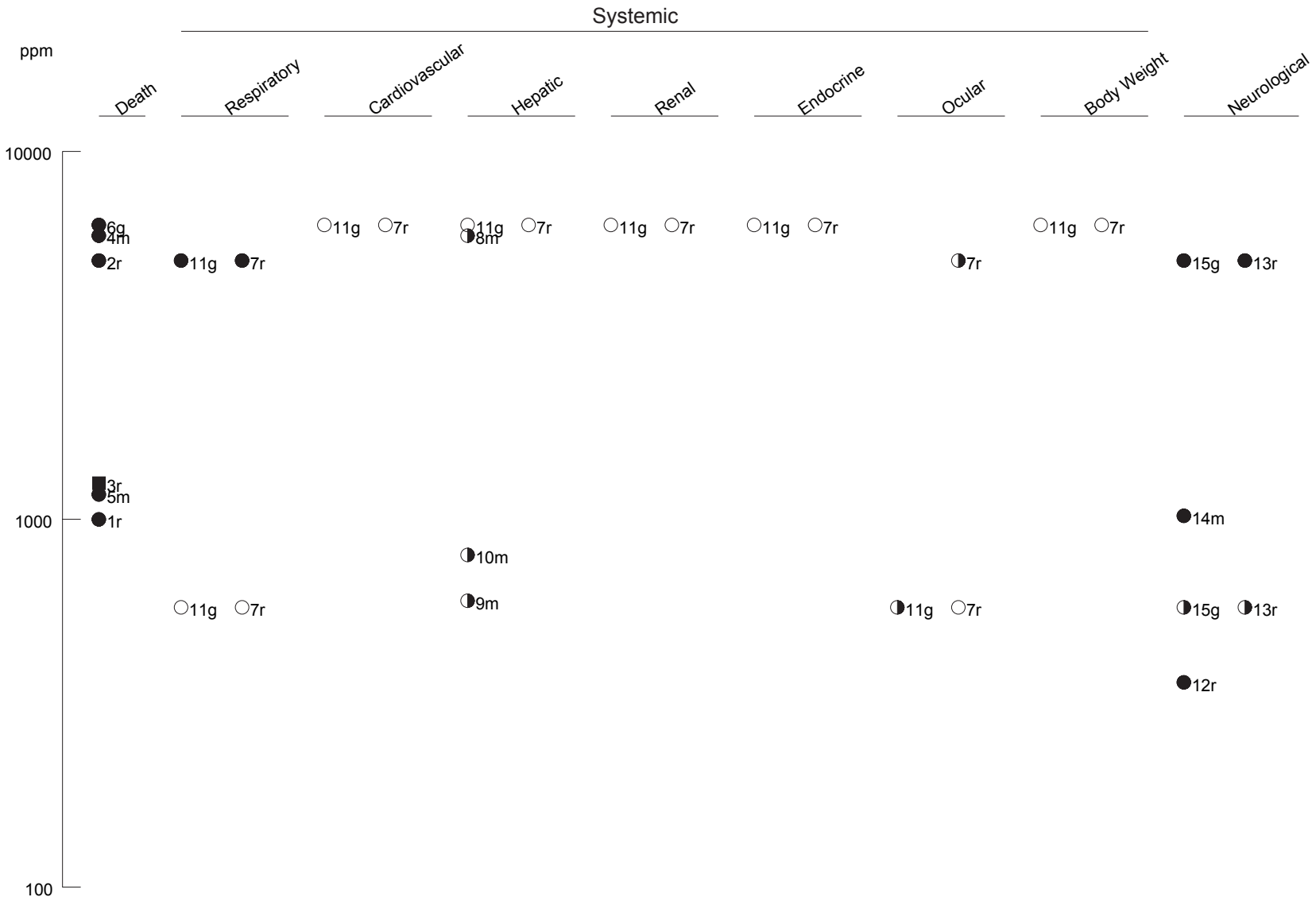
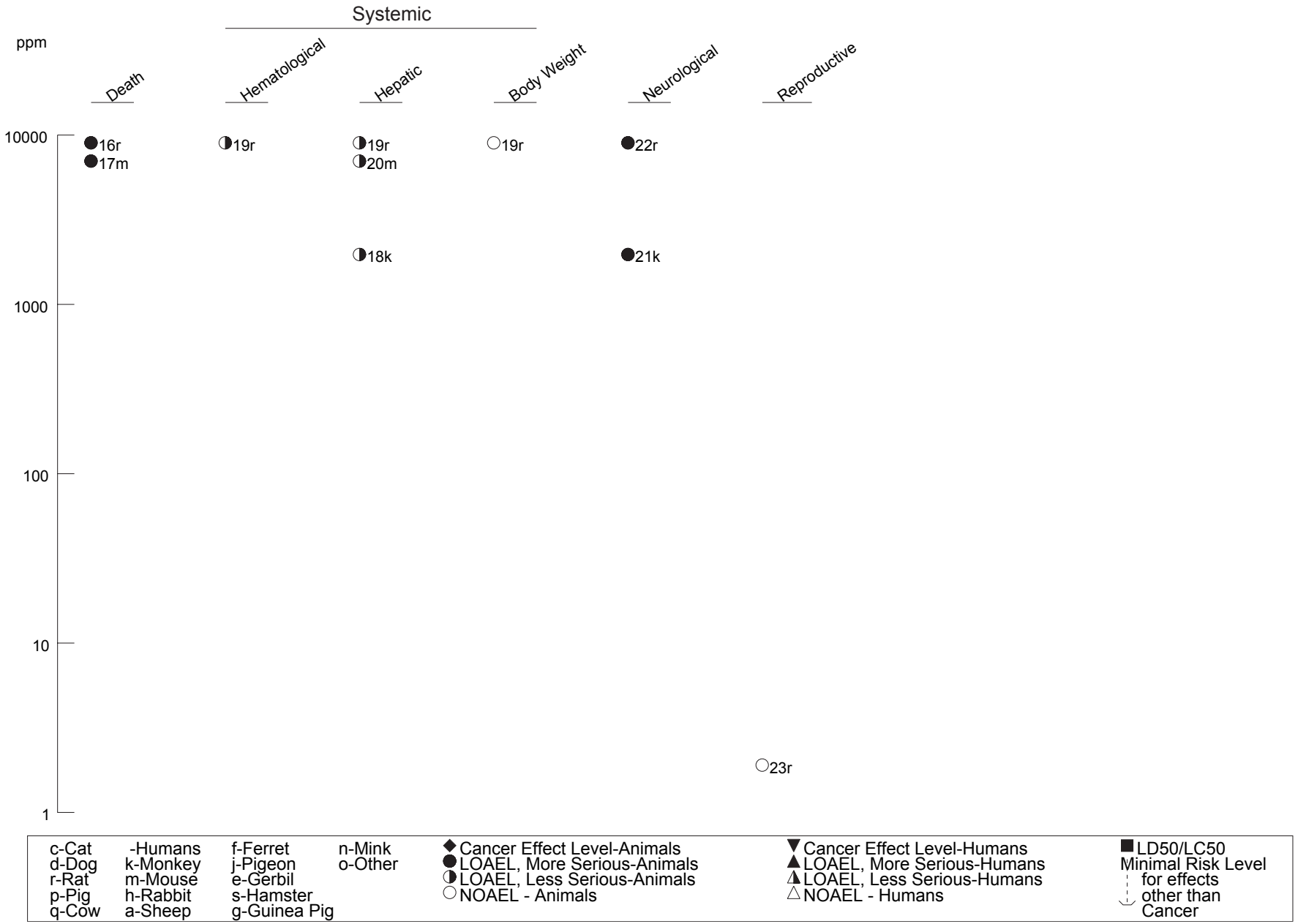


Figure 3-1 Levels of Significant Exposure to 1,1,2,2-tetrachloroethane - Inhalation *(Continued)*

Intermediate (15-364 days)



Cardiovascular Effects. Humans exposed to 1,1,2,2-tetrachloroethane in factories showed few, if any, effects on the cardiovascular system. World War II army workers who were exposed to unknown levels of 1,1,2,2-tetrachloroethane during its use as a solvent in a clothing impregnation process showed no increase in deaths due to cardiovascular diseases in a 30-year follow-up period (Norman et al. 1981). When compared with cause-, age-, race-, and calendar year-specific U.S. mortality rates, the standard mortality ratio (SMR) for cardiovascular disease was 0.79 (confidence intervals not reported); additional information on this study is presented in Section 3.2.1.7. Workers exposed to 1,1,2,2-tetrachloroethane in a chemical plant in Italy showed no important clinical changes in cardiovascular function (Gobbato and Bobbio 1968). Exposure levels were not measured in either of these studies.

No pathological changes in rat hearts were found after a 6-hour exposure to 100 ppm (Deguchi 1972). Myocardial damage was found in 1 of 10 rats following exposure to 6,310 ppm for 30 minutes; no such effect occurred in a guinea pig subjected to this same exposure (NIOSH 1978).

No histopathological changes were seen in the heart of a monkey that was exposed to a TWA concentration of 1,974 ppm 1,1,2,2-tetrachloroethane for 2 hours/day, 6 days/week for 9 months (Horiuchi et al. 1962). However, only one monkey was studied, and a control was not included.

Gastrointestinal Effects. Humans exposed to 1,1,2,2-tetrachloroethane in the workplace often developed gastric distress including pain, nausea, vomiting, loss of appetite, and loss of body weight. Such symptoms were found in workers in the fabric airplane wing varnish industry in World War I (Coyer 1944; Willcox et al. 1915), in a penicillin factory in Czechoslovakia (Jeney et al. 1957), and in a jewelry factory in India (Lobo-Mendonca 1963). Although specific complaints were not associated with specific levels of exposure, the exposure levels in the facilities ranged from 1 to 248 ppm. The adverse health effects generally disappeared when the workers left their employment.

Two volunteers who inhaled 1,1,2,2-tetrachloroethane fumes for 10–30 minutes experienced nausea and vomiting after exposure to 2.9 ppm for 20 minutes (Lehmann and Schmidt-Kehl 1936).

Data regarding gastrointestinal effects in animals following inhalation exposure to 1,1,2,2-tetrachloroethane are limited. One monkey exposed to 1,974 ppm for 2 hours/day, 6 days/week for 9 months had diarrhea and anorexia between the twelfth and fifteenth exposures and subsequently recovered (Horiuchi et al. 1962). However, no control monkey was included.

Hematological Effects. An increase in the number of large mononuclear cells, white blood cells, and platelets, and slight anemia, were found in workers in an artificial silk factory who were exposed to 1,1,2,2-tetrachloroethane vapors (Minot and Smith 1921). 1,1,2,2-Tetrachloroethane levels were not accurately measured.

Two of three male rats that were intermittently exposed to 9,000 ppm for 29 days showed decreases in red blood cells and hemoglobin content (Horiuchi et al. 1962). A monkey exposed to 1,974 ppm intermittently for 9 months showed sporadic changes in hematocrit, red blood cell, and white blood cell counts, but these changes showed no clear trend and only one animal was tested (Horiuchi et al. 1962).

Hepatic Effects. One of the most significant systemic effects of 1,1,2,2-tetrachloroethane is on the liver. Some humans exposed to 1,1,2,2-tetrachloroethane vapors in the workplace have developed jaundice and an enlarged liver (Coyer 1944; Horiuchi et al. 1962; Jeney et al. 1957; Koelsch 1915; Willcox et al. 1915). Specific clinical signs were not associated with specific exposure levels. Vapor concentrations were reported in one study to range from 1.5 to 248 ppm (Jeney et al. 1957).

Liver degeneration, as evidenced by liver congestion and necrosis, was observed in the autopsies of two humans who died after exposure to 1,1,2,2-tetrachloroethane (Willcox et al. 1915). World War II army workers who were exposed to unknown levels of 1,1,2,2-tetrachloroethane during its use as a solvent in a clothing impregnation process showed no increase in deaths due to cirrhosis of the liver in a 30-year follow-up period (Norman et al. 1981). When compared with cause-, age-, race-, and calendar year-specific U.S. mortality rates, the SMR for liver cirrhosis was 0.48 (confidence intervals not reported). Additional information on this study is presented in Section 3.2.1.7.

The liver is also the major target organ for 1,1,2,2-tetrachloroethane toxicity in animals. Fine droplet fatty degeneration of the liver was observed in rats following a single exposure to 60 ppm for 4 hours or exposure to 2 ppm for 4 hours/day for 8 of 10 days, but there were no clear changes in serum or liver chemistry indices at these exposure levels (Gohlke and Schmidt 1972; Schmidt et al. 1972). This histological alteration appeared to be mild and was accompanied by clear or suggestive increases in hepatic ascorbic acid and serum glutamate dehydrogenase and decreases in serum triglycerides at 102 ppm, increases in serum triglycerides and hexobarbital sleep time at 307 ppm, and increases in serum alanine aminotransferase and leukin aminopeptidase at 613 ppm (Schmidt et al. 1972), suggesting that 102 ppm was a minimal LOAEL for acute hepatic effects. No treatment-related histological effects were found in the liver of rats or guinea pigs exposed to 6,310 ppm of 1,1,2,2-tetrachloroethane for 30 minutes

(NIOSH 1978), although rats that were exposed to 9,000 ppm for 2 hours/day, 2 days/week for 4 weeks showed fatty livers (Horiuchi et al. 1962). Hepatic lipids and triglycerides were increased in mice exposed to 600–800 ppm for 3 hours (Tomokuni 1969, 1970), and fatty degeneration of the liver occurred in mice exposed to a lethal concentration of 5,900 ppm for 3 hours (Horiuchi et al. 1962). Rabbits that were exposed to 15 ppm for 7–11 months showed early signs of liver degeneration at necropsy (Navrotskiy et al. 1971). A single monkey exposed to a TWA concentration of 1,974 ppm of 1,1,2,2-tetrachloroethane for 2 hours/day, 6 days/week for 9 months also showed fatty degeneration of the liver (Horiuchi et al. 1962).

Additional information on liver effects following intermediate-duration exposure to 1,1,2,2-tetrachloroethane is available from poorly reported studies that cannot be used to identify reliable effect levels. For example, Truffert et al. (1977) reported unquantified increases in relative liver weights and histopathological liver alterations in female rats exposed to 1,1,2,2-tetrachloroethane vapors at a reported concentration of 560 mL/m^3, for 5 or 6 hours/day, 5 days/week for up to 15 weeks. The histological liver alterations were observed after nine exposures and included granular appearance, cytoplasmic vacuolization, and evidence of hyperplasia (increase in number of binuclear cells and appearance of mitosis), but the alterations regressed after 19 exposures and were no longer observed after 39 exposures. Incidences and severity of the liver lesions were not reported. Reliable effect levels cannot be established for this study due to the lack of information regarding incidence and severity of effects and exposure-response (due to the use of a single exposure level), as well as uncertainty regarding the actual exposure concentration. If it is assumed that mL/m^3 is a volume/volume vapor concentration, then the reported concentration is equivalent to 560 ppm. If it is assumed that 560 mL is the volume of liquid volatilized in 1 m^3 of air, then the reported concentration is equivalent to 130,325 ppm, a level over 100 times higher than the acute LC_{50}.

Renal Effects. No recent studies were located regarding renal effects in humans following inhalation exposure to 1,1,2,2-tetrachloroethane. Fatty degeneration and congestion of the kidney were found in one female who had died following inhalation of 1,1,2,2-tetrachloroethane over a 2–3-month period (Willcox et al. 1915), but exposure concentrations were not defined.

No treatment-related histological effects were found in the kidneys of rats or guinea pigs exposed to 6,310 ppm for 30 minutes (NIOSH 1978), rats exposed to 613 ppm for 4 hours (Schmidt et al. 1972), or rats exposed to 2 ppm for 4 hours/day for 8 of 10 days (Gohlke and Schmidt 1972). Similarly, no treatment-related histopathological lesions in the kidney were found in one monkey exposed to a TWA

concentration of 1,974 ppm for 2 hours/day, 6 days/week for 9 months (Horiuchi et al. 1962), although this study is limited by the use of a single animal.

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to 1,1,2,2-tetrachloroethane.

No treatment-related histological effects were found in the adrenals of rats or guinea pigs exposed to 6,310 ppm for 30 minutes (NIOSH 1978) or pancreas of one monkey exposed to a TWA concentration of 1,974 ppm for 2 hours/day, 6 days/week for 9 months (Horiuchi et al. 1962). There were no changes in thyroid histology, morphometry (diameter and number of follicles and epithelial nuclei, height of follicular epithelium), or absorption of injected ^{131}I in rats exposed to 2 ppm for 4 hours/day for 8 of 10 days (Gohlke and Schmidt 1972).

Ocular Effects. Humans exposed to 1,1,2,2-tetrachloroethane vapors (130 ppm) for 10 minutes experienced ocular mucosal irritation (Lehmann and Schmidt-Kehl 1936). Similarly, guinea pigs exposed to 576 ppm for 5 minutes exhibited eye closure and squinting; by 15 minutes, lacrimation was common (NIOSH 1978). Rats showed these effects at 5,050 ppm. These ocular effects are due to direct contact of the eyes with the vapors, rather than a true systemic effect due to inhalation of the vapor.

Body Weight Effects. Humans exposed to 1,1,2,2-tetrachloroethane vapors in an occupational setting experienced a 5–15-pound weight loss (Parmenter 1921). However, this weight loss was probably attributable to gastrointestinal disturbances (i.e., nausea, diarrhea, and vomiting) (Parmenter 1921).

No effects on body weight were found in several inhalation studies in animals (Horiuchi et al. 1962; NIOSH 1978; Schmidt et al. 1972, 1980b).

3.2.1.3 Immunological and Lymphoreticular Effects

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

Rabbits were exposed 0, 0.3, 1.5, or 14.6 ppm of 1,1,2,2-tetrachloroethane for 3 hours/day, 6 days/week for 8–10 months (Shmuter 1977). Animals were vaccinated with typhoid vaccine 1.5, 4.5–5, and 7.5–8 months after the initiation of 1,1,2,2-tetrachloroethane exposure. Significant increases and decreases in

total antibody levels were observed in the 0.3 and 14.6 ppm groups, respectively. No significant changes in 7S-typhoid antibody levels were observed. Significant alterations in the levels of "normal hemolysins to the Forssmann antigen of sheep erythrocytes" were observed in the 1.5 and 14.6 ppm groups; levels were increased at 1.5 ppm after 1.5, 2, and 2.5 months of exposure and decreased after 4 months of exposure, and decreased at 14.6 ppm[3] during the first 6 months of exposure. Increases in the electrophoretic mobility of specific antibodies were also reported. Exposure to 14.6 ppm resulted in a decrease in the relative content of antibodies in the γ globulin fraction and an increase in the α and β fractions. This is a poorly reported study that provides inadequate quantitative data. The reporting limitations, end points of uncertain toxicological significance, and inconsistent patterns of response preclude assessing biological significance and identification of a NOAEL or LOAEL. No histopathological changes were noted in the spleens of rats that inhaled 100 ppm 1,1,2,2-tetrachloroethane for 6 hours (Deguchi 1972). The significance of this finding is unclear due to a lack of immune function tests.

3.2.1.4 Neurological Effects

Volunteers who inhaled 1,1,2,2-tetrachloroethane (116 ppm and higher for 10–30 minutes) reported being dizzy. These effects did not occur when the exposure was 13 ppm (Lehmann and Schmidt-Kehl 1936). Humans exposed to 1,1,2,2-tetrachloroethane fumes in the workplace showed symptoms such as headache, tremors, dizziness, numbness, and drowsiness (Hamilton 1917; Jeney et al. 1957; Lobo-Mendonca 1963; Minot and Smith 1921; Parmenter 1921). Length of exposure was not specifically noted, but the reports seem to indicate that the exposures were generally for a period of about 18 months or less. Exposure levels were only noted in one study, and these ranged from 9 to 98 ppm, with significant skin exposure in addition to the inhalation exposure (Lobo-Mendonca 1963).

In acute-duration experiments, rats showed a 50% decrease in spontaneous motor activity after being exposed to 360 ppm for 6 hours (Horvath and Frantik 1973). As the concentration of, or duration of exposure to, 1,1,2,2-tetrachloroethane increased, mice, rats, and guinea pigs showed some combination of a loss of reflexes, loss of spontaneous motor activity, ataxia, prostration, and narcosis (Lazarew 1929; Pantelitsch 1933; NIOSH 1978). Rats and guinea pigs that were exposed for 30 minutes had reduced activity at 576 ppm and narcosis at 5,050 ppm (NIOSH 1978), and mice showed prostration and loss of reflexes after being exposed to 1,022–1,091 ppm for 2 hours (Lazarew 1929; Pantelitsch 1933). Narcosis was observed in a cat exposed to 8,300 ppm for 5 hours (Lehmann 1911). Rats exposed to 9,000 ppm for 2 hours/day, twice a day for 4 weeks exhibited hyperactivity, ataxia, and then unconsciousness (Horiuchi

et al. 1962). One monkey exposed to a TWA of 1,974 ppm of 1,1,2,2-tetrachloroethane for 2 hours/day, 6 days/week for 9 months exhibited unconsciousness after each 2-hour exposure, starting at the 15th exposure (Horiuchi et al. 1962).

The highest NOAEL and all LOAEL values from each reliable study for neurological end points in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

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

Male rats were exposed to 0 or 2.2 ppm of 1,1,2,2-tetrachloroethane 4 hours/day for up to 8 days in a 10-day period (Gohlke and Schmidt 1972; Schmidt et al. 1972). Reproductive function was not tested, but evaluations included histological examinations of the testes in groups of seven control and seven treated males following the second, fourth, and eighth exposures. This study is limited by imprecise and incomplete reporting of results. It was noted that testicular histopathology, described as atrophy of the seminal tubules with strongly restricted or absent spermatogenesis, was observed in five exposed animals following the fourth exposure; data for the other time periods and the control group were not reported. It seems unlikely that the testicular histological changes were biologically significant because they apparently were not observed at the end of the study, and there were no effects on reproductive function in male rats that were chronically exposed to a similar concentration of 1,1,2,2-tetrachloroethane (1.9 ppm) (Schmidt et al. 1972).

Male rats were exposed to 0 or 1.9 ppm of 1,1,2,2-tetrachloroethane 4 hours/day for 265 days. One week before the end of the exposure period, each of 7 control and 7 exposed males was mated with 5 unexposed virgin females, yielding corresponding groups of 35 mated females. The offspring were observed for 84 days and were examined macroscopically for malformations. Other reported study end points were percentage of mated females having offspring, littering interval, time to 50% littered, total number of pups, pups per litter, average birth weight, postnatal survival on days 1, 2, 7, 14, 21, and 84, and sex ratio and average body weight on postnatal day 84. No macroscopic malformations or significant group differences in the other indices were found, indicating that 1.9 ppm was a NOAEL for male reproductive toxicity in rats.

Rats and guinea pigs that were exposed to 6,310 ppm (43,350 mg/m^3) 1,1,2,2-tetrachloroethane for 30 minutes had no exposure-related organ weight or gross or histological changes in the testes, epididymides, ovaries, or uterus when examined 14 days post-exposure (NIOSH 1978). There were no histopathological changes in the testes of one monkey that was exposed to a TWA concentration of 1,974 ppm for 2 hours/day, 6 days/week for 9 months (Horiuchi et al. 1962). Lack of histopathology, however, does not necessarily indicate that these male and female animals could produce appropriate numbers of healthy offspring. Since no mating studies with rats, guinea pigs, or monkeys exposed to high levels of 1,1,2,2-tetrachloroethane vapors have been conducted, no reproductive effect levels are indicated in Table 3-1 or Figure 3-1.

3.2.1.6 Developmental Effects

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

The potential for 1,1,2,2-tetrachloroethane-induced developmental effects in animals was assessed in a study that included inhalation exposure of male rats to 1.9 ppm 1,1,2,2-tetrachloroethane 4 hours/day, for an unspecified number of times during a 9-month period (Schmidt et al. 1972). One week before the end of the exposure period, exposed males and control males were mated with unexposed females and the F_1 generation was observed for 12 weeks. There was no effect on the number of offspring per litter, neonatal body weight, viability of the offspring, sex ratios, and body weight on day 84. No gross malformations were observed in the offspring.

3.2.1.7 Cancer

Mortality experience was evaluated in 1,099 white male World War II army workers who were exposed to 1,1,2,2-tetrachloroethane in 10 plants during its use as a solvent for impregnating clothing with N-dichloro-hexachloro-diphenyl-urea as a protectant against mustard gas (Norman et al. 1981). Exposure could have included the dermal route and was not measured, estimated, or documented on a man-for-man basis, but wasbased on job category (processing, laundry, or dry cleaning duties). Information from seven of the companies indicated that exposure to the solvent ranged from 5 weeks to 1 year (average approximately 5 months), and the workers were followed for 31 years. When compared with cause-, age-, race-, and calendar year-specific U.S. mortality rates, the SMR for all malignancies was 0.96

(confidence intervals not reported). When the exposed group was compared with 1,319 workers in 29 other plants that used a water suspension instead of 1,1,2,2-tetrachloroethane in the impregnating process, there were slight increases for mortality from leukemia and aleukemia (relative risk [RR]=2.72, 90% confidence interval [CI] 0.96–7.70) and cancer of the genital organs (RR=1.58, 90% CI 0.58–4.83). This comparison showed no increases for the following cancer sites: all malignancies, buccal cavity and pharynx, digestive organs and peritoneum, respiratory system, urinary organs, and other lymphatic. Since the numbers of deaths were small (four from leukemia and aleukemia and three from gential organ cancers in the solvent-exposed group), the increases in risk were small, no significant excesses were found, and other confounding factors may have been present (i.e., exposure to other chemicals and a lack of occupational histories following exposure), the authors concluded that the results are difficult to interpret and the observed increases in cancer mortality may not have been due to 1,1,2,2-tetrachloroethane exposure. This information is inconclusive as to whether 1,1,2,2-tetrachloroethane causes cancer in humans.

No other studies were located regarding carcinogenicity in animals following inhalation exposure to 1,1,2,2-tetrachloroethane.

3.2.2 Oral Exposure

3.2.2.1 Death

A number of human suicides from drinking 1,1,2,2-tetrachloroethane have been reported. In reports of intentional ingestion of lethal amounts of 1,1,2,2-tetrachloroethane (Elliott 1933; Forbes 1943; Hepple 1927; Lilliman 1949; Mant 1953; Sherman 1953), subjects usually lost consciousness within approximately 1 hour and died 3–20 hours postingestion, depending on the amount of food in the stomach. Postmortem examinations showed gross congestion in the esophagus, stomach, kidneys, spleen, and trachea, gross congestion and edema in the lungs, and histological effects of congestion and cloudy swelling in the lungs, liver, and/or kidneys (Hepple 1927; Mant 1953). Amounts of 1,1,2,2-tetrachloroethane recovered from the stomach and intestines of these deceased subjects included 12 mL (Hepple 1927), 25 g (Lilliman 1949), 48.5 mL (Mant 1953), and 425 mL (Mant 1953). Assuming a density of 1.594 g/mL and an average body weight of 70 kg, the approximate minimum doses ingested in these cases are estimated to be approximately 273, 357, 1,100, and 9,700 mg/kg, respectively, although the actual doses are likely higher because the estimates are based on amounts of chemical recovered from the gastrointestinal tract. No deaths occurred in eight patients (six males and two females) who were

accidentally given 3 mL (68 mg/kg, using the above assumptions), or three patients (one young man, one young woman, one 12-year-old girl) accidentally administered 2 or 3 mL (98–118 mg/kg, using the assumed density and reported body weights), as medicinal treatment for hookworm (Sherman 1953; Ward 1955).

Mortality following oral exposure to 1,1,2,2-tetrachloroethane has been assessed in rats and mice. Single dose gavage LD_{50} values in rats range from 250 to 800 mg/kg (Gohlke et al. 1977; NTP 2004; Schmidt et al. 1980a; Smyth et al. 1969). Gavage exposure to 540 mg/kg/day for 3–5 days (NTP 1993a, 1993b), 300 mg/kg/day for 3 days (Hanley et al. 1988), or 208 mg/kg/day for 13–21 days (NTP 1996) also caused mortality in rats. In mice, a gavage dose of 1,350 mg/kg/day for 3 days was lethal (NTP 1993d). Dietary exposure caused moribundity or death in rats at 558 mg/kg/day for 11 days (NTP 2004), pregnant mice at 2,120 mg/kg/day for 14 days (NTP 1991b), and mice at 2,394 mg/kg/day for 6 days (NTP 1993c, 2004). NCI (1978) performed 6-week range-finding gavage studies that appear to have used mortality and body weight as the only end points to assess toxicity. The 316 mg/kg treatment level resulted in reported mortality in rats, but not mice. There was no treatment-related mortality in rats or mice administered 1,1,2,2-tetrachloroethane in the diet for 14 weeks at concentrations resulting in reported daily doses as high as 320 and 1,400 mg/kg/day, respectively (NTP 2004).

Significantly decreased survival was observed in male and female mice administered 1,1,2,2-tetrachloroethane via oral gavage for 78 weeks at a reported TWA dose of 284 mg/kg/day (NCI 1978). Male and female rats were also administered 1,1,2,2-tetrachloroethane at TWA doses of 62 and 108 mg/kg/day (males) and 43 and 76 mg/kg/day (females) for 78 weeks (NCI 1978). Reduced survival was reported in the high-dose female rats, but survival in the female rats may have been influenced by high incidences of chronic murine pneumonia in controls and treatment groups alike; there was no apparent effect on survival in the male rats.

All reliable LOAEL values from each reliable study for death in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located regarding musculoskeletal effects in humans or animals following oral exposure to 1,1,2,2-tetrachloroethane. The highest NOAEL and all LOAEL values from each reliable study for

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Human	once (IN)				273 M (one death)	Hepple 1927	
2	Human	once (IN)				357 (one death)	Lilliman 1949	Dose based on amount recovered from stomach.
3	Human	once (IN)				1100 M (one death)	Mant 1953	Dose based on amount recovered from stomach.
4	Human	once (IN)				9600 M (one death)	Mant 1953	Dose based on amount recovered from stomach.
5	Rat (NS)	once (GO)				250 M (LD50)	Gohlke et al. 1977	
6	Rat (Osborne-Mendel)	3 d 1 x/d (GO)				300 M (1/5 died)	Hanley et al. 1988	
7	Rat (Fischer- 344)	3 d 1 x/d (GO)				540 M (5/5 males died)	NTP 1993a	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
8	Rat (Fischer- 344)	3-5 d 1 x/d (GO)				540 (5/5 males and 5/5 females died)	NTP 1993b	
9	Rat (Fischer- 344)	13-14 d 7 d/wk 1 x/d (GO)				208 M (5/5 moribund or dead)	NTP 1996	
10	Rat (Fischer- 344)	11 d ad lib (F)				558 F (moribund)	NTP 2004	Doses not reported; estimated using reported food intake and body weight data.
11	Rat (NS)	once (G)				800 (LD50)	NTP 2004	
12	Rat (Wistar-C)	once (GO)				330 M (LD50)	Schmidt et al. 1980a	
13	Rat (Carnworth-Wistar)	once (G)				319 M (LD50)	Smyth et al. 1969	
14	Mouse (CD-1)	11 d Gd 6-16 ad lib (F)				2120 F (2/10 maternal deaths)	NTP 1991b	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
15	Mouse (B6C3F1)	3 d 1 x/d (GO)				1350 (5/5 males and 5/5 females moribund or dead)	NTP 1993d	
16	Mouse (B6C3F1)	6 d ad lib (F)				2394 M (2/5 died)	NTP 2004	Doses not reported; estimated using reference food intake and body weight data for B6C3F1 mice.
Systemic								
17	Rat (Sprague-Dawley)	once (GO)	Hepatic	287 M	574 M (increased serum AST and ALT)		Cottalasso et al. 1998	
18	Rat (Osborne-Mendel)	3 d 1 x/d (GO)	Hepatic	300 M			Hanley et al. 1988	
			Bd Wt	150 M	300 M (16% reduced body weight)			
19	Rat (Sprague-Dawley)	11d Gd 6-16 ad lib (F)	Bd Wt	34 F			NTP 1991a	
20	Rat (Fischer- 344)	12 of 14 d 1 x/d (GO)	Bd Wt	135 M		270 M (55% reduced body weight gain)	NTP 1993a	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
21	Rat (Fischer- 344)	12 of 14 d 1 x/d (GO)	Bd Wt	135	270 (17-22% decreased final body weight)		NTP 1993b	
22	Mouse (B6C3F1)	4 d 1 x/d (GO)	Hepatic	300 M			Hanley et al. 1988	
			Bd Wt	300 M				
23	Mouse (CD-1)	11 d Gd 6-16 ad lib (F)	Bd Wt		987 F (14% decreased maternal body weight gain during treatment)		NTP 1991b	
24	Mouse (B6C3F1)	6 d ad lib (F)	Hepatic		2394 (hepatocellular degeneration)		NTP 2004	
Neurological								
25	Human	once (IN)				68 (unconsciousness and other signs of narcosis)	Sherman 1953	
26	Human	once (IN)				98 (unconsciousness and other signs of narcosis)	Ward 1955	
27	Rat (Osborne-Mendel)	3-4 d 1 x/d (GO)				300 M (CNS depression and debilitation)	Hanley et al. 1988	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
28	Rat (Fischer- 344)	12 of 14 d 1 x/d (GO)		135 M		270 M (lethargy)	NTP 1993a	
29	Rat (Fischer- 344)	1 d (GO)		135		270 (lethargy)	NTP 1993b	
30	Rat (Fischer- 344)	11 d ad lib (F)				591 M (lethargy) 558 F[b] (lethargy)	NTP 2004	
31	Rat (Wistar)	once (G)		25 F	50 F (increased electric shock perception threshold)	100 F (ataxia)	Wolff 1978	
32	Mouse (B6C3F1)	4 d 1 x/d (GO)		300 M			Hanley et al. 1988	
33	Mouse (B6C3F1)	4 d ad lib (F)				4788 M (lethargy)	NTP 2004	
Developmental								
34	Rat (Sprague-Dawley)	11d GD 6-16 ad lib (F)		34			NTP 1991a	Maternal toxicity at higher doses precluded assessment of developmental toxicity.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
35	Mouse (CD-1)	11 d Gd 6-16 ad lib (F)		987 F			NTP 1991b	
INTERMEDIATE EXPOSURE								
Death								
36	Rat (Osborne-Mendel)	6 wk 5 d/wk (GO)				316 F (5/5 died)	NCI 1978	
Systemic								
37	Rat (Osborne-Mendel)	6 wk 5 d/wk (GO)	Bd Wt	100 M 56[b] F		178 M (38% reduced body weight gain) 100[b] F (24% reduced body weight gain)	NCI 1978	Food consumption data not reported.
38	Rat (Fischer- 344)	21 d 7 d/wk 1 x/d (GO)	Hepatic		104 M (increased liver weight, cytoplasmic vacuolation)		NTP 1996	
			Renal	104 M				
			Bd Wt	104 M				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
39	Rat (Fischer- 344)	14 wk ad lib (F)	Resp	320					NTP 2004	Reduced body weight was likely the result of decreased food intake.
			Cardio	320						
			Gastro	320						
			Hemato	320						
			Musc/skel	320						
			Hepatic	80[c]	170	(minimal hepatocyte necrosis)				
			Renal	320						
			Endocr	320						
			Bd Wt	80			170	(29% reduced final body weight)		
40	Rat (Fischer- 344)	15 d ad lib (F)	Dermal	400 F	500 F	(alopecia and acanthosis)			NTP 2004	Reduced body weight was likely the result of decreased food intake.
			Bd Wt				300	(25-29% reduced final body weight)		
41	Mouse (B6C3F1)	6 wk 5 d/wk (GO)	Bd Wt	316					NCI 1978	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
42	Mouse (B6C3F1)	12 of 16 d 1 x/d (GO)	Hepatic		337.5 F (hepatocellular degeneration)		NTP 1993d	
			Bd Wt	675				
43	Mouse (B6C3F1)	14 wk ad lib (F)	Cardio	1360			NTP 2004	
			Gastro	1360				
			Musc/skel	1360				
			Hepatic	200 F	300 F (minimal hepatocyte necrosis)			
			Renal	1360				
			Endocr	1360				
			Bd Wt	200 M	370 M (12% reduced body weight gain)	1360 M (33% reduced body weight gain)		
44	Mouse (B6C3F1)	15 d ad lib (F)	Hepatic		599 (hepatocellular degeneration)		NTP 2004	
			Bd Wt		599 (10-14% reduced final body weight)			

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
45	Rat (Fischer- 344)	15 d ad lib (F)		300	400 (reduced relative thymus weights)		NTP 2004	
46	Rat (Fischer- 344)	14 wk ad lib (F)		170 F	320 F (reduced relative thymus weight)		NTP 2004	
47	Mouse (B6C3F1)	15 d ad lib (F)			599 F (reduced relative thymus weights)		NTP 2004	
Neurological								
48	Rat (Fischer- 344)	21 d 7 d/wk 1 x/d (GO)		104 M		208 M (lethargy)	NTP 1996	
49	Rat (Fischer- 344)	14 wk ad lib (F)		80			NTP 2004	Functional observational battery. 80 mg/kg/day is highest tested dose.
50	Mouse (B6C3F1)	12 of 16 d 1 x/d (GO)		337.5		675 (lethargy)	NTP 1993d	
51	Mouse (B6C3F1)	14 wk ad lib (F)		1360			NTP 2004	Functional observational battery. 700 mg/kg/day is highest tested dose.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
52	Mouse (B6C3F1)	15 d ad lib (F)			599 (hyperactivity)		NTP 2004	
Reproductive								
53	Rat (Fischer- 344)	14 wk ad lib (F)		170 M 80[b] F		320 M (atrophy of prostate gland, seminal vesicle and testicular germinal epithelium) 170[b] F (uterine atrophy and changes in lengths of estrus cycle stages)	NTP 2004	Atrophy of reproductive organs and tissues occurred at doses also resulting in serious body weight effects.
54	Mouse (B6C3F1)	14 wk ad lib (F)		1360			NTP 2004	
CHRONIC EXPOSURE								
Death								
55	Mouse (B6C3F1)	78 wk 5 d/wk (GO)				284 (reduced survival in both sexes; 55% in females)	NCI 1978	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
56	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)	Cardio	108 M			NCI 1978	
			Gastro	108 M				
			Hepatic	62 M	108 M (fatty metamorphosis)			
			Renal	108 M				
			Endocr	108 M				
			Dermal	108 M				
			Bd Wt	62 M 43[b] F	108 M (18% depressed body weight) 76[b] F (14% depressed body weight)			

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
57	Mouse (B6C3F1)	78 wk 5 d/wk (GO)	Resp	284			NCI 1978	
			Cardio	284				
			Gastro	284				
			Hepatic	284				
			Renal	142		284 M (acute toxic tubular nephrosis)		
			Endocr	284				
			Dermal	284				
			Bd Wt	284				
Reproductive								
58	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)		108 M 76[b] F			NCI 1978	
59	Mouse (B6C3F1)	78 wk 5 d/wk (GO)		284			NCI 1978	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
Cancer									
60	Mouse (B6C3F1)	78 wk 5 d/wk (GO)				142	(CEL: hepatocellular carcinoma)	NCI 1978	

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

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Benchmark dose (BMD) analysis of the minimal hepatocyte necrosis data was used to calculate a benchmark dose limit (BMDL10) of 53.88 mg/kg/day. An intermediate-duration oral minimal risk level (MRL) of 0.5 mg/kg/day was derived by dividing the BMDL by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; CNS = central nervous system; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; gd = gestational day; (GO) = gavage in oil; Hemato = hematological; hr = hour(s); Immuno = immunological; (IN) = ingestion; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; Resp = respiratory; SDH = sorbitol dehydrogenase; x = time(s); wk = week(s)

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

Acute (≤14 days)

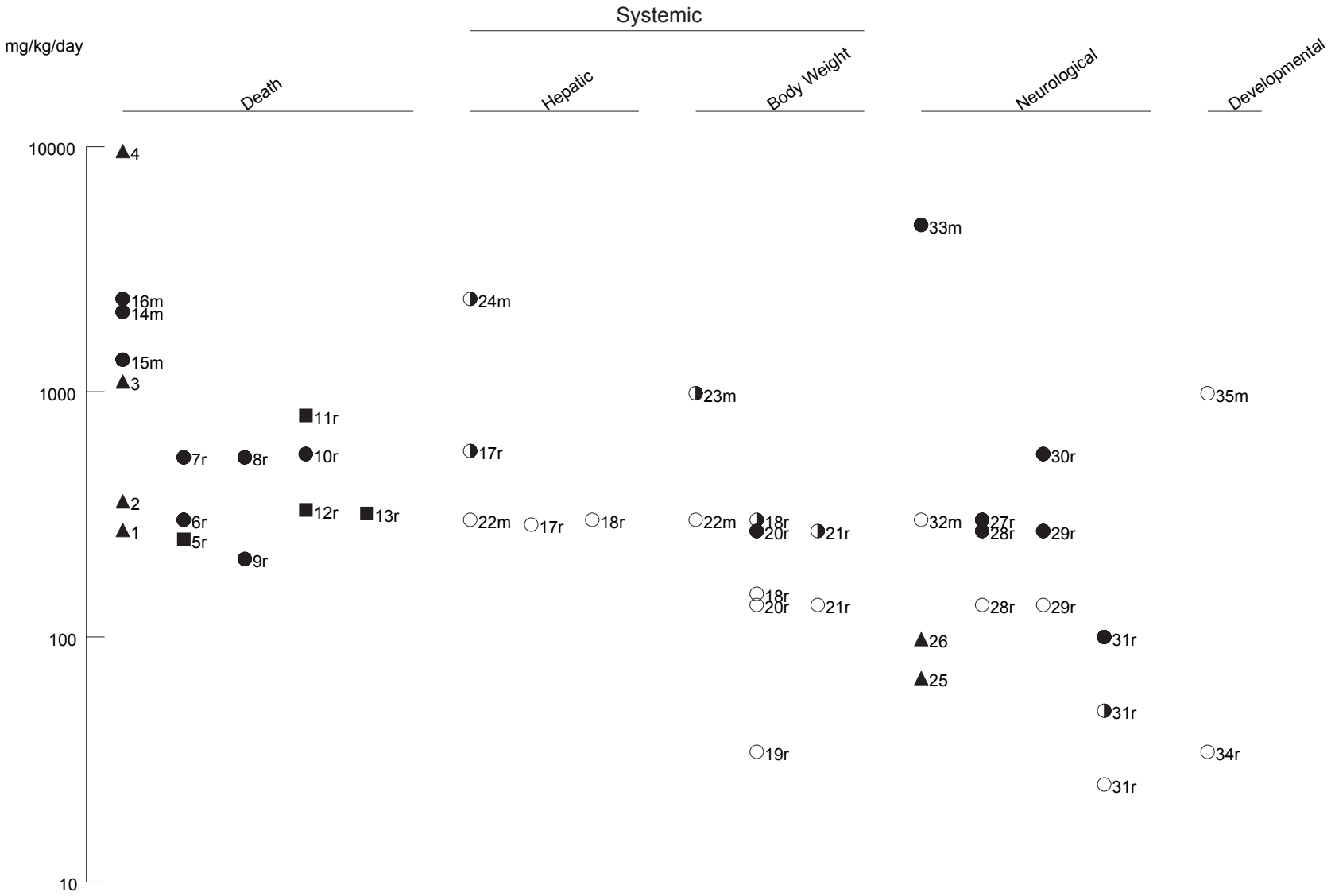


Figure 3-2 Levels of Significant Exposure to 1,1,2,2-tetrachloroethane - Oral *(Continued)*

Intermediate (15-364 days)

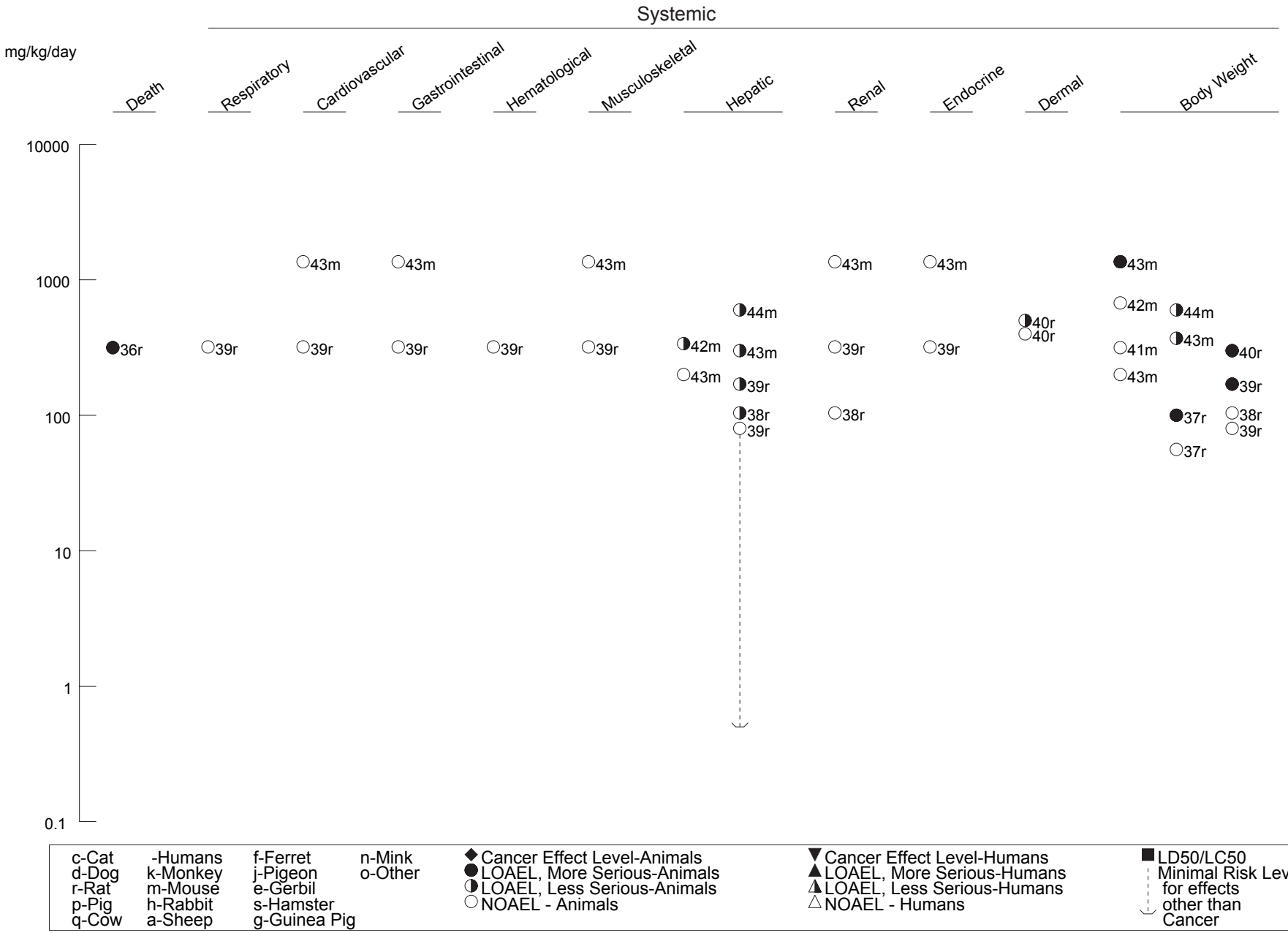


Figure 3-2 Levels of Significant Exposure to 1,1,2,2-tetrachloroethane - Oral *(Continued)*

Intermediate (15-364 days)

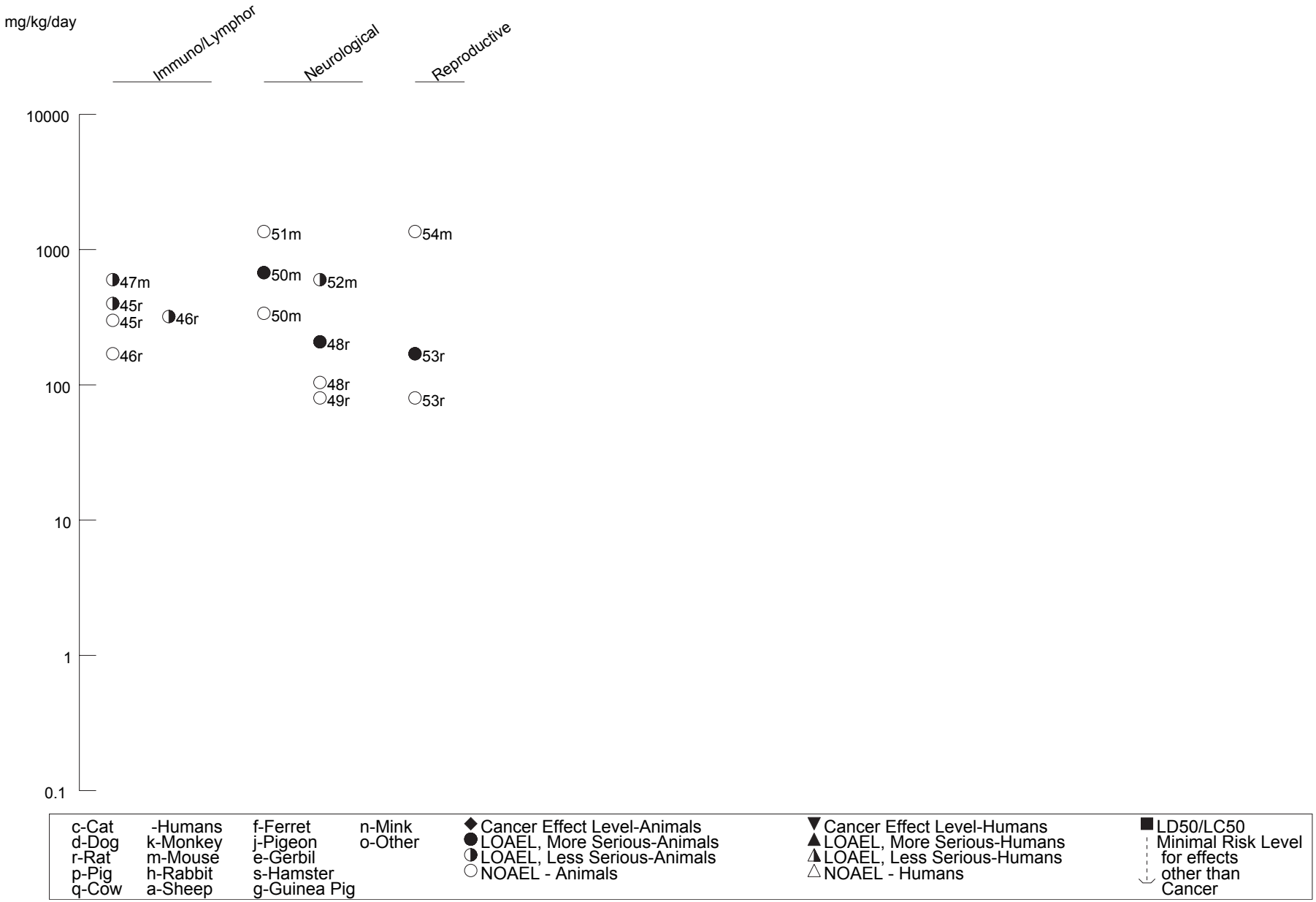
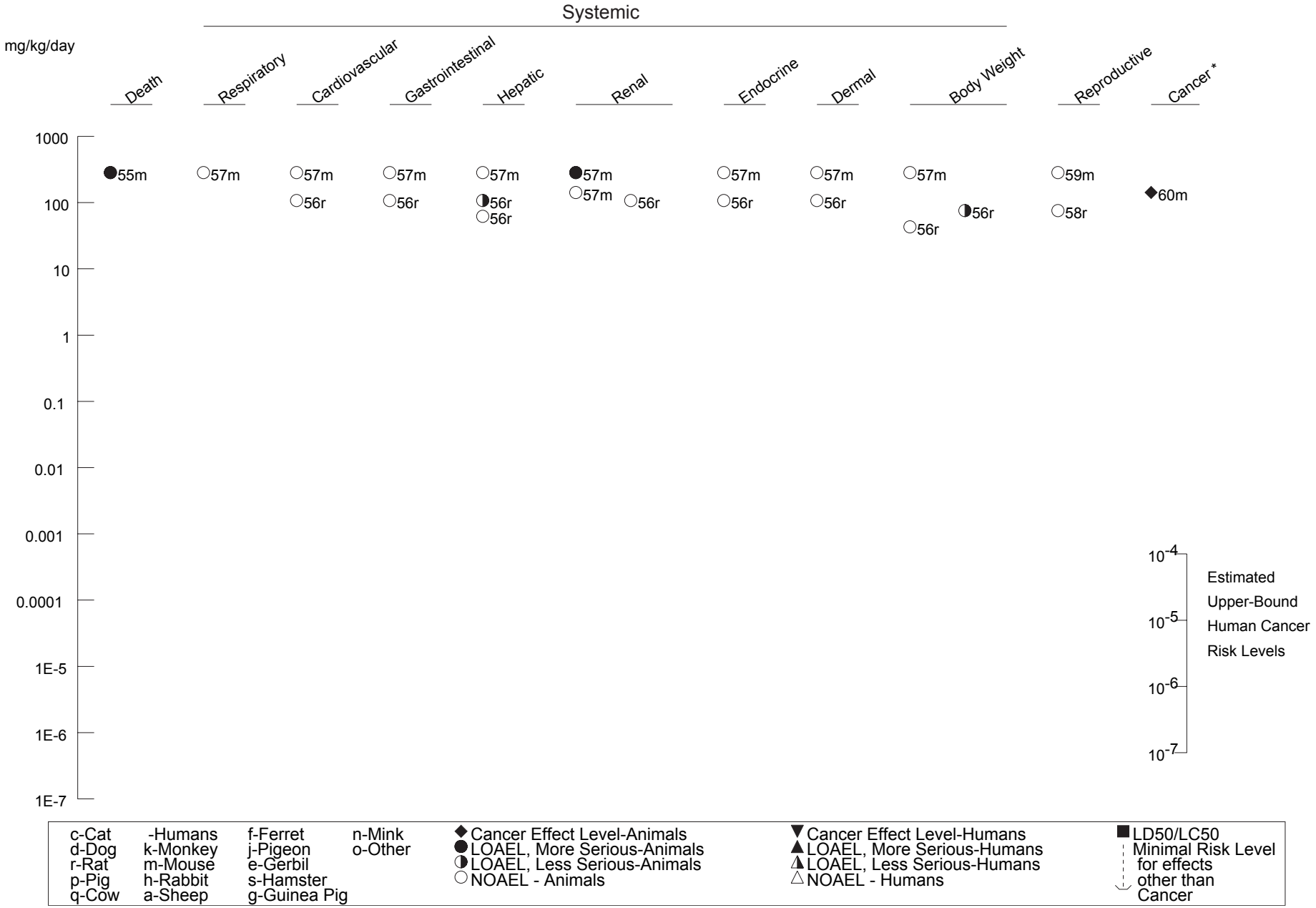


Figure 3-2 Levels of Significant Exposure to 1,1,2,2-tetrachloroethane - Oral *(Continued)*

Chronic (≥365 days)



systemic end points in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. Autopsy reports in humans following suicidal ingestion of at least 1,100 mg/kg of 1,1,2,2-tetrachloroethane revealed congestion and edema in the lungs (Hepple 1927; Mant 1953), but this did not appear to be the primary cause of death. A case of exposure at 9,600 mg/kg was reported to have caused lung collapse (Mant 1953). African men and women accidentally given oral doses of undiluted 1,1,2,2-tetrachloroethane (approximately 70–117 mg/kg) experienced shallow breathing during ensuing unconsciousness (Sherman 1953; Ward 1955).

Labored respiration, wheezing, and/or nasal discharge were observed in rats administered 1,1,2,2-tetrachloroethane in the diet for 78 weeks at reported TWA doses ranging from 43 to 108 mg/kg/day (NCI 1978). However, these effects may be at least partially attributable to the development of chronic murine pneumonia in controls and treatment groups alike. Mice treated for the same duration at concentrations resulting in daily 1,1,2,2-tetrachloroethane doses as high as 284 mg/kg/day experienced no respiratory effects (NCI 1978).

Cardiovascular Effects. African men and women accidentally given oral doses (approximately 70–117 mg/kg undiluted) experienced pronounced lowering of blood pressure (to 60/46) and faint pulse during ensuing unconsciousness (Sherman 1953; Ward 1955). A lethal oral dose (suicide) of 1,100 mg/kg produced epicardial and endocardial anoxic hemorrhage (Mant 1953).

Rats receiving up to 108 mg/kg/day and mice receiving 284 mg/kg/day orally for 78 weeks showed no gross or histological alterations of the heart (NCI 1978).

Gastrointestinal Effects. Single doses of 357 mg/kg or more caused mucosal congestion of the esophagus and upper stomach of humans (Lilliman 1949; Mant 1953). Rats receiving up to 108 mg/kg/day and mice receiving 284 mg/kg/day oral doses for 78 weeks showed no gross or microscopic histological alterations of the stomach, colon, pancreas, or bile duct (NCI 1978).

Hematological Effects. No information was located regarding 1,1,2,2-tetrachloroethane-induced hematological effects following oral exposure in humans. 1,1,2,2-Tetrachloroethane did not appear to cause hematological effects in male or female rats administered the chemical in the diet for 14 weeks at TWA doses as high as 320 mg/kg/day (NTP 2004).

Hepatic Effects. Autopsy reports showed no evidence of damage to the livers of humans who ingested suicidal doses of 1,1,2,2-tetrachloroethane (Mant 1953). The lack of effect in the liver can be ascribed to the rapid lethality. In another autopsy report, slight congestion of the liver was reported from an accidental poisoning or suicide attempt with 1,1,2,2-tetrachloroethane (Lilliman 1949).

Rats administered a single gavage dose of 1,1,2,2-tetrachloroethane had toxicologically significant increases (>2-fold greater than controls) in serum AST at ≥574 mg/kg and serum ALT at 1,148 mg/kg (Cottalasso et al. 1998), but this study is limited by a lack of liver histology examinations; the NOAEL was 287 mg/kg. Hepatocellular degeneration occurred in mice exposed to a lethal dietary dose of 2,394 mg/kg/day for 6 days (NTP 2004). Rats and mice that were exposed by gavage for 4 days had increased liver cell DNA synthesis (as shown by increased incorporation of [^{3}H]-thymidine) and increased mitotic activity at 75–300 mg/kg/day, but the only hepatic histological changes were centrilobular swelling and decreased periportal hepatocyte size in the mice at ≥75 mg/kg/day (Hanley et al. 1988). Because increased DNA synthesis and mitosis are not necessarily indicative of hepatotoxicity and the histological examinations showed no accompanying degenerative or other adverse liver lesions, this study identified a NOAEL of 300 mg/kg/day for hepatic effects. Rats that were exposed to a single 100 mg/kg gavage dose had no clearly adverse changes in serum ALT or other clinical chemistry indices, but the study was limited by inadequately reported liver histology data (Schmidt et al. 1980a). This study includes a general statement implying that the 100 mg/kg dose induced liver lesions, including necrosis and fatty degeneration, but the significance of the statement cannot be assessed because incidences and other specific histology data were not reported. These findings are not necessarily inconsistent with the lack of degenerative liver lesions in the rats exposed to gavage doses of 75–300 mg/kg/day for 4 days (Hanley et al. 1988), because 1,1,2,2-tetrachlorethane could have acted as a suicide substrate (see Section 3.4.3) in the single dose study (i.e., inactivated the metabolic enzymes needed to activate subsequent doses).

Hepatocellular degeneration was noted in mice exposed to 1,1,2,2-tetrachloroethane at levels of 599 mg/kg/day in the diet for 15 days (NTP 2004) or 337.5 mg/kg/day by gavage for 16 days (NTP 1993d). Exposure to 104 mg/kg/day by gavage for 21 days caused mild to moderate hepatocellular cytoplasmic vacuolation in rats (NTP 1996), but no degenerative or other liver lesions. Hepatic effects in rats receiving 1,1,2,2-tetrachloroethane in the diet for 14 weeks included increases in hepatic cytoplasmic vacuolization at 20 mg/kg/day (lowest tested dose), liver weight at 40 mg/kg/day, and hepatocellular hypertrophy at 80 mg/kg/day (NTP 2004). These hepatic effects are not considered adverse because the

severity of the vacuolation was minimal to mild and did not increase with dose, and the increases in liver weight and hepatocellular hypertrophy are considered adaptive responses to chemical exposure. Increases in serum ALT and SDH and decreases in serum cholesterol also occurred at ≥80 mg/kg/day, but the magnitudes of these changes were biologically significant only at 170 and 320 mg/kg/day. Other effects that occurred at 170 and 320 mg/kg/day included increases in serum ALP and bile acids, hepatocyte necrosis, bile duct hyperplasia, hepatocellular mitotic alterations, foci of cellular alterations, and liver pigmentation. This 14-week rat study (NTP 2004) identified a NOAEL of 80 mg/kg/day and a LOAEL of 170 mg/kg/day based on adverse liver-related serum chemistry changes and histological manifestations of hepatocellular damage and was used as the basis for deriving an intermediate-duration oral MRL for 1,1,2,2-tetrachloroethane. NTP (2004) similarly exposed mice to 1,1,2,2-tetrachloroethane in the diet for 14 weeks. Effects in the mice included minimal hepatocellular hypertrophy, increases in serum SDH, ALT, and bile acids, and decreased serum cholesterol at 160–200 mg/kg/day, but the magnitudes of these changes were biologically significant only at 300–370 mg/kg/day. Other effects that occurred in the mice at 300–370 mg/kg/day included increases in serum ALP and 5'-nucleotidase, necrosis, pigmentation, and bile duct hyperplasia. Based on the adverse serum chemistry and histopathological changes at 300 mg/kg/day and higher doses, this study identified a NOAEL of 200 mg/kg/day and a LOAEL of 300 mg/kg/day for liver toxicity in mice.

In the only chronic oral study, gavage exposure to 108 mg/kg/day for 78 weeks caused fatty degeneration in the liver of rats (NCI 1978). Interpretation of the results is confounded by high incidences of endemic chronic murine pneumonia, but this is unlikely to have contributed to effects observed in the liver.

Renal Effects. Autopsy reports showed no evidence of damage to the kidney of humans who ingested suicidal doses of 1,1,2,2-tetrachloroethane (Mant 1953). The lack of effect can be ascribed to the rapid lethality. No other studies were located regarding renal effects in humans following oral exposure to 1,1,2,2-tetrachloroethane.

No treatment-related renal effects were seen in rats or mice administered 1,1,2,2-tetrachloroethane in the diet for 14 weeks at concentrations resulting in doses as high as 320 and 1,400 mg/kg/day, respectively (NTP 2004). In studies conducted by the NCI (1978), rats treated with up to 108 mg/kg/day for 78 weeks showed no gross or histopathological changes in the kidney. Mice treated for the same duration at 142 mg/kg/day also showed no changes, but at 284 mg/kg/day, toxic tubular nephrosis was determined to be the probable cause of death in male mice. However, this renal effect may have been secondary to hepatocellular carcinoma noted in most of these high-dose (284 mg/kg/day) male mice.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to 1,1,2,2-tetrachloroethane. No treatment-related histopathological effects were seen in major endocrine tissues, including pituitary, thyroid, parathyroid, and adrenals of rats or mice administered 1,1,2,2-tetrachloroethane in the diet for 14 weeks at concentrations resulting in doses as high as 320 and 1,400 mg/kg/day, respectively (NTP 2004) or in other rats or mice chronically administered the chemical (5 days/week for 78 weeks) via oral gavage at doses as high as 108 and 284 mg/kg/day, respectively (NCI 1978).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to 1,1,2,2-tetrachloroethane. No changes were noted in the gross appearance of skin or subcutaneous tissues in rats or mice exposed to 1,1,2,2-tetrachloroethane at doses up to 284 mg/kg/day for 78 weeks (NCI 1978).

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to 1,1,2,2-tetrachloroethane. Squinted or reddened eyes with a reddish-brown discharge were noted in male and female rats at all dose levels treated with 1,1,2,2-tetrachloroethane for 78 weeks (NCI 1978).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to 1,1,2,2-tetrachloroethane.

No treatment-related effects on body weight were seen in rats administered 1,1,2,2-tetrachloroethane in daily gavage doses up to 104 mg/kg for 21 days (NTP 1996). In a study that employed higher dose levels, oral gavage administration of 1,1,2,2-tetrachloroethane for 3–14 days in the range of 270–300 mg/kg/day resulted in body weights that were 17–55% lower than controls; no adverse body weight effects were seen at the lower doses ranging from 135 to 150 mg/kg/day (Hanley et al. 1988; NTP 1993a, 1993b). No adverse body weight effects were seen in mice administered 1,1,2,2-tetrachloroethane via oral gavage at doses as high as 300 mg/kg/day for 4 days (Hanley et al. 1988) or other mice receiving up to 1,350 mg/kg/day for 12 of 16 days (NTP 1993d). Daily doses of 178 mg/kg/day, 5 days/week for 6 weeks resulted in 38–41% depressed body weight gains in male and female rats, relative to controls; at 100 mg/kg/day, respective body weight gains were 9 and 24% less than controls (NCI 1978). In contrast, no effects on body weight gain were seen in mice similarly exposed at doses as high as 316 mg/kg/day.

Similar effect levels were reported following dietary exposure. A dietary concentration resulting in a daily dose of 300 mg/kg for 15 days resulted in a 25–29% depressed final body weights in rats (NTP 2004). In a 14-week dietary study in rats, concentrations of 1,1,2,2-tetrachloroethane resulting in a dose level of 170 mg/kg/day caused a 29% depression in final body weight; at a dose level of 320 mg/kg/day, actual body weight loss was noted (NTP 2004). In mice, dosing at 599 mg/kg/day for 15 days resulted in a 10–14% depressed final body weight (NTP 2004). A 12% depression in final body weight was noted in mice receiving 370 mg/kg/day for 14 weeks; the 200 mg/kg/day level did not elicit treatment-related body weight effects (NTP 2004). Approximately 14–18% depressed body weight was noted in male and female rats administered 1,1,2,2-tetrachloroethane via oral gavage at doses of 108 and 76 mg/kg/day, respectively; no body weight effects were seen at the lower dose (62 and 43 mg/kg/day in males and females, respectively) (NCI 1978). No treatment-related adverse body weight effects were elicited by similar treatment of male and female mice for 78 weeks at doses of 142 or 284 mg/kg/day (NCI 1978).

3.2.2.3 Immunological and Lymphoreticular Effects

One investigator reported that the results of an autopsy showed an enlarged and congested spleen in a case of intentional or accidental ingestion of 1,1,2,2-tetrachloroethane (Hepple 1927), while another autopsy study reported that the gross appearance of the spleen was normal (Elliott 1933).

Limited information is available regarding the potential for 1,1,2,2-tetrachloroethane-induced immunological or lymphoreticular effects following oral exposure. In a 14-week dietary study of rats, pigmentation of the spleen was increased in males receiving 1,1,2,2-tetrachloroethane at doses of ≥80 mg/kg/day and in females receiving doses of ≥170 mg/kg/day; high incidences (70–100%) of atrophy in the spleen (red pulp and lymphoid follicle) of both sexes were noted at 320 mg/kg/day (NTP 2004). Relative thymus weights were reduced in rats that were exposed to 400 mg/kg/day for 15 days or 320 mg/kg/day for 14 weeks, and in mice exposed to 599 mg/kg/day for 15 days (NTP 2004). No gross or histological alterations were seen in the spleen or lymph nodes of rats and mice exposed to 1,1,2,2-tetrachloroethane for 78 weeks at doses up to 108 and 284 mg/kg/day, respectively (NCI 1978).

3.2.2.4 Neurological Effects

Information on the neurotoxicity of oral exposure to 1,1,2,2-tetrachloroethane in humans is available from several case reports. People who intentionally ingested lethal amounts usually lost consciousness within

approximately 1 hour and died 3–20 hours postingestion (Elliott 1933; Forbes 1943; Hepple 1927; Lilliman 1949; Mant 1953; Sherman 1953). Patients who were accidentally given an estimated oral dose of 68–118 mg/kg as medicinal treatment for hookworm experienced loss of consciousness and other clinical signs of narcosis that included shallow breathing, faint pulse, and pronounced lowering of blood pressure (Sherman 1953; Ward 1955). In animals, lethargy and central nervous system depression occurred in rats gavaged with 270–300 mg/kg/day for 1–12 days (Hanley et al. 1988; NTP 1993a, 1993b) or 208 mg/kg/day for 21 days (NTP 1996). Information on neurological effects of lower acute oral doses is limited to a rat study in which a single gavage dose of 100 mg/kg caused ataxia and 50 mg/kg caused decreased passive avoidance to an electric shock, possibly due to an increased threshold of shock perception due to a subtle anesthetic effect (Wolff 1978). Evaluation of this study is complicated by incomplete reporting and insufficient quantitative data, but the possible anesthetic effect suggests that 50 mg/kg is a LOAEL for neurotoxicity in rats. The LOAEL values for each reliable study for neurological effects after acute-duration exposure are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to 1,1,2,2-tetrachloroethane. No gross or histological alterations in the reproductive organs of male or female rats or mice administered 1,1,2,2-tetrachloroethane by oral gavage 5 days/week for 78 weeks at doses as high as 108 and 76 mg/kg/day in male and female rats, respectively, and 284 mg/kg/day in mice (NCI 1978). Atrophy of prostate gland, seminal vesicle, and testicular germinal epithelium was noted in male rats administered 1,1,2,2-tetrachloroethane in the diet for 14 weeks at a concentration resulting in a dose level of 320 mg/kg/day; similar treatment of female rats at a dose level of 170 mg/kg/day resulted in uterine atrophy and changes in lengths of estrus cycle stages (NTP 2004).

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

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to 1,1,2,2-tetrachloroethane. In a developmental toxicity report submitted to NTP (1991a), no changes in numbers of live fetuses per litter, dead fetuses per litter, resorptions per litter, or implants per litter were

seen following dietary exposure of pregnant rats to 1,1,2,2-tetrachloroethane during gestation days 6–16 at maternal doses ranging from 34 to 330 mg/kg/day. One dam in the 98 mg/kg/day group and four of nine dams in the 330 mg/kg/day group completely resorbed their litters. At scheduled sacrifice, average fetal weights were statistically significantly decreased in all dose groups except the 34 mg/kg/day group (4.9, 4, 12.8, 10.6, and 20.7% decrease in the 34, 98, 180, 278, and 330 mg/kg/day groups, respectively). However, in this study, 1,1,2,2-tetrachloroethane treatment resulted in dose-related significantly decreased maternal body weight (9.3, 11.6, 13.8, and 24% lower than controls in the 98, 180, 278, and 330 mg/kg/day groups, respectively) and dose-related decreased food consumption ranging in magnitude from 16 to 60% less than that of controls. Because complete resorptions occurred only at doses resulting in significantly reduced food consumption and serious maternal body weight effects, the results of this developmental toxicity study (NTP 1991a) are not included in Table 3-2 or Figure 3-2. In a similar study report of dietary exposure of pregnant mice (NTP 1991b), the lowest exposure level (0.5% in the food; dose of approximately 987 mg/kg/day) resulted in 14% decreased maternal body weight gain during the treatment period, but no indications of developmental effects with respect to number of implantation sites, number of resorptions, numbers of dead and live fetuses, or gravid uterine weight. Exposure at higher levels resulted in maternal death, precluding assessment of treatment-related developmental toxicity at the higher doses.

3.2.2.7 Cancer

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

A study in humans evaluated the possible carcinogenic effects of 1,1,2,2-tetrachloroethane in clothing-treatment workers (Norman et al. 1981). Inhalation exposure concentrations and durations were not reported, and coexposures to other chemicals and dermal exposures were likely. No increases in standard mortality ratios were found for total mortality, cardiovascular disease, cirrhosis of the liver, or cancer of the digestive and respiratory systems. The mortality ratio for lymphatic cancers was increased, although the number of deaths was small (4 cases observed compared to 0.85 expected).

Carcinogenicity of 1,1,2,2-tetrachloroethane in animals was evaluated in chronic oral studies in rats and mice (NCI 1978). The purity of the 1,1,2,2-tetrachloroethane was approximately 90% (contaminants not identified). Male and female rats were exposed to time-weighted average (TWA) doses of 0, 62, or 108 mg/kg/day (males) or 0, 43, or 76 mg/kg/day (females) by gavage 5 days/week for 78 weeks,

followed by a 32-week period during which the rats were not exposed. There was a high prevalence of endemic chronic murine pneumonia in both sexes that likely contributed to early mortality that occurred in 20% of the females. No significant increases in tumor incidences were observed in the rats. Male and female B6C3F1 mice were similarly exposed to TWA doses of 0, 142, or 284 mg/kg/day for 78 weeks, followed by a 12-week period during which the mice were not exposed. Survival was markedly decreased after 45 weeks of exposure in the high-dose male and female mice; the cause of death appeared to be acute toxic tubular nephrosis in the males but was not reported in the females. Significant, dose-related increases in the incidence of hepatocellular carcinoma were observed in the male mice (3/36, 13/50, and 44/49 in the control, low-dose, and high-dose groups, respectively) and female mice (1/40, 30/48, and 43/47, respectively).

The EPA has classified the carcinogenicity of 1,1,2,2-tetrachloroethane as Group C, possible human carcinogen (IRIS 2006). The EPA (IRIS 2006) calculated an oral slope factor of 0.2 $(mg/kg/day)^{-1}$ for 1,1,2,2-tetrachloroethane (verified June 26, 1986), based on the NCI (1978) study showing increased hepatocellular carcinomas in female mice. This q_1* corresponds to upper bound individual lifetime cancer risks ranging from $5x10^{-4}$ mg/kg/day (10^{-4} risk level) to $5x10^{-7}$ mg/kg/day (10^{-7} risk level). These risk levels are indicated on Figure 3-2.

3.2.3 Dermal Exposure

3.2.3.1 Death

One human death was reported when a man cleaned up a 1,1,2,2-tetrachloroethane spill with his bare hands (Coyer 1944). He was also exposed to unmeasured levels of 1,1,2,2-tetrachloroethane vapors.

The dermal LD_{50} (lethal dose, 50% kill) for 1,1,2,2-tetrachloroethane in rabbits is 6,360 mg/kg (Smyth et al. 1969).

3.2.3.2 Systemic Effects

Since humans dermally exposed to 1,1,2,2-tetrachloroethane invariably were reported to have considerable inhalation exposure as well, separation of effects due solely to dermal exposure could not be determined. Those exposed to 1,1,2,2-tetrachloroethane in the workplace showed cardiovascular, gastric, hematological, and hepatic disturbances as noted in the discussion on systemic effects due to inhalation

exposure discussed in Section 2.2.1.2 (Coyer 1944; Lobo-Mendonca 1963; Minot and Smith 1921). Total exposure levels and effects due to inhalation versus dermal exposure were not determined in these studies, but air concentrations were reported to vary from 9 to 98 ppm in one study (Lobo-Mendonca 1963).

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, and renal effects in animals after dermal exposure to 1,1,2,2-tetrachloroethane.

Dermal Effects. Direct application of 514 mg/cm^2 of 1,1,2,2-tetrachloroethane for 16 hours damaged the skin of guinea pigs, causing karyopyknosis and pseudoeosinophilic infiltration (Kronevi et al. 1981). Application of 1,1,2,2-tetrachloroethane (concentration not reported) to the shaved abdomen of rabbits caused hyperemia, edema, and severe blistering (Dow 1944). Smyth et al. (1969) similarly found that application of 1,1,2,2-tetrachloroethane to the uncovered abdomen of rabbits caused local skin irritation (severity of 6 on a scale of 1–10).

Ocular Effects. Humans exposed to 1,1,2,2-tetrachloroethane vapors (130 ppm) for 10 minutes experienced mucosal irritation around the eyes (Lehmann and Schmidt-Kehl 1936). Similarly, guinea pigs exposed to 576 ppm for 5 minutes demonstrated eye closure and squinting; by 15 minutes, lacrimation was common (NIOSH 1978). Rats showed these effects at 5,050 ppm. These ocular effects are due to direct contact of the eyes with the vapors rather than a true systemic effect due to inhalation of the vapor. No studies were located in which liquid 1,1,2,2-tetrachloroethane was instilled directly into the eye.

3.2.3.3 Immunological and Lymphoreticular Effects

Data on the immunological and lymphoreticular effects in humans and animals following dermal exposure are limited. One person who died following dermal exposure to 1,1,2,2-tetrachloroethane had an enlarged spleen with nodular areas on its surface (Coyer 1944). This individual cleaned up a spill with his bare hands, and the nature and extent of the exposure were poorly defined.

No dermal hypersensitivity tests in guinea pigs or other kinds of studies were located regarding immunological or lymphoreticular effects in animals after dermal exposure to 1,1,2,2-tetrachloroethane.

3.2.3.4 Neurological Effects

Workers in India's bangle industry who dipped their hands into 1,1,2,2-tetrachloroethane and inhaled it had tremors and vertigo in addition to gastric disturbances (Lobo-Mendonca 1963). Specific exposure levels were not measured, but air concentrations were measured at between 9 and 98 ppm. The incidence of tremors was higher among factory workers exposed to higher concentrations, suggesting a dose-response relationship. Workers in an artificial silk plant experienced fatigue, irritability, headache, and coma (Minot and Smith 1921). Exposure levels were not estimated.

No studies were located regarding neurological effects in animals following dermal application of 1,1,2,2-tetrachloroethane.

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

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

No studies were located regarding genotoxic effects in humans following inhalation, oral, or dermal exposure to 1,1,2,2-tetrachloroethane. *In vitro* and *in vivo* tests of genotoxicity of 1,1,2,2-tetrachloroethane have produced mixed results, as discussed below and summarized in Tables 3-3 and 3-4.

1,1,2,2-Tetrachloroethane has been shown to be predominantly inactive in reverse mutation assays in *Salmonella typhimurium* (strains TA97, TA98, TA100, TA1530, TA1535, TA1537, and TA1538), either with or without the addition of S9 metabolic activating mixture, even at concentrations that lead to cytotoxicity (Haworth et al. 1983; Milman et al. 1988; Mitoma et al. 1984; Nestmann et al. 1980; NTP 2004; Ono et al. 1996; Warner et al. 1988). However, a few studies reported reverse mutation activity in *S. typhimurium* (Brem et al. 1974; Rosenkranz 1977; Strobel and Grummt 1987). Results of studies employing methods to prevent volatilization were not notably different from those that did not use those methods. 1,1,2,2-Tetrachloroethane also did not induce forward mutations (L-arabinose resistance) in

Table 3-3. Genotoxicity of 1,1,2,2-Tetrachloroethane *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	References
Salmonella typhimurium	Reverse mutation	–	–	Haworth et al. 1983
		–[a]	–[a]	Milman et al. 1988
		–[a,b]	–[a,b]	Nestmann et al. 1980
		–[c]	–[c]	NTP 2004
		–	–	Ono et al. 1996
		–[a]	–[a]	Mitoma et al. 1984
		–[a]	–[a]	Warner et al. 1988
		Not tested	+[a,c]	Brem et al. 1974
		Not tested	+[a,c]	Rosenkranz 1977
		+[d]	+[d]	Strobel and Grummt 1987
	Forward mutation	–[b]	–[b]	Roldan-Arjona et al. 1991
Saccharomyces cerevisiae	Gene mutation	Not tested	+[b]	Callen et al. 1980
		Not tested	–	Nestmann and Lee 1983
Escherichia coli	DNA growth, repair, or synthesis	Not tested	+[a,d]	Brem et al. 1974
		Not tested	+[a,d]	Rosenkranz 1977
		+[d]	–[d]	DeMarini and Brooks, 1992
Aspergillus nidulans	Mitotic cross-over	Not tested	–[b]	Crebelli et al. 1988
	Aneuploidy	Not tested	+[b]	Crebelli et al. 1988
L5178Y mouse lymphoma cells	Gene mutation	–[b]	–[b]	NTP 2004
Chinese hamster ovary cells	Chromosomal aberrations	–[b]	–[b]	Galloway et al. 1987
		–[b]	–[b]	NTP 2004
Chinese hamster ovary cells	Sister chromatid exchange	+[b]	+[b]	Galloway et al. 1987
		+[b]	+[b]	NTP 2004
BALB/c 3T3 mouse cells	Sister chromatid exchange	+[b]	+[b]	Colacci et al. 1992
	Cell transformation	Not tested	–[a,b]	Arthur Little Inc. 1983
		Not tested	–[a,b]	Tu et al. 1985
		–[a]	–[a]	Milman et al. 1988
		+[b]	+[b]	Colacci et al. 1990
	Promotion of cell transformation	Not tested	–[b]	Colacci et al. 1996
Rat hepatocytes	DNA growth, repair, or synthesis	Not tested	–[a,b]	Milman et al. 1988
		Not tested	–[a,b]	Naylor Dana Institute 1983
Mouse hepatocytes	DNA growth, repair, or synthesis	Not tested	–[a,b]	Milman et al. 1988
		Not tested	–[a,b]	Naylor Dana Institute 1983
Human embryonic intestinal cells	DNA growth, repair, or synthesis	–	Not tested	NIOSH 1980

[a]Adjusted for volatility
[b]Tested up to cytotoxic concentrations
[c]Not adjusted for volatility
[d]Cytotoxic concentrations not included

– = negative result; + = positive result

Table 3-4. Genotoxicity of 1,1,2,2-Tetrachloroethane *In Vivo*

Species/test system	End point	Result	Reference
Drosophila melanogaster	Sex-linked recessive lethal mutation	–	NIOSH 1980; NTP 2004; Woodruff et al. 1985
	Mitotic recombination	–	Vogel and Nivard 1993
Mouse hepatocytes	Unscheduled DNA synthesis	+	Miyagawa et al. 1995
Mouse hepatocytes, male	Unscheduled DNA synthesis	–	Mirsalis et al. 1989
	S-Phase DNA synthesis	–	Mirsalis et al. 1989
Mouse hepatocytes, female	Unscheduled DNA synthesis	–	Mirsalis et al. 1989
	S-Phase DNA synthesis	+/–	Mirsalis et al. 1989
Rat bone marrow cells, male	Chromosomal aberrations	–	NIOSH 1980
Rat bone marrow cells, female	Chromosomal aberrations	+	NIOSH 1980
Mouse peripheral blood erythrocytes	Micronucleus formation	+	NTP 2004

+ = active; – = inactive; +/– = equivocal

S. typhimurium strain BA13 (Roldan-Arjona et al. 1991). Assays with *Escherichia coli* indicated that 1,1,2,2-tetrachloroethane induced DNA damage, as shown by growth inhibition in DNA polymerase deficient *E. coli* (Brem et al. 1974; Rosenkranz 1977) and induction of prophage lambda (DeMarini and Brooks 1992). In *Saccharomyces cerevisiae*, 1,1,2,2-tetrachloroethane induced gene conversion, reversion, and recombination in one study (Callen et al. 1980), whereas another study found no conversion or reversion (Nestmann and Lee 1983). In *Aspergillus nidulans*, 1,1,2,2-tetrachloroethane induced aneuploidy, but no crossing over (Crebelli et al. 1988).

1,1,2,2-Tetrachloroethane did not induce trifluorothymidine resistance in L5178Y mouse lymphoma cells, with or without S9, at concentrations up to those producing lethality (NTP 2004). Primary hepatocytes from rats and mice exposed *in vitro* to 1,1,2,2-tetrachloroethane did not show altered DNA repair at concentrations that were not cytotoxic (Milman et al. 1988; Naylor Dana Institute 1983). NIOSH (1980) reported no increase in unscheduled DNA synthesis (UDS) in human embryonic intestinal fibroblasts exposed to 1,1,2,2-tetrachloroethane. Treatment of Chinese hamster ovary (CHO) cells with up to 653 μg/mL (which was cytotoxic) did not result in increased induction of chromosomal aberrations, but did produce an increased frequency of sister chromatid exchanges (SCEs) at concentrations of 55.8 μg/mL or higher (Galloway et al. 1987; NTP 2004). SCEs were also induced in BALB/c-3T3 cells treated *in vitro* with high concentrations (500 μg/mL or higher) of 1,1,2,2-tetrachloroethane, either with or without S9 activating mixture (Colacci et al. 1992).

In BALB/c-3T3 cells, 1,1,2,2-tetrachloroethane exposure of up to 250 μg/mL in the absence of exogenous metabolic activation did not result in increased numbers of transformed cells (Arthur Little Inc. 1983; Colacci et al. 1992; Milman et al. 1988; Tu et al. 1985); survival was generally 70% or higher. Higher doses (500 μg/mL or more) were capable of transforming the cells, but also showed higher levels of cytotoxicity (Colacci et al. 1990). In the presence of exogenous metabolic activation, however, even relatively low levels (31.25 μg/mL) of 1,1,2,2-tetrachloroethane used as an initiating agent, followed by promotion with 12-O-tetradecanoylphorbol-13-acetate (TPA), resulted in increased numbers of transformed cells (Colacci et al. 1992). 1,1,2,2-Tetrachloroethane did not act as a promoter in BALB/c-3T3 cells *in vitro* without metabolic activation (Colacci et al. 1996).

1,1,2,2-Tetrachloroethane tested negative for sex-linked recessive lethal mutations and mitotic recombination in *Drosophila melanogaster* (NIOSH 1980; NTP 2004; Vogel and Nivard 1993; Woodruff et al. 1985). Replicative DNA synthesis was increased in hepatocytes isolated from male B6C3F1 mice exposed to a single gavage dose of 200 mg/kg (24 and 48 hours postexposure) or 400 mg/kg (24, 39, and

48 hours postexposure) relative to hepatocytes from unexposed mice (Miyagawa et al. 1995). Hepatocytes isolated from mice following a single gavage dose of up to 1,000 mg/kg did not show an increase in UDS or S-phase DNA synthesis (Mirsalis et al. 1989). Inhalation exposure to 5 or 50 ppm (34.3 or 343 mg/m^3) for 7 hours/day, 5 days/week did not result in increased frequency of chromosomal aberrations in bone marrow cells isolated from male rats (NIOSH 1980); female rats exposed to 50 ppm (343 mg/m^3), but not to 5 ppm (34.3 mg/m^3), showed an increase in bone marrow cell aberrations other than gaps (NIOSH 1980). Covalent binding of radiolabeled 1,1,2,2-tetrachloroethane to DNA, ribonucleic acid (RNA), and protein in the liver, kidney, lung, and stomach occurred in rats and mice exposed to a single intravenous dose and analyzed 22 hours postexposure (Colacci et al. 1987).

3.4 TOXICOKINETICS

In both humans and laboratory animals, 1,1,2,2-tetrachloroethane is well absorbed from the respiratory and gastrointestinal tracts, and is absorbed through the skin of animals after dermal exposure. When administered by oral or inhalation routes, 1,1,2,2-tetrachloroethane is extensively metabolized and excreted chiefly as metabolites in the urine and breath. In rats and mice, 1,1,2,2-tetrachloroethane is metabolized to trichloroethanol, trichloroacetic acid, and dichloroacetic acid, which is then broken down to glyoxylic acid, oxalic acid, and carbon dioxide; a small percentage of the dose is expired in the breath as the parent compound and as carbon dioxide. In reductive and oxidative metabolism, 1,1,2,2-tetrachloroethane is known to produce reactive radical and acid chloride intermediates, respectively.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

While studies of the systemic toxicity of 1,1,2,2-tetrachloroethane following inhalation in humans are indicative of some level of systemic absorption, comparatively few studies have quantitatively addressed this issue. A study in volunteers was carried out in which a bulb containing [38Cl]-labeled 1,1,2,2-tetrachloroethane was inserted into their mouths; they immediately inhaled deeply, held their breaths for 20 seconds, and then exhaled through a trap containing granulated charcoal. The study showed that 97% of a single breath of 1,1,2,2-tetrachloroethane was absorbed systemically (Morgan et al. 1970). The accuracy of this value is unclear because the procedure used to measure uptake is unorthodox and high retention of volatile organic compounds on the charcoal was not validated. Additionally, there were other potential sources of 1,1,2,2-tetrachloroethane loss and inexact measurements (e.g., volume of air exhaled

across the trap) that could affect the results. Two subjects were reported to retain approximately 40–60% of inspired 1,1,2,2-tetrachloroethane after a 30-minute exposure of up to 2,300 mg/m^3 (Lehmann and Schmidt-Kehl 1936), but additional details were not provided.

The total body burden of radioactivity in male Osborne-Mendel rats and B6C3F1 mice exposed to 10 ppm (68.7 mg/m^3) of ^{14}C-1,1,2,2-tetrachloroethane vapor for 6 hours (Hanley et al. 1988) was 38.7 µmol equivalents per kg in rats (9.50 µmol equivalents and using a body weight of 245 g from the study) and 127 µmol equivalents per kg in mice (3.059 µmol equivalents and using a body weight of 24.1 g from the study), indicating that the mice absorbed proportionally more 1,1,2,2-tetrachloroethane on a per-body-weight basis. Between 92 and 98% of the body burdens were recovered as metabolites, indicating that very high uptake of the 10 ppm exposure occurred in both species. Ikeda and Ohtsuji (1972) detected metabolites in the urine of rats exposed to 200 ppm (1,370 mg/m^3) of 1,1,2,2-tetrachloroethane, indicating that absorption had occurred, but did not provide a quantitative estimate of absorption rate or fraction. Similarly, Gargas and Andersen (1989) followed the elimination of 1,1,2,2-tetrachloroethane from the blood after a 6-hour exposure to 350 ppm (2,400 mg/m^3), but did not provide quantitative estimates of absorption.

3.4.1.2 Oral Exposure

Studies that quantify absorption following oral exposure in humans were not available. The profound effect of ingestion of large amounts of 1,1,2,2-tetrachloroethane indicates that appreciable amounts are absorbed.

Observations in animals also indicate that the oral absorption of 1,1,2,2-tetrachloroethane is rapid and extensive. Cottalasso et al. (1998) reported hepatic effects only 15–30 minutes following a single oral exposure in rats. Following a single oral exposure of male Osborne-Mendel rats and B6C3F1 mice to 150 mg/kg of radiolabeled 1,1,2,2-tetrachloroethane in corn oil, only 4–6% of the activity was recovered in the feces 72 hours postexposure, while >90% of the administered activity was found in both species as metabolites, indicating that the compound was nearly completely absorbed in both rats and mice within 72 hours (Hanley et al. 1988). Mitoma et al. (1985) exposed groups of male Osborne-Mendel rats to 25 or 100 mg/kg and B6C3F1 mice to 50 or 200 mg/kg of 1,1,2,2-tetrachloroethane, 5 days/week for 4 weeks followed by a single radiolabeled dose of the compound, and evaluated its disposition over the next 48 hours. While absorption was not quantified, 79% of the dose was metabolized in rats and 68% was metabolized in mice, suggesting that at least those levels of compound had been absorbed within

48 hours. In an abstract, Milman et al. (1984) noted that rats and mice that received 1,1,2,2-tetrachloroethane orally absorbed most of the dose; no further details were available on this study.

3.4.1.3 Dermal Exposure

No studies were located regarding absorption following dermal exposure in humans.

Up to 1 mL of 1,1,2,2-tetrachloroethane applied to the skin of mice or guinea pigs was absorbed within a half hour (dose site sealed to prevent evaporation) (Jakobson et al. 1982; Tsuruta 1975).

3.4.2 Distribution

No studies were located regarding distribution in humans following inhalation, oral, or dermal exposure to 1,1,2,2-tetrachloroethane.

Following absorption in animals, 1,1,2,2-tetrachloroethane appears to be distributed throughout the body, but may selectively accumulate to a degree in certain cells and tissues. The human blood-air partition coefficient for 1,1,2,2-tetrachloroethane has been reported to be in the range of 72.6–116 (Gargas et al. 1989; Meulenberg and Vijverberg 2000; Morgan et al. 1970). The large blood-air partition coefficient contributes to low exhaled breath concentrations of unmetabolized 1,1,2,2-tetrachloroethane (Section 3.4.4). Although 1,1,2,2-tetrachloroethane is well metabolized (Section 3.4.3), the fraction that is metabolized would be less if the blood-air partition coefficient was less. The tissue:air partition coefficients for 1,1,2,2-tetrachloroethane in rats have been reported to be 142 (blood), 3,767 (fat), 196 (liver), and 101 (muscle) (Gargas et al. 1989), indicating that 1,1,2,2-tetrachloroethane is likely to partition into fatty tissues, consistent with its low water solubility.

A high level of hepatic protein-binding radioactivity was seen in mice administered 1,1,2,2-tetrachloroethane by gavage, followed by a single dose of ^{14}C-1,1,2,2-tetrachloroethane. The amount of 1,1,2,2-tetrachloroethane-derived radioactivity covalently bound to liver protein was about 2 times that seen in rats (Mitoma et al. 1985). The difference in toxicity of 1,1,2,2-tetrachloroethane in rats and mice may well be due to the higher metabolic rate in mice.

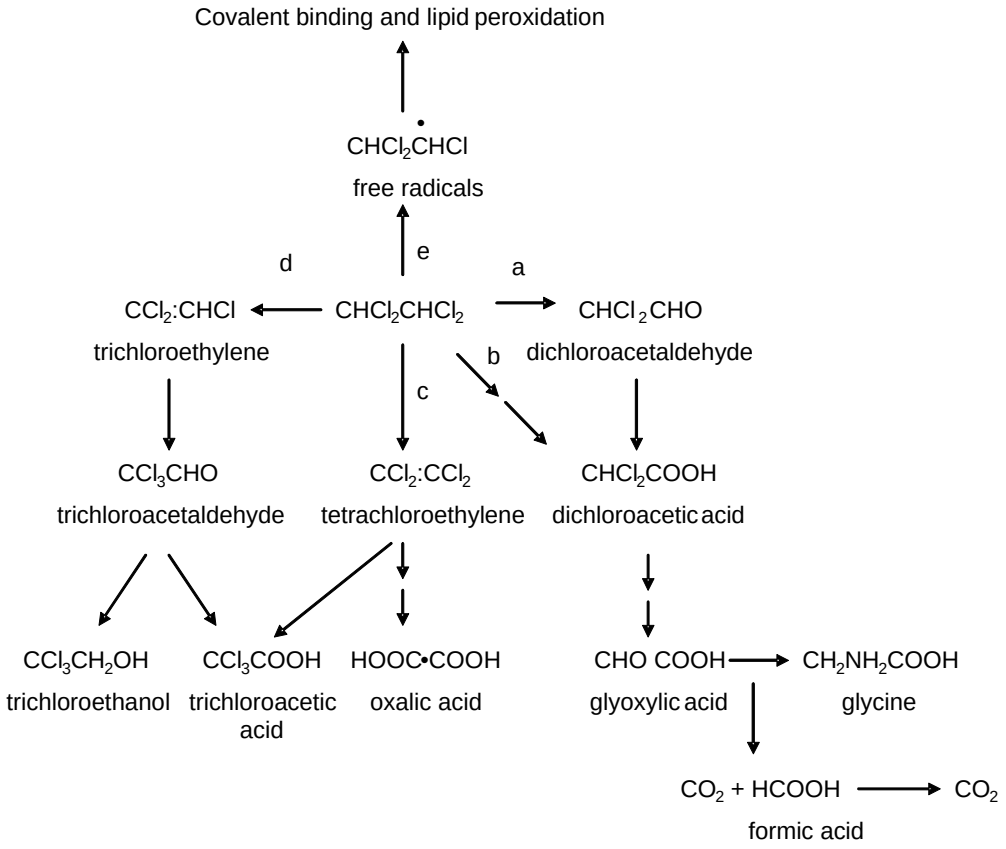
Following a single intravenous injection of radiolabeled 1,1,2,2-tetrachloroethane, Eriksson and Brittebo (1991) reported that a high and selective uptake of nonvolatile radioactivity occurred in the mucosal tissues of olfactory and tracheobronchial regions of the respiratory tract and in the mucosae of the oral cavity, tongue, nasopharynx, esophagus, and cardiac region of the forestomach. High levels of activity were also found in the liver, bile, inner zone of the adrenal cortex, and interstitium of the testis, although the levels were not quantified.

3.4.3 Metabolism

No studies were located regarding metabolism of 1,1,2,2-tetrachloroethane in humans following inhalation, oral, or dermal exposure.

Information regarding 1,1,2,2-tetrachloroethane metabolism in animals is summarized below, and a metabolic scheme based on *in vivo* and *in vitro* data in rodents is presented in Figure 3-3. *In vivo* and *in vitro* studies indicate that the metabolism of 1,1,2,2-tetrachloroethane proceeds via multiple pathways in rodents (Casciola and Ivanetich 1984; Halpert 1982; Halpert and Neal 1981; Ikeda and Ohtsuji 1972; Koizumi et al. 1982; Mitoma et al. 1985; Yllner 1971). The predominant pathway appears to involve production of dichloroacetic acid, formed as an initial metabolite via stagewise hydrolytic cleavage of 1,1,2,2-tetrachloroethane (nonenzymatic degradation yielding dichloroacetyl chloride and dichloroacetaldehyde as intermediates), or by cytochrome P450-based oxidation of 1,1,2,2-tetrachloroethane (Halpert and Neal 1981; Yllner 1971). Dichloroacetic acid was identified as the major urinary metabolite in mice treated with 1,1,2,2-tetrachloroethane by intraperitoneal injection (Yllner 1971) and in *in vitro* systems with rat liver microsomal and nuclear cytochrome P450 (Casciola and Ivanetich 1984; Halpert 1982; Halpert and Neal 1981). Dichloroacetic acid can be further metabolized to glyoxylic acid, formic acid, and carbon dioxide (Yllner 1971), with carbon dioxide a potential major component of the end products (Mitoma et al. 1985; Yllner 1971). Other pathways involve the formation of trichloroethylene or tetrachloroethylene as initial metabolites, with subsequent reactions yielding trichloroethanol, trichloroacetic acid, and oxalic acid as important end products (Ikeda and Ohtsuji 1972; Mitoma et al. 1985; Yllner 1971).

Figure 3-3. Suggested Metabolic Pathways of 1,1,2,2-Tetrachloroethane



Key

→ single metabolic step

→ → multiple metabolic steps

a stagewise hydrolytic cleavage

b P450-dependent oxidation

c non-p450 oxidation

d non-enzymatic dehydrochlorination

e reductive dechlorination

Metabolism of 1,1,2,2-tetrachloroethane is generally extensive, with 68% or more of a total administered dose found as metabolites (Hanley et al. 1988; Mitoma et al. 1985; Yllner 1971). Mice that were given a single 0.16–0.32 g/kg intraperitoneal dose of ^{14}C-labeled 1,1,2,2-tetrachloroethane eliminated 45–61% of the administered radioactivity as carbon dioxide in the expired air and 23–34% of the radioactivity in urine in the following 3 days (Yllner 1971). Dichloroacetic acid, trichloroacetic acid, trichloroethanol, oxalic acid, glyoxylic acid, and urea accounted for 27, 4, 10, 7, 0.9, and 2% (mean) of the urinary radioactivity excreted in 24 hours, respectively. In rats, trichloroethanol appeared to be present as a urinary metabolite at approximately 4-fold greater levels than trichloroacetic acid following a single 8-hour inhalation exposure (Ikeda and Ohtsuji 1972). Several studies have reported that metabolism of 1,1,2,2-tetrachloroethane is greater in mice than in rats; the magnitudes of the reported differences are generally in the range of a 1.1–3.5-fold greater metabolic activity, on a per-kg basis, in mice (Hanley et al. 1988; Milman et al. 1984; Mitoma et al. 1985).

As indicated above, cytochrome P450-based metabolism of 1,1,2,2-tetrachloroethane to dichloroacetic acid has been demonstrated *in vitro*. Multiple P450 isozymes are likely to be involved, as demonstrated by studies reporting increased metabolism and covalent binding of metabolites following pretreatment with phenobarbital (Casciola and Ivanetich 1984; Halpert 1982), xylene (Halpert 1982), or ethanol (Sato et al. 1980); isozymes induced by these chemicals include members of the CYPIIA, CYPIIB, CYPIIE, and CYPIIIA subfamilies (Nebert et al. 1987; Omiecinski et al. 1999). Pretreatment with acetone did not appear to alter the toxicity of 1,1,2,2-tetrachloroethane, although cytochrome P450 levels were not evaluated (Charbonneau et al. 1991). 1,1,2,2-Tetrachloroethane also has been reported to cause inactivation of cytochrome P450. 1,1,2,2-Tetrachloroethane effectively inactivated the major phenobarbital-inducible P450 isozyme, but not the major P450 isozyme induced by β-naphthoflavone, in rat liver *in vitro* (Halpert et al. 1986). Rat liver nuclear cytochrome P450 activity was reduced following *in vitro* incubation with 1,1,2,2-tetrachloroethane and a NADPH-generating system (Casciola and Ivanetich 1984). In an *in vivo* study, cytochrome P450 activity was evaluated in male and female Swiss Albino mice 24 hours after a single 0, 300, or 600 mg/kg intraperitoneal dose of 1,1,2,2-tetrachloroethane (Paolini et al. 1992). 1,1,2,2-Tetrachloroethane treatment reduced total cytochrome P450 activity significantly in both sexes at both dose levels, suggesting that it may act as a suicide inhibitor of the enzyme. Treatment with 600 mg/kg reduced the microsomal activity of P450 isozymes IIIA, IIE1, IA2, IIB1, and IA1 in both sexes, and 300 mg/kg reduced the activity of P450IIIA in both sexes and P450IIB1 in males. The 600 mg/kg dose also reduced the activity of glutathione S-transferase (GST) toward 1-chloro-2,4-dinitrobenzene, a general GST substrate.

Following an intravenous injection of radiolabeled 1,1,2,2-tetrachloroethane, parts of the radioactivity could not be extracted from liver, adrenal cortex, and testis, indicating the presence of covalently bound metabolites (Eriksson and Brittebo 1991) and implicating the formation of free radical intermediates during the metabolic process; the formation of free radicals from 1,1,2,2-tetrachloroethane metabolism has been demonstrated in spin-trapping experiments (Paolini et al. 1992; Tomasi et al. 1984). The observation of covalent binding to tissues is supported by the studies of Hanley et al. (1988), which reported significant levels of covalent binding in hepatic tissues after inhalation of radiolabeled 1,1,2,2-tetrachloroethane; mice were found to have approximately a 1.9-fold greater extent of hepatic covalent binding than rats, which the study authors noted was consistent with the greater metabolism, on a per-kg basis, in mice compared to rats. Other findings suggested that at least a portion of the binding of radiolabel in liver DNA in mice exposed to a single 150 mg/kg oral dose of ^{14}C-1,1,2,2-tetrachloroethane may have been from metabolic breakdown (Hanley et al. 1988). After a 4-week oral exposure of unlabeled 1,1,2,2-tetrachloroethane followed by a single oral dose of labeled 1,1,2,2-tetrachloroethane, Mitoma et al. (1985) also reported greater levels of tissue covalent binding in mice compared to rats; the differences were on the order of 2-fold greater binding in mice, which would be consistent both with the Hanley et al. (1988) studies and with the observed differences in metabolism of the two species discussed above. This may also be related to the 3.2–3.5-fold greater absorption, on a per-kg basis, following inhalation exposure to mice than to rats (Hanley et al. 1988).

The kinetic constants of 1,1,2,2-tetrachloroethane metabolism in rats exposed to 350 ppm of the chemical for 6 hours were determined in gas uptake studies performed by Gargas and Andersen (1989). The rate of exhalation of 1,1,2,2-tetrachloroethane was measured and, combined with previously published values for partition coefficients for blood/air, liver/blood, muscle/blood, and fat/blood, allowed the successful estimation of the disposition of the chemical in rat (Gargas et al. 1989). A K_m of 4.77 μM and a V_{max} of 12 mg/hour (scaled to a l-kg rat) were measured.

3.4.4 Elimination and Excretion

Available animal data indicate that following absorption into the body, 1,1,2,2-tetrachloroethane is eliminated mainly as metabolites in urine and carbon dioxide and unchanged compound in expired air (Gargas and Andersen 1989; Hanley et al. 1988; Ikeda and Ohtsuji 1972; Mitoma et al. 1985; Yllner 1971). The patterns of elimination in rats and mice are qualitatively similar (Hanley et al. 1988; Mitoma et al. 1985), although covalent binding is somewhat greater in mice than rats. Elimination is fairly rapid,

with significant amounts present in the urine and expired air at 48–72 hours postexposure (Hanley et al. 1988; Ikeda and Ohtsuji 1972; Mitoma et al. 1985; Yllner 1971).

Covalent binding of metabolites of 1,1,2,2-tetrachloroethane may result in delays in elimination, as reflected in high levels of compound detected in the carcass of animals. Milman et al. (1984) reported in an abstract that 45% of the activity from a single radiolabeled oral dose of 1,1,2,2-tetrachloroethane was recovered in the carcass, although the evaluation time was not reported. A later study by the same authors (Mitoma et al. 1985) reported a 30.75% retention in the carcass of rats and a 27.44% retention in the carcass of mice 48 hours after exposure to a single labeled dose of 1,1,2,2-tetrachloroethane. Hanley et al. (1988) reported 30% retention in the carcass in rats exposed to 10 ppm by inhalation, 25% in mice exposed to 10 ppm by inhalation, 23% in rats exposed to 150 mg/kg by gavage, and 17.3% in mice exposed to 150 mg/kg by gavage. Colacci et al. (1987) reported covalent binding of radiolabeled 1,1,2,2-tetrachloroethane to DNA, RNA, and protein in the liver, kidney, lung, and stomach of rats and mice exposed to a single intravenous dose and analyzed 22 hours postexposure. *In vitro* binding to calf thymus DNA was found to be greatest when the microsomal fraction was present, and was inhibited by SKF-525A, indicating that metabolic activation was likely required for DNA binding (Colacci et al. 1987).

3.4.4.1 Inhalation Exposure

A study on volunteers showed that 3% of inhaled 1,1,2,2-tetrachloroethane was excreted in the breath, and that the urinary excretion rate was 0.015% of the absorbed dose/minute (Morgan et al. 1970).

The excretion of 1,1,2,2-tetrachloroethane was tracked for 72 hours following exposure of rats and mice to vapor concentrations of 10 ppm ^{14}C-1,1,2,2-tetrachloroethane for 6 hours (Hanley et al. 1988). More than 90% of the absorbed dose was metabolized in both species. The percentage of the recovered radioactivity was reported as follows: in rats, 33% in breath (25% as CO_2 and 8% as unchanged compound), 19% in urine, and 5% in feces; in mice, 34% in breath (32% as CO_2 and 2% as unchanged compound), 26% in urine, and 6% in feces. Radioactivity in urine and feces was nonvolatile (inferred by the researchers to be product(s) of metabolism), but was not otherwise characterized.

3.4.4.2 Oral Exposure

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

The excretion of 1,1,2,2-tetrachloroethane was followed for 72 hours following oral administration of 150 mg/kg doses to rats and mice (Hanley et al. 1988). Greater than 90% of the absorbed dose was metabolized in both species. In rats, 41% was excreted in breath (32% as CO_2 and 9% as unchanged compound), 23% in urine, and 4% in feces. In mice, 51% was excreted in breath, 22% in urine, and 6% in feces. Radioactivity in urine and feces was nonvolatile (inferred by the researchers to be product(s) of metabolism), but was not otherwise characterized.

Mice given an oral dose of 1,1,2,2-tetrachloroethane excreted about 10% of the dose unchanged in the breath. The rest was metabolized and excreted in the breath as CO_2 (10%), in the urine and feces (30%, measured together), and retained in the carcass (27%) after 48 hours. Rats showed similar patterns of excretion (Mitoma et al. 1985).

3.4.4.3 Dermal Exposure

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

A study describing the elimination of 1,1,2,2-tetrachloroethane in guinea pigs demonstrated that, following dermal absorption, about half of the 1,1,2,2-tetrachloroethane in the blood is eliminated in 2 hours (Jakobson et al. 1982).

3.4.4.4 Other Routes of Exposure

The most comprehensive study of the metabolism and excretion of 1,1,2,2-tetrachloroethane was an intraperitoneal study in mice using ^{14}C-labeled 1,1,2,2-tetrachloroethane. This study showed that after 72 hours, about 4% of the radioactivity was expired unchanged in the breath, 50% was expired as CO_2, 28% was excreted in the urine, 1% was in the feces, and 16% remained in the carcass (Yllner 1971).

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

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

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

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

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for

many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

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

If PBPK models for 1,1,2,2-tetrachloroethane exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

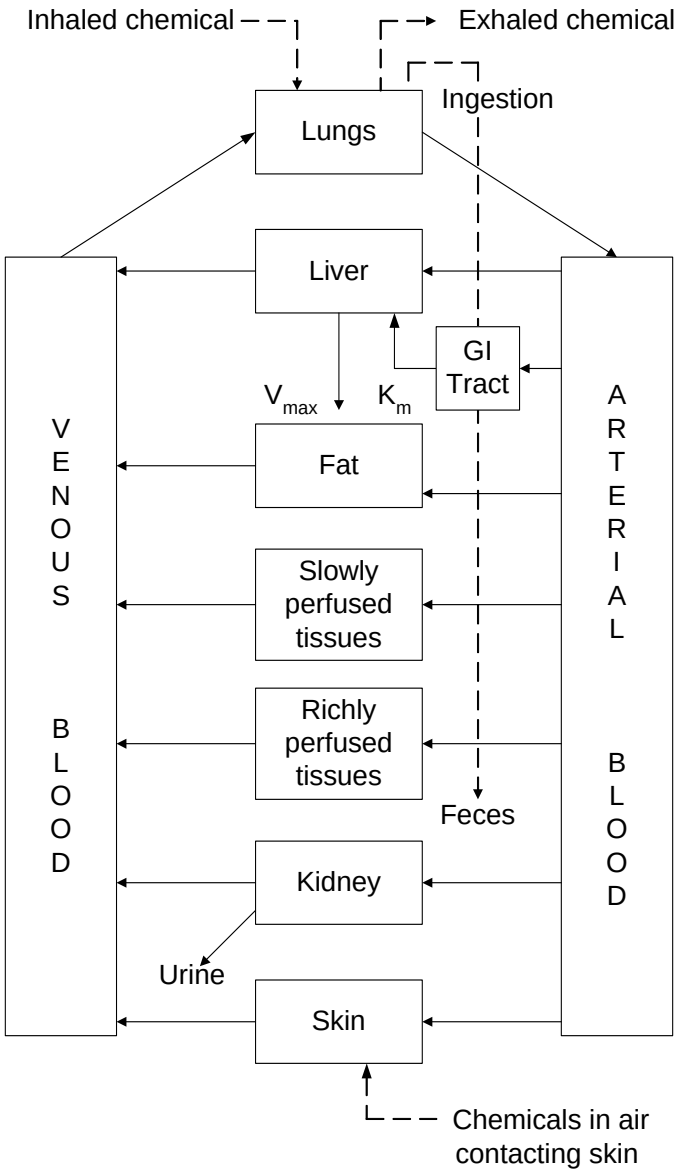
No PBPK models for 1,1,2,2-tetrachloroethane were located. Gargas and Andersen (1989) described using a generic model to estimate the elimination of 1,1,2,2-tetrachloroethane following a single inhalation exposure; however, model details were not provided and the results of model optimizations have not been reported.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Based upon its physical and chemical properties (a low molecular weight and highly lipophilic volatile organic compound), 1,1,2,2-tetrachloroethane is likely to be rapidly and extensively absorbed following both oral and inhalation exposures. This expectation is consistent with reported absorption of 70–100% in oral animal studies (Hanley et al. 1988; Mitoma et al. 1985) and 40–97% in human inhalation studies (Lehmann and Schmidt-Kehl 1936; Morgan et al. 1970), although the human data are uncertain due to unorthodox and dated study protocols that were used to assess uptake. Because 1,1,2,2-tetrachloroethane is a volatile, lipophilic molecule of small molecular size that appears to be readily absorbed from the respiratory and gastrointestinal tracts, passive diffusion is the most likely mechanism of absorption.

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



Source: adapted from Krishnan et al. 1994

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

Following absorption, 1,1,2,2-tetrachloroethane is readily distributed throughout the body, although the high tissue:air partition coefficient for fat (Gargas et al. 1989) suggests that 1,1,2,2-tetrachloroethane may accumulate more in lipid-rich tissues. Distribution likely occurs predominantly via passive diffusion.

Metabolism of 1,1,2,2-tetrachloroethane is extensive, with 68% or more of a total administered dose generally found as metabolites (Hanley et al. 1988; Mitoma et al. 1985; Yllner 1971). The metabolism of 1,1,2,2-tetrachloroethane, as well as covalent binding of reactive metabolites to protein and DNA, is likely to be most prominent in the liver.

Urinary elimination occurs mainly as metabolites, including glyoxalic acid, formic acid, trichloroethanol, and trichloroacetic acid, while a fraction of an absorbed dose may be eliminated in the expired air as parent compound or carbon dioxide (Gargas and Andersen 1989; Hanley et al. 1988; Ikeda and Ohtsuji 1972; Mitoma et al. 1985; Yllner 1971). Passive diffusion is the most likely major mechanism of excretion. Covalent binding of metabolites of 1,1,2,2-tetrachloroethane (Colacci et al. 1987; Hanley et al. 1988; Milman et al. 1984; Mitoma et al. 1985) may result in delays in elimination.

3.5.2 Mechanisms of Toxicity

Metabolism of 1,1,2,2-tetrachloroethane to reactive products is likely to play a key role in its toxicity. Both nuclear and microsomal cytochrome P450 enzymes have been implicated in the metabolism of the compound, possibly releasing a number of biologically active compounds, including aldehydes, alkenes, acids, and free radicals (see Figure 3-3 in Section 3.3) that may react with biological tissues. Evidence for metabolism to reactive compounds comes from studies of binding of radiolabeled 1,1,2,2-tetrachloroethane to tissues that was enhanced by pretreatment with phenobarbital, xylene, or ethanol; the variety of inducers capable of influencing this effect suggests that multiple P450 isozymes may be involved. Additionally, mice are known to metabolize 1,1,2,2-tetrachloroethane at a 1.1–3.5-fold greater rate than rats (Hanley et al. 1988; Milman et al. 1984; Mitoma et al. 1985) and have been demonstrated to have approximately 2-fold greater covalent binding to tissues (Mitoma et al. 1985), further implicating metabolic activation as a possible mode of action. Thus, for tissues high in metabolic capacity, such as the liver, the formation of active metabolites is a likely mechanism for the toxicity of 1,1,2,2-tetrachloroethane.

The presence of the functional group consisting of a terminal dichloromethyl moiety in a molecule, as typified by the drug chloramphenicol, is known to confer toxicity. Chloramphenicol and other

dichloromethyl compounds are hydroxylated to form, after spontaneous dehydrohalogenation, reactive acyl chloride intermediates (Halpert 1981; Halpert et al. 1986), which subsequently bind to crucial proteins to exert their effects. Alternately, these acid chlorides can hydrolyze to form their respective acids. There was clear evidence in the literature reviewed that these pathways were operant for 1,1,2,2-tetrachloroethane. Cytochrome P-450 was found to catalyze the formation of both dichloroacetylated protein adducts (Halpert 1982) and dichloroacetic acid (Halpert 1981). These biotransformation reactions were increased by chronic ethanol consumption and fasting, preconditions that are known to induce the levels of cytochrome P-450 isoenzyme IIE1 (Johansson et al. 1988; Soucek and Gut 1992). Significantly, a number of low molecular weight volatile halocarbons are metabolized by this isoform, suggesting that it may be the major contributor to the metabolism of 1,1,2,2-tetrachloroethane as well (Guengerich et al. 1991).

Paolini et al. (1992) investigated the reductive metabolism of 1,1,2,2-tetrachloroethane in mice. Those workers trapped a carbon-centered radical formed *in vivo* by reductive dehalogenation of 1,1,2,2-tetrachloroethane, a reaction presumably mediated by cytochrome P-450. Tomasi et al. (1984) also demonstrated the formation of free radicals from 1,1,2,2-tetrachloroethane metabolism in spin-trapping experiments. Additionally, there was evidence of lipid peroxidation (Paolini et al. 1992). These properties are reminiscent of the metabolism of carbon tetrachloride, where reductive formation of radical products leads to the stimulation of lipid peroxidation and its attendant hepatotoxic effects.

Both dichloro- and trichloroacetic acids are known to cause proliferation of peroxisomes (DeAngelo et al. 1986). In the work presented by Hanley et al. (1988), this property of the acid metabolites of 1,1,2,2-tetrachloroethane was noted, and suggested as a possible mechanism by which the halocarbon could elicit hepatotoxic responses.

The mechanism behind the neurological effects of high-dose exposures to 1,1,2,2-tetrachloroethane has not been well characterized. While it is possible that metabolic activation may play a role in causing these effects, studies of similar compounds suggest that the parent compound may be the causative agent. In general, the highly lipophilic nature of chlorinated hydrocarbons, such as 1,1,2,2-tetrachloroethane, allows them to cross the blood-brain barrier readily and partition into lipids in neuronal membranes. This property allows them to interfere with neural membrane function, bringing about central nervous system depression, behavioral changes, and anesthesia (Klaassen 1996). However, studies describing the mechanism of 1,1,2,2-tetrachloroethane-induced neurological effects are not available.

The mode of action of the carcinogenic effects of 1,1,2,2-tetrachloroethane is incompletely characterized. Genotoxicity studies provide only limited evidence of a genotoxic mode of action. 1,1,2,2-Tetrachloroethane has weak genotoxic activity, with *in vitro* genotoxicity tests generally reporting negative results except for assays of SCE and cell transformation; *in vivo* tests of genotoxicity have shown a similar pattern. 1,1,2,2-Tetrachloroethane has been shown to bind to DNA in the liver and several other organs organs in rats and mice *in vivo* (Colacci et al. 1987; Hanley et al. 1988), indicating that this mechanism may contribute to the carcinogenic process. Several studies of 1,1,2,2-tetrachloroethane toxicity have reported increases in the number of hepatocytes in mitosis, but the possible role these effects may have on the carcinogenicity of 1,1,2,2-tetrachloroethane has not been evaluated. The results of rat liver preneoplastic foci and mouse BALB/c-3T3 cell neoplastic transformation assays suggest that 1,1,2,2-tetrachloroethane may have initiating and promoting activity (Colacci et al. 1992, 1996; Milman et al. 1988; Story et al. 1986), but tumor initiation and promotion studies have not been conducted to elucidate these potential modes of action.

It is likely that tumor formation by 1,1,2,2-tetrachloroethane involves metabolism to one or more active compounds, that in turn result in carcinogenicity. 1,1,2,2-Tetrachloroethane is metabolized extensively following absorption, presumably at least in part by cytochrome P450 enzymes. Urinary metabolites of 1,1,2,2-tetrachloroethane include dichloroacetic acid, trichloroacetic acid, trichloroethylene, and tetrachloroethylene (Section 3.4.3). Chronic exposure of rats and mice to trichloroacetic acid, trichloroethylene, and tetrachloroethlyene had similar effects as were reported in the NCI (1978) carcinogenicity study of 1,1,2,2-tetrachloroethane, with hepatic tumors in male and female mice but not in rats of either sex (Bull et al. 1990; Herren-Freund et al. 1987; NCI 1976, 1977; NTP 1986, 1990; Pereira 1996; Pereira and Phelps 1996). Dichloroacetic acid has also been demonstrated to cause hepatocellular tumors in both male and female mice (Bull et al. 1990; Daniel et al. 1992; DeAngelo et al. 1991, 1999; Pereira 1996; Pereira and Phelps 1996); dichloroacetic acid has been shown to cause liver tumors in rats as well, but the results are not as striking as in mice (DeAngelo et al. 1996; Richmond et al. 1995). Dichloroacetic acid, trichloroacetic acid, trichloroethylene, and tetrachloroethylene have similar genotoxicity profiles as 1,1,2,2-tetrachloroethane, adding further support to the possibility that metabolism to one or more of these compounds may be involved in the carcinogenicity of 1,1,2,2-tetrachloroethane. Mice are known to metabolize 1,1,2,2-tetrachloroethane to a greater extent than rats, which may in part account for the fact that liver tumors occurred in mice, but not in rats, following chronic oral exposure. Although it is plausible that the carcinogenicity of 1,1,2,2-tetrachloroethane involves metabolism to one or more active compounds, there is no direct evidence linking one or more metabolites to its carcinogenic effects.

In addition to being metabolized to carcinogenic compounds, 1,1,2,2-tetrachloroethane may be metabolized to form free radicals, which can, in turn, covalently bind to tissues, including DNA. Formation of free radicals during 1,1,2,2-tetrachloroethane metabolism has been demonstrated in spin-trapping experiments (Paolini et al. 1992; Tomasi et al. 1984). Both nuclear and microsomal forms of cytochrome P450 enzymes have been implicated in this process, as increased metabolism and covalent binding of metabolites following pretreatment with phenobarbital (Casciola and Ivanetich 1984; Halpert 1982), xylene (Halpert 1982), or ethanol (Sato et al. 1980) have been reported. The presence of covalently bound label has been reported following inhalation (Hanley et al. 1988), oral (Mitoma et al. 1985), and intravenous (Eriksson and Brittebo 1991) administration of radiolabeled 1,1,2,2-tetrachloroethane.

3.5.3 Animal-to-Human Extrapolations

Limited information is available regarding the pharmacokinetic properties of 1,1,2,2-tetrachloroethane in humans. Species-specific differences in pharmacokinetic properties of 1,1,2,2-tetrachloroethane have been demonstrated in rats and mice. Results of Hanley et al. (1988) indicate a 3.2–3.5-fold greater absorption of 1,1,2,2-tetrachloroethane (on a per-kg basis) in mice than rats following inhalation exposure. Several studies have reported that metabolism of 1,1,2,2-tetrachloroethane is greater in mice than in rats; the magnitudes of the reported differences are generally in the range of a 1.1–3.5-fold greater metabolic activity in mice (Hanley et al. 1988; Milman et al. 1984; Mitoma et al. 1985). After a 4-week oral exposure of unlabeled 1,1,2,2-tetrachloroethane followed by a single oral dose of labeled 1,1,2,2-tetrachloroethane, Mitoma et al. (1985) also reported greater levels of tissue covalent binding in mice compared to rats; the differences were on the order of 2-fold greater binding in mice.

Based on pharmacokinetic differences between rats and mice and limited human pharmacokinetic data for 1,1,2,2-tetrachloroethane, animal-to-human extrapolations include considerable uncertainty.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate

terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No human data were located regarding the potential for 1,1,2,2-tetrachloroethane to affect the endocrine system. Based on available animal data, the endocrine system does not appear to be a target of 1,1,2,2-tetrachloroethane toxicity (Gohlke and Schmidt 1972; Horiuchi et al. 1962; NCI 1978; NIOSH 1978; NTP 2004).

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect

effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

Studies in humans and animals have not examined the effect of 1,1,2,2-tetrachloroethane exposure on the immature organism. The limited data evaluating the effect of 1,1,2,2-tetrachloroethane on developing rats and mice have not indicated effects on the offspring at levels that did not also cause maternal effects (NTP 1991a, 1991b; Schmidt et al. 1972). Because metabolism of 1,1,2,2-tetrachloroethane to reactive products is likely to play a key role in 1,1,2,2-tetrachloroethane toxicity, potential age-related differences in metabolism could result in age-related differences in susceptibility to the toxic effects of exposure to 1,1,2,2-tetrachloroethane. For example, the well-recognized metabolic immaturity of hepatic enzymes during infancy (Ginsberg et al. 2002, 2004) might be protective against 1,1,2,2-tetrachloroethane-induced liver effects since these effects appear to require hepatic metabolism. How this would ultimately affect risk is difficult to predict since the ability to remove toxic metabolites may also be immature.

The mechanism behind the neurological effects of high-dose exposures to 1,1,2,2-tetrachloroethane is not well characterized, but studies of similar compounds suggest that the parent compound may be the causal agent (Section 3.5.2). The amount of parent 1,1,2,2-tetrachloroethane that has the opportunity to reach the central nervous system and produce neurotoxicity may be greater in infants than adults. Reasons for this include immaturity in hepatic metabolism (which could lead to longer-half life of parent compound, higher blood levels and thus greater amounts reaching the central nervous system), and immaturity of the blood-brain barrier (which could result in increased distribution into the central nervous system).

Children may be more vulnerable to 1,1,2,2-tetrachloroethane since intake dose per kilogram of body weight may be greater in early life than in mature humans, because children eat more food, drink more water, breathe more air, and ingest more soil/house dust per kilogram body weight than older age groups (EPA 2002; NRC 1993). There are no reports on levels of 1,1,2,2-tetrachloroethane in breast milk (Section 6.6). PBPK models for similar chlorinated solvents (e.g., Fisher et al. 1997) suggest that 1,1,2,2-tetrachloroethane may not present a particularly large breast milk concern for nursing infants, largely because of its rapid metabolism by the maternal system.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1,1,2,2-tetrachloroethane are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,1,2,2-tetrachloroethane are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the

biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to 1,1,2,2-Tetrachloroethane

There currently are no specific biomarkers available to quantify exposure to 1,1,2,2-tetrachloroethane. Metabolites of 1,1,2,2-tetrachloroethane, including trichloroacetic acid, trichloroethanol, and trichloroethanol glucuronide, may be measured in blood and urine (Breimer et al. 1974; Christensen et al. 1988; Koppen et al. 1988) (see Chapter 7). However, these metabolites are common to several types of chlorinated ethanes and would not be specifically indicative of exposure to 1,1,2,2-tetrachloroethane. Also, 1,1,2,2-tetrachloroethane is metabolized and excreted rather quickly, and the test might only indicate whether the person had been exposed within the last few days. If such a test of metabolite levels were available, the levels in the human body might be used to determine if adverse health symptoms were specifically the result of 1,1,2,2-tetrachloroethane exposure.

3.8.2 Biomarkers Used to Characterize Effects Caused by 1,1,2,2-Tetrachloroethane

There currently are no biomarkers available to characterize effects caused by 1,1,2,2-tetrachloroethane. However, since 1,1,2,2-tetrachloroethane has the potential to cause liver damage at high doses, it may be possible to correlate changes in urinary metabolites with serum indicators of liver malfunction, although the metabolites would not be specific for 1,1,2,2-tetrachloroethane. 1,1,2,2-Tetrachloroethane has been shown to bind to DNA in the liver several tissues in rats and mice *in vivo* (Colacci et al. 1987; Hanley et al. 1988), suggesting that it may be plausible to use DNA adducts in peripheral blood lymphocytes as a biomarker of effects (as has been done for numerous genotoxic agents).

3.9 INTERACTIONS WITH OTHER CHEMICALS

In efforts to find treatments for acute-duration 1,1,2,2-tetrachloroethane poisoning, various substances have been tested to determine if they altered the toxicity of 1,1,2,2-tetrachloroethane in rats (Laass 1973a, 1973b, 1974a, 1974b). The survival times were increased when 1,1,2,2-tetrachloroethane was administered with castor oil, but decreased when administered orally with milk. Survival time was also decreased when 1,1,2,2-tetrachloroethane was given with mineral oil or with paraffin.

Alcohol, an inducer of cytochrome P-450 form IIE1, increased the metabolism of 1,1,2,2-tetrachloroethane (Sato et al. 1980) and intensified the effects of 1,1,2,2-tetrachloroethane in rats (Gohlke and Schmidt 1972). This indicates that humans who consume alcohol may be at increased risk for toxic effects from 1,1,2,2-tetrachloroethane. This is also the case for several other chlorinated aliphatic hydrocarbons. However, although alcohol combined with 1,1,2,2-tetrachloroethane increased the relative weight of the testes in rats (Schmidt et al. 1972), it did not alter the effects of 1,1,2,2-tetrachloroethane on the histopathology or function in the liver, nor was there damage to the kidneys, spleen, adrenals, brain, or thyroid.

Acetone pretreatment did not increase the severity of liver injury in rats given 1,1,2,2-tetrachloroethane. Additionally, rats given 1,1,2,2-tetrachloroethane in addition to 1,1-dichloroethylene or tetrachloroethylene exhibited a decrease in hepatotoxicity from animals given 1,1-dichloroethylene or tetrachloroethylene alone (Charbonneau et al. 1991), possibly due to competitive inhibition of metabolism.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,1,2,2-tetrachloroethane than will most persons exposed to the same level of 1,1,2,2-tetrachloroethane in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of 1,1,2,2-tetrachloroethane, or compromised function of organs affected by 1,1,2,2-tetrachloroethane. Populations who are at greater risk due to their unusually high exposure to 1,1,2,2-tetrachloroethane are discussed in Section 6.7, Populations with Potentially High Exposures.

As metabolism is believed to play an important role in the toxicity of 1,1,2,2-tetrachloroethane, particularly in the liver, individuals with elevated levels of cytochrome P450 enzymes may have an increased susceptibility to the compound. Halpert (1982) reported an increase in *in vitro* metabolite formation and in covalently bound metabolites following pretreatment with xylene or phenobarbital, both of which increased cytochrome P450 activity. Sato et al. (1980) similarly reported an increased metabolism of 1,1,2,2-tetrachloroethane in rats following ethanol pretreatment. Since 1,1,2,2-tetrachloroethane has been demonstrated to inhibit cytochrome P450 enzymes (Halpert 1982; Paolini et al. 1992), presumably through a suicide inhibition mechanism, it is also possible that people coexposed to chemicals that are inactivated by cytochrome P450 enzymes will be more susceptible to those compounds.

Studies directly evaluating sex-related differences in toxicity following exposure to 1,1,2,2-tetrachloroethane are not available. Toxicity studies that evaluated both sexes in the same study did not show consistent sex-related differences.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Ellenhorn MJ, Schonwald S, Ordog G, et al. 1997. 1,1,2,2-Tetrachloroethane. Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1436-1440.

Goldfrank LR, Flomenbaum NE, Lewin NA, et al. 2002. Hydrocarbons. In: Goldfrank's toxicologic emergencies. New York, NY: McGraw Hill, 1303-1322.

Haddad LM, Shannon MW, Winchester JF. 1998. Clinical management of poisoning and drug overdose. 3rd edition. Philadelphia, PA: W.B Saunders Company, 931-939.

Parraga M, West JM. 1998. Hydrocarbons. In: Viccellio P, ed. Emergency toxicology. 2nd edition. Philadelphia, PA: Lippincott-Raven Publishers, 299-313.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to 1,1,2,2-tetrachloroethane may occur by inhalation, ingestion, or dermal contact. Concentrated vapors are irritating to the eyes and upper respiratory tract, and once absorbed can cause central nervous system and respiratory depression. Unprotected skin exposure can cause defatting and subsequent dermatitis. Suggested treatment for exposed individuals includes moving them to fresh air and administering 100% humidified supplemental oxygen. The potential risk of rapid central nervous system and respiratory depression usually outweighs the potential risk (e.g., aspiration of vomitus) of administering syrup of ipecac to induce emesis (TOMES 1993). Once in the care of a health professional, gastric lavage is suggested if it can be performed within minutes of the exposure to reduce the amount of absorbed solvent.

Following acute high-level exposure to some chlorinated solvents by any route, hypotension and cardiac arrhythmias due to myocardial sensitization to catecholamines have led to ventricular fibrillation and death (TOMES 1993). There is no specific treatment for 1,1,2,2-tetrachloroethane exposure except for supportive measures to combat the effects of central nervous system and respiratory depression, and cardiac arrhythmias.

3.11.2 Reducing Body Burden

The body does not retain significant amounts of 1,1,2,2-tetrachloroethane. Currently, there is no recognized treatment to enhance elimination. The orthodox treatment for ingestion is entirely supportive. One potential method for enhancing elimination is to increase the ventilation rate, thereby enhancing elimination via the lung. In a 6-year-old boy who had ingested 12–16 g of tetrachloroethylene, controlled hyperventilation over a 5-day period enhanced pulmonary excretion of the chemical (Koppel et al. 1985). This technique may be applicable to other volatile solvents like 1,1,2,2-tetrachloroethane, although its effectiveness for clearing 1,1,2,2-tetrachloroethane from the body is likely to be lower than for tetrachloroethylene, because tetrachloroethylene is particularly slowly metabolized (providing a better opportunity for clearance via exhalation) and has a much lower human blood-air partition coefficient (10.3–19.8 [Agency for Toxic Substances and Disease Registry 1997] compared to 72.6–116 [Section 3.4.2]).

Stimulation of the metabolism of 1,1,2,2-tetrachloroethane may also lead to enhanced elimination, but it can also result in formation of larger amounts of toxic metabolites. Thus, the risks of this approach may outweigh the benefits.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Clinical effects caused by acute 1,1,2,2-tetrachloroethane exposure include central nervous system depression, nephritis, and toxic hepatitis (HSDB 2006). Other effects include malaise, dizziness, fatigue, headache, and lightheadedness, all of which may disappear rapidly after the exposure ceases. The mechanism of action for the central nervous system effects has not been clearly established, but it is probable that it is related to solvent effects on neuronal membranes exerted by many halogenated aliphatic hydrocarbons.

Ethanol in alcoholic beverages may compete with or enhance the metabolic activation of solvents and could possibly increase the severity of health effects, particularly liver toxicity. Alcoholic beverages should be avoided by persons exposed to 1,1,2,2-tetrachloroethane and other solvents of this nature.

Mechanisms have been proposed for the hepatotoxic action of this halocarbon (Halpert 1981; Halpert et al. 1986; Hanley et al. 1988). These include generation of reactive free radicals and acid chlorides. Dietary antioxidants may modulate the toxicity caused by the former, but no established treatments are available for the latter. It is concluded that avoiding co-exposures to substances that enhance the activation of 1,1,2,2-tetrachloroethane (e.g., acetone and ethanol) provide the best means of interfering with the toxification of the absorbed chemical.

3.12 ADEQUACY OF THE DATABASE

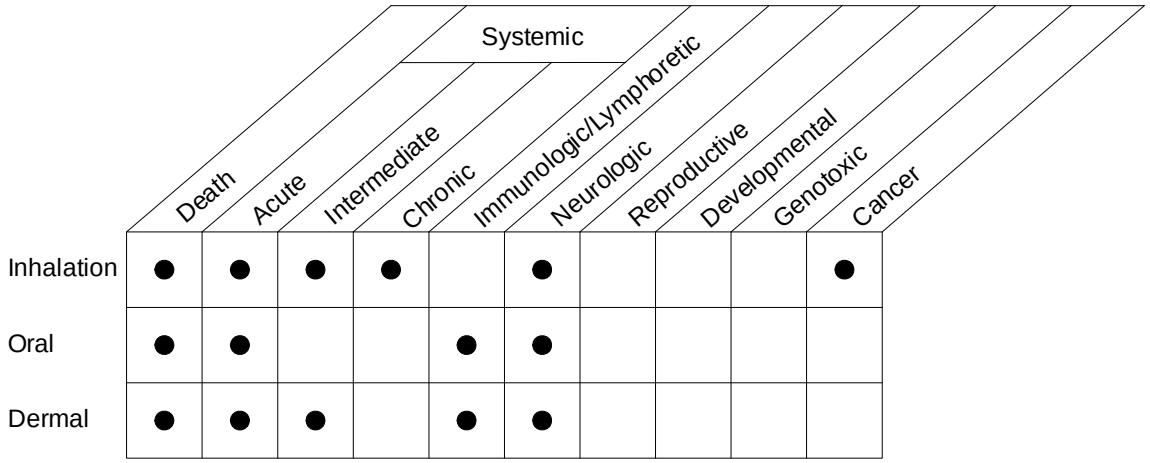
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1,2,2-tetrachloroethane is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1,2,2-tetrachloroethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

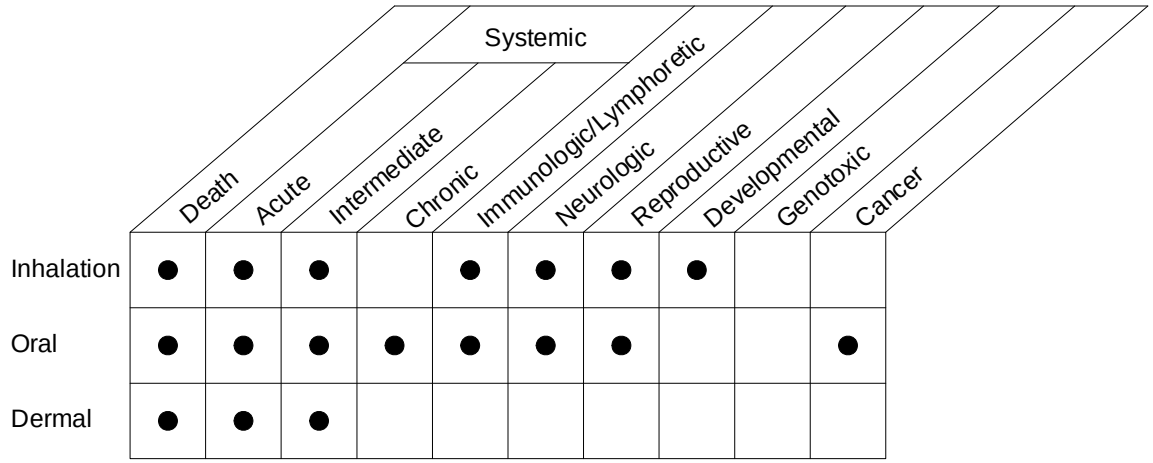
3.12.1 Existing Information on Health Effects of 1,1,2,2-Tetrachloroethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1,2,2-tetrachloroethane are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,1,2,2-tetrachloroethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does

Figure 3-5. Existing Information on Health Effects of 1,1,2,2-Tetrachloroethane



Human



Animal

● Existing Studies

not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As seen in Figures 3-5, data exist for inhalation exposure of humans for death, systemic effects of acute-, intermediate-, and chronic-duration exposure, neurological effects, and cancer. A few human deaths have been reported following excessive inhalation exposure to 1,1,2,2-tetrachloroethane in occupational settings. Effects reported in humans exposed in the workplace consist of gastric distress including pain, nausea, vomiting, loss of appetite, and loss of body weight; increases in the number of white blood cells; jaundice, enlarged liver, liver degeneration, and cirrhosis; neurological symptoms such as headache, tremors, dizziness, numbness, and drowsiness; and possibly genital cancer and leukemia or lymphoma. In one experimental inhalation study, male volunteers experienced mucosal irritation, nausea, vomiting, and dizziness upon exposure to high levels of 1,1,2,2-tetrachloroethane. Data for oral exposure of humans consist mainly of case reports of suicidal or accidental ingestion of 1,1,2,2-tetrachloroethane, with data for death, systemic effects of acute-duration exposure, immunological/lymphoreticular, and neurological effects. Autopsy findings in suicide cases included congestion and edema in the lungs and lung collapse, mucosal congestion of the esophagus and upper stomach, and epicardial and endocardial anoxic hemorrhage. In cases of humans accidentally given oral doses of 1,1,2,2-tetrachloroethane for parasite treatment, effects consisted of shallow breathing, pronounced lowering of blood pressure, and faint pulse during ensuing unconsciousness. One death was reported when a man cleaned up a 1,1,2,2-tetrachloroethane spill with his bare hands. Workers in India's bangle industry who dipped their hands in 1,1,2,2-tetrachloroethane, as well as inhaled it, had tremors, headache, and dizziness in addition to gastric disturbances. Mucosal irritation of the eyes has also been observed in humans exposed to 1,1,2,2-tetrachloroethane in air by direct contact of the concentrated vapor with the eyes.

For animals exposed by inhalation, data exist for death; systemic effects of acute- and intermediate-duration; and immunological/lymphoreticular, neurological, reproductive, and developmental effects. Systemic effects consisted of labored respiration, hematological effects, and hepatic effects. Immunological effects consisted of a decrease in titer and an increase in the electrophoretic mobility of specific antibodies to typhoid in rabbits. Neurological effects included decreased motor activity, loss of reflexes, ataxia, prostration, and narcosis. No reproductive or developmental toxicity was associated with

inhalation exposure of animals. Data for oral exposure of animals exist for death; systemic effects of acute-, intermediate-, and chronic-duration exposure; immunological/lymphoreticular, neurological, and reproductive effects; and cancer. Systemic effects consisted of hepatic, thyroid, and adrenal effects, and decreases in body weight gain. Information on immunological/lymphoreticular effects is limited to histopathological effects on the spleen. Neurological effects consisted of central nervous system depression, debilitation, and decreased avoidance learning. An oral study in rats indicated an effect on spermatogenesis; however, the interpretation of the study was confounded by the fact that the rats had been maintained at a high temperature (35 °C). Cancer data consist of a significantly increased incidence of hepatocellular carcinoma in mice exposed orally. Existing data in animals exposed dermally to 1,1,2,2-tetrachloroethane are limited to an LD_{50} in rabbits; karyopyknosis and pseudoeosinophilic infiltration in guinea pigs; and eye closure, squinting, and lacrimation in guinea pigs and rats acutely exposed to the vapors.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Numerous studies are available regarding the effects of acute-duration exposures to 1,1,2,2-tetrachloroethane, both in humans (Coyer 1944; Hepple 1927; Lehmann and Schmidt-Kehl 1936; Lilliman 1949; Mant 1953; Sherman 1953; Ward 1955) and animals (Cottalasso et al. 1998; Deguchi 1972; Hanley et al. 1988; Horiuchi et al. 1962; Horvath and Frantik 1973; NTP 1991a, 1991b, 1993a, 1993b, 2004; Pantelitsch 1933; NIOSH 1978; Schmidt et al. 1980a; Tomokuni 1969, 1970; Wolff 1978). These studies have identified the liver and central nervous system as the major organ systems affected in both humans and animals following inhalation and oral exposure.

Information on the toxicity of acute inhalation exposure to 1,1,2,2-tetrachloroethane in humans comes from a poorly reported experimental study in which two volunteers self-inhaled various concentrations of the chemical for up to 30 minutes (Lehmann and Schmidt-Kehl 1936). The results of this study suggest that 3 ppm was the odor detection threshold, 13 ppm was tolerated without effect for 10 minutes, and 146 ppm for 30 minutes or 336 ppm for 10 minutes caused irritation of the mucous membranes, pressure in the head, vertigo, and fatigue. Other early reports similarly indicate that common symptoms of high-dose acute inhalation exposure to 1,1,2,2-tetrachloroethane include drowsiness, nausea, headache, and weakness, and at extremely high concentrations, jaundice, unconsciousness, and respiratory failure (Coyer 1944; Hamilton 1917).

The preponderance of information on the acute inhalation toxicity of 1,1,2,2-tetrachloroethane in animals pertains to neurological and hepatic effects of near-lethal to lethal exposures (Carpenter et al. 1949; Horiuchi et al. 1962; Pantelitsch 1933; NIOSH 1978; Schmidt et al. 1980b). Death was typically preceded by signs of central nervous system toxicity (e.g., incoordination, loss of reflexes, labored respiration, prostration, and loss of consciousness), and postmortem examinations mainly showed congestion and fatty degeneration of the liver. Hepatotoxicity (Gohlke and Schmidt 1972; Schmidt et al. 1972, 1980a; Tomokuni 1969, 1970) and neurotoxicity (Horvath and Frantik 1973; NIOSH 1978) have been reported in animals acutely exposed to nonlethal concentrations of 1,1,2,2-tetrachloroethane vapors.

Information on the acute oral toxicity of 1,1,2,2-tetrachloroethane in humans is available from several case reports. In reports of intentional ingestion of lethal amounts of 1,1,2,2-tetrachloroethane (Elliott 1933; Forbes 1943; Hepple 1927; Lilliman 1949; Mant 1953; Sherman 1953), subjects usually lost consciousness within approximately 1 hour and died 3–20 hours postingestion, depending on the amount of food in the stomach. Postmortem examinations showed gross congestion in the esophagus, stomach, kidneys, spleen, and trachea, gross congestion and edema in the lungs, and histological effects of congestion and cloudy swelling in the lungs, liver, and/or kidneys (Hepple 1927; Mant 1953).

The preponderance of information on the acute-duration oral toxicity of 1,1,2,2-tetrachloroethane in animals is provided by gavage studies of rats and mice in which lethality was one of the end points evaluated. LD_{50} values in rats range from 250 to 800 mg/kg (Gohlke et al. 1977; NTP 2004; Schmidt et al. 1980a; Smyth et al. 1969). Lethality data are available for repeated gavage exposure in rats (NTP 1993a, 1996) and mice (NTP 1993d). Dietary exposure for acute and intermediate exposure durations caused moribundity or death in rats (NTP 2004) and mice (NTP 1991b, 2004). Information is available on acute neurological, body weight, and liver effects in animals following acute-duration oral exposure to 1,1,2,2-tetrachloroethane (Cottalasso et al. 1998; Hanley et al. 1988; NTP 1993a, 1993b, 2004; Schmidt et al. 1980a; Wolff 1978), but most adverse changes were observed at near-lethal to lethal dose levels.

In summary, derivation of acute-duration inhalation and oral MRLs for 1,1,2,2-tetrachloroethane are precluded by the lack of information regarding threshold response levels for less serious effects. Well designed studies that assess less serious threshold effects following acute-duration inhalation and oral exposure to 1,1,2,2-tetrachloroethane would facilitate the development of acute-duration MRL values for 1,1,2,2-tetrachloroethane. Data for dermal exposure routes are limited, but this is not a primary route of human exposure for persons living near hazardous waste sites where 1,1,2,2-tetrachloroethane may be found.

Intermediate-Duration Exposure. Reports of intermediate-duration exposures to humans by the inhalation and oral routes have been somewhat anecdotal and dated, and their interpretations complicated by uncertainties in levels of exposure to 1,1,2,2-tetrachloroethane and other chemicals (Jeney et al. 1957; Koelsch 1915; Lobo-Mendonca 1963; Minot and Smith 1921; Parmenter 1921; Willcox et al. 1915). Though mostly qualitative, these studies have confirmed that the same organ systems are affected as those for acute-duration exposure.

Intermediate-duration inhalation exposure of animals to intermittent high concentrations of 1,1,2,2-tetrachloroethane caused mortality and neurological and liver effects that are essentially acute in nature (Horiuchi et al. 1962). Information on effects of intermediate-duration inhalation exposure to lower concentrations of 1,1,2,2-tetrachloroethane is available from poorly reported studies in rats and rabbits (Kulinskaya and Verlinskaya 1972; Union Carbide Corporation 1947; Schmidt et al. 1972; Shmuter 1977; Truffert et al. 1977). These studies provide information on hepatic, reproductive, and other non-neurological effects. With the exception of the reproductive effects (Schmidt et al. 1972), these studies are inadequate for identifying a NOAEL or LOAEL due to insufficient data on incidence, magnitude, and/or severity of effects.

Intermediate-duration oral toxicity studies of 1,1,2,2-tetrachloroethane include a 21-day gavage study in rats (NTP 1996), a 16-day gavage study in mice (NTP 1993d), 6-week gavage studies in rats and mice (NCI 1978), and 15-day diet studies in rats and mice (NTP 2004). These studies are mainly dose range-finding studies that used small numbers of animals and had limited or no evaluations of clinical chemistry and histology. Additional information on the intermediate-duration oral toxicity of 1,1,2,2-tetrachloroethane is available from comprehensive 14-week dietary studies in rats and mice (NTP 2004) that tested wider ranges of doses and varieties of end points than the studies summarized above. The NTP (2004) study in rats found liver-related serum chemistry changes at 80 mg/kg/day and hepatocellular necrosis at 170 mg/kg/day (NTP 2004). Mice exposed for 14 weeks in the diet had similar liver effects at higher doses than the rats (NTP 2004). Comprehensive neurological testing in the 14-week studies showed no effects in either species, indicating that the liver was more sensitive than the nervous system for intermediate-duration dietary exposure. The NTP (2004) study in rats served as the basis for deriving an intermediate-duration oral MRL for 1,1,2,2-tetrachloroethane, as described in detail in Chapter 2 and Appendix A.

Additional intermediate-duration oral studies are not necessary at this time. An intermediate-duration inhalation study in laboratory animals could be designed to provide information necessary to derive an intermediate-duration inhalation MRL for 1,1,2,2-tetrachloroethane.

Chronic-Duration Exposure and Cancer. Information on the chronic inhalation toxicity of 1,1,2,2-tetrachloroethane in humans is available from several occupational studies (Jeney et al. 1957; Lobo-Mendonca 1963; Minot and Smith 1921; Norman et al. 1981) that are inadequate for identification of effect levels due to limitations that include insufficient characterization of exposure levels, lack of control data, dermal exposures, and/or mixed chemical exposures. Although not sufficient for identification of effect levels or MRL derivation, the occupational studies provide limited supporting information on the neurotoxicity and hepatotoxicity of 1,1,2,2-tetrachloroethane. Chronic inhalation studies in animals have not been performed.

The systemic effects of long-term repetitive oral exposure of mice and rats to 1,1,2,2-tetrachloroethane have been studied via gavage using several dose levels (NCI 1978). The NCI (1978) study identified LOAELs of 108 mg/kg/day for liver lesions in rats and a serious LOAEL of 284 mg/kg/day for lethal kidney lesions and reduced survival in mice. Derivation of a chronic oral MRL is precluded because lower LOAELs are identified in the more comprehensive and sensitive 14-week diet study in these species (NTP 2004) used to derive the intermediate-duration MRL.

There is one study on the possible carcinogenic effect of 1,1,2,2-tetrachloroethane on humans via inhalation exposure (Norman et al. 1981), and there are oral studies of the effects on rats and mice (NCI 1978). The human study was inconclusive and in the NCI (1978) study, liver tumors were found in mice after long-term oral exposure. However, this species has a high rate of spontaneous incidence of these tumors, and these data may not be indicative of carcinogenic risk in humans.

There are no studies of the effect of chronic-duration dermal administration of 1,1,2,2-tetrachloroethane in humans or animals. Determination of the effect of chronic-duration dermal administration of 1,1,2,2-tetrachloroethane to animals would be methodologically problematic due to inadvertent oral and/or inhalation exposures. Additionally, chronic-duration dermal exposure is unlikely for humans. Therefore, chronic-duration studies by this route are not recommended.

Since humans are most likely to be exposed via the inhalation or oral routes, long-term animal studies that include a range of exposure levels for inhalation and oral exposure should be designed to better assess

cancer and noncancer end points. Such studies would provide support to existing oral cancer data and facilitate derivation of an inhalation unit risk as well as chronic-duration inhalation and oral MRLs for 1,1,2,2-tetrachloroethane.

Genotoxicity. Information on the *in vivo* genotoxic effects of 1,1,2,2-tetrachloroethane is lacking for humans and limited for animals (see Table 3-4), although there are a number of *in vitro* tests of the mutagenicity of 1,1,2,2-tetrachloroethane (see Table 3-3). This type of data is not sufficient to determine if 1,1,2,2-tetrachloroethane is genotoxic in humans. *In vivo* testing and *in vitro* testing on human cell lines would help determine if 1,1,2,2-tetrachloroethane is genotoxic in humans. The known metabolism of 1,1,2,2-tetrachloroethane to reactive acid chlorides and/or free radical products suggests that genotoxic effects in humans and other mammals are possible.

Reproductive Toxicity. There were no human reproductive toxicity studies reported for 1,1,2,2-tetrachloroethane. The reproductive toxicity of 1,1,2,2-tetrachloroethane has not been adequately evaluated in animals. After acute-duration inhalation exposure at 6,310 ppm, no effects on the testes, epididymes, ovaries, or uteruses were found in rats (NIOSH 1978). Similarly, an intermediate-duration study by inhalation (Horiuchi et al. 1962) reported no effects on the testes in one monkey. Inhalation exposure to 1.9 ppm for 4 hours/day for 9 months had no reproductive effects in male mice; when mated with unexposed females, there were no significant changes in percentage of females having offspring, littering times, or offspring numbers, sex ratio, birth weight, or postnatal survival (Schmidt et al. 1972). The effect of oral exposure on male or female reproductive function has not been tested. Male rats that were exposed to 1,1,2,2-tetrachloroethane in the diet for 14 weeks had no adverse changes in sperm number or motility at 80 mg/kg/day (highest tested dose), although minimal to moderate atrophy of the testicular germinal epithelium, prostate gland, and seminal vesicle occurred at 320 mg/kg/day (NTP 2004). Reproductive effects in similarly exposed female rats included estrus alterations and minimal to mild uterine atrophy at 170 mg/kg/day, and clitoral gland atrophy and ovarian interstitial cell cytoplasmic alterations at 320 mg/kg/day (NTP 2004). Body weight loss at 320 mg/kg/day and reduced body weight gain at lower dose levels could have contributed to the effects observed in the male and female rats. There were no clear effects on histology of male or female reproductive tissues, sperm indices, or estrus cycle in mice exposed to dietary doses as high as 1,360–1,400 mg/kg/day for 14 weeks (NTP 2004). Chronic-duration oral administration of 1,1,2,2-tetrachloroethane to rats and mice caused no increase in histological alterations in reproductive organs (NCI 1978). A well designed reproductive toxicity study in laboratory animals would serve to adequately assess the potential for 1,1,2,2-tetrachloroethane-induced reproductive toxicity.

Developmental Toxicity. Information regarding the potential for 1,1,2,2-tetrachloroethane-induced developmental toxicity following inhalation or oral exposure is restricted to a single rat study by the inhalation exposure route (Schmidt et al. 1972) and one set of rat (NTP 1991a) and mouse (NTP 1991b) studies using oral administration. In the inhalation study, male rats were exposed to 1,1,2,2-tetrachloroethane and mated with unexposed females, and the F_1 generation was observed for 12 weeks. No effects on the number of offspring per litter, neonatal body weight, offspring viability, or sex ratios were observed. No gross malformations in offspring were detected (Schmidt et al. 1972). In the oral (dietary) rat study, completely resorbed litters and significantly decreased fetal weights were reported (NTP 1991a). However, because the oral treatment also resulted in dose-related significantly reduced food consumption and serious maternal body weight effects, a direct treatment-related developmental effect could not be discerned. Fetuses were not examined for malformations. In the oral (dietary) mouse study (NTP 1991b), the lowest exposure level (0.5% in the food; dose of approximately 987 mg/kg/day) resulted in 14% decreased maternal body weight gain during the treatment period, but there were no indications of developmental effects with respect to number of implantation sites, number of resorptions, numbers of dead and live fetuses, or gravid uterine weight. Exposure at higher levels resulted in maternal death, precluding assessment of treatment-related developmental toxicity at the higher doses.

Additional well-designed developmental toxicity studies that include comprehensive assessment of developmental toxicity end points at exposure levels below those resulting in serious maternal toxicity would provide a better understanding of the potential developmental toxicity of 1,1,2,2-tetrachloroethane.

Immunotoxicity. There is a lack of useful information on the effects of 1,1,2,2-tetrachloroethane on the immune system in humans, and the information available from animal studies in this area is very limited. The human studies were dated, lacked information on the dose received and duration of exposure, and reported only gross effects on the appearance of the spleen following acute ingestion (Coyer 1944; Elliott 1933; Hepple 1927). No histopathological changes were noted in the spleens of rats that inhaled 100 ppm 1,1,2,2-tetrachloroethane for 6 hours (Deguchi 1972). In a 14-week dietary study of rats, pigmentation of the spleen was increased in males receiving 1,1,2,2-tetrachloroethane at doses ≥80 mg/kg/day and in females receiving doses ≥170 mg/kg/day; high incidences (70–100%) of atrophy in the spleen (red pulp and lymphoid follicle) of both sexes were noted at 320 mg/kg/day (NTP 2004). No gross or histological alterations were seen in the spleen or lymph nodes of rats and mice exposed to 1,1,2,2-tetrachloroethane at doses up to 284 mg/kg/day for 78 weeks. Rabbits intermittently exposed to 1.5 ppm of 1,1,2,2-tetrachloroethane vapor for 8 months and then immunized with a typhoid vaccine

showed a decrease in titers and an increase in the electrophoretic mobility of the specific antibodies (Shmuter 1977). Since immunological end points are known to be very sensitive indicators of the toxicity of many chemicals, a battery of immunological function tests in animals would be helpful in clarifying whether 1,1,2,2-tetrachloroethane is an immunotoxicant.

There are no data on sensitization as a result of exposure to 1,1,2,2-tetrachloroethane by any route in humans or animals. Dermal sensitization tests in animals may be useful based on potential for dermal exposure from soil and water near hazardous waste sites.

Neurotoxicity. Information on the neurotoxicity of acute inhalation exposure to 1,1,2,2-tetrachloroethane in humans comes from a poorly reported experimental study in which two volunteers self-inhaled various concentrations of the chemical for up to 30 minutes (Lehmann and Schmidt-Kehl 1936). The results of this study suggest that 3 ppm was the odor detection threshold, 13 ppm was tolerated without effect for 10 minutes, and 146 ppm for 30 minutes or 336 ppm for 10 minutes caused irritation of the mucous membranes, pressure in the head, vertigo, and fatigue. Other early human reports similarly found that clinical signs of high-dose acute inhalation exposure to 1,1,2,2-tetrachloroethane include drowsiness, nausea, headache, and weakness, and at extremely high concentrations, unconsciousness and respiratory failure (Coyer 1944; Hamilton 1917). In animals, signs of acute central nervous system toxicity (e.g., incoordination, loss of reflexes, labored respiration, prostration, and loss of consciousness) typically proceeded death, which occurred at concentrations of 1,000–1,253 ppm for 4–6 hours in rats (Carpenter et al. 1949; Schmidt et al. 1980b), 1,168–5,900 ppm for 1.5–3 hours in mice (Horiuchi et al. 1962; Pantelitsch 1933), and 5,050–6,310 ppm for 30 minutes in rats and guinea pigs (NIOSH 1978). Exposure to 576 ppm for 30 minutes caused reduced activity and alertness in rats and guinea pigs (NIOSH 1978). The effective concentration for a 50% decrease in spontaneous motor activity in rats was 360 ppm for a 6-hour exposure (Horvath and Frantik 1973). Intermediate-duration inhalation exposure to intermittent high concentrations of 1,1,2,2-tetrachloroethane caused neurological effects that are essentially acute in nature. Rats that were exposed to 9,000 ppm for 2 hours/day 2–3 times/week for 29 days became hyperactive within the first few minutes of each exposure, followed by ataxic gait within approximately 20 minutes and eventual near-complete loss of consciousness within 1–1.5 hours (Horiuchi et al. 1962). A monkey that was exposed to 1,974 ppm for 2 hours/day, 6 days/week for 190 exposures in 9 months developed, beginning at the fifteenth exposure, near-complete unconsciousness for 20–60 minutes after each exposure (Horiuchi et al. 1962).

Information on the neurotoxicity of oral exposure to 1,1,2,2-tetrachloroethane in humans is available from several case reports. People who intentionally ingested lethal amounts usually lost consciousness within approximately 1 hour and died 3–20 hours postingestion (Elliott 1933; Forbes 1943; Hepple 1927; Lilliman 1949; Mant 1953; Sherman 1953). No deaths occurred in 11 patients who were accidentally given an estimated oral dose of 68–118 mg/kg as medicinal treatment for hookworm, although they experienced loss of consciousness and other clinical signs of narcosis that included shallow breathing, faint pulse, and pronounced lowering of blood pressure (Sherman 1953; Ward 1955). In animals, lethargy and central nervous system depression occurred in rats gavaged with 270–300 mg/kg/day for 1–12 days (Hanley et al. 1988; NTP 1993a, 1993b) or 208 mg/kg/day for 21 days (NTP 1996). Information on neurological effects of lower acute oral doses is limited to a poorly reported rat study in which a single gavage dose of 100 mg/kg caused ataxia and 50 mg/kg caused decreased passive avoidance to an electric shock, possibly due to an increased threshold of shock perception due to a subtle anesthetic effect (Wolff 1978). No clinical signs of neurotoxicity were observed in 14-week dietary studies in which rats and mice were exposed to doses as high as 320 and 1,400 mg/kg/day, respectively (NTP 2004). Comprehensive neurological evaluations (functional observational batteries) in the 14-week studies showed no effects in either species, although 80 mg/kg/day was the highest tested dose in the rats.

Tests to show the site of action would be helpful in determining exactly how 1,1,2,2-tetrachloroethane affects the nervous system of humans.

Epidemiological and Human Dosimetry Studies. An epidemiological study was conducted analyzing the cancer mortality of service men exposed to 1,1,2,2-tetrachloroethane during World War II (Norman et al. 1981). The exposure was presumed to be mostly by inhalation, but dermal exposure was also possible and precise dosimetry was unknown. Over 1,000 subjects were used in each of the control and exposed groups. There were only very slightly elevated incidences (not statistically significant) of cancer of the genital organs, as well as leukemia and lymphoma. It is possible that humans who live near hazardous waste sites may be exposed to this substance in the air, water, and soil. Additional epidemiological studies examining neurological effects and effects on the liver and kidney would be helpful to better define the effects of chronic-duration low-level exposures to 1,1,2,2-tetrachloroethane in humans.

Biomarkers of Exposure and Effect.

Exposure. Since the metabolites of 1,1,2,2-tetrachloroethane are known, and can be measured in the urine of rats (Yllner 1971), it is possible to measure these metabolites in urine to see if a person has been exposed to 1,1,2,2-tetrachloroethane. However, these metabolites are common to several types of chlorinated ethanes and would not be specific for exposure to 1,1,2,2-tetrachloroethane. Also, 1,1,2,2-tetrachloroethane is metabolized and excreted rather quickly, and the test might only indicate whether the person had been exposed in the last few days. It would be useful to ascertain if measurements of parent compounds and metabolites in excreta or in biopsy samples (e.g., adipose) could be used to quantitate the body burden associated with exposures to known concentrations of 1,1,2,2-tetrachloroethane.

Effect. 1,1,2,2-Tetrachloroethane may cause liver damage. In cases where humans have been exposed to high levels of 1,1,2,2-tetrachloroethane, it may be possible to correlate urinary metabolites with serum indicators of liver malfunction. Although this is a data need, the metabolites would not be specific for 1,1,2,2-tetrachloroethane.

Absorption, Distribution, Metabolism, and Excretion. In both humans (Lehmann and Schmidt-Kehl 1936; Morgan et al. 1970) and laboratory animals (Hanley et al. 1988), 1,1,2,2-tetrachloroethane is well absorbed after acute-duration inhalation exposure. While studies in which the quantitation of absorption following oral exposure was measured in humans were not available, the profound effects following ingestion of 1,1,2,2-tetrachloroethane indicate that appreciable amounts are absorbed by this route also. This is consistent with the data from animal studies, which indicate that oral doses are mostly absorbed (Milman et al. 1984; Mitoma et al. 1985). No studies were located regarding absorption following dermal exposure in humans. Only limited information was found regarding the distribution of 1,1,2,2-tetrachloroethane following inhalation, oral, or dermal exposure in humans and animals. High levels of binding of 1,1,2,2-tetrachloroethane equivalents to hepatic proteins were found in rats and mice following oral dosing. 1,1,2,2-Tetrachloroethane is extensively metabolized in animals and excreted chiefly as metabolites in urine and breath (Ikeda and Ohtsuji 1972; Mitoma et al. 1985; Yllner 1971).

Modern techniques employing mass spectrometry and/or nuclear magnetic resonance coupled with high resolution chromatographic methods to provide unambiguous structural identification were used only in a few recent studies. Unfortunately, the emphasis in those studies was the elucidation of particular mechanisms of reactive intermediate metabolite formation. A more broadly based evaluation of the

formation of nontoxic or less toxic metabolites was not fully pursued. Fuller studies, such as that of Yllner (1971), employed less rigorous characterization methodology and structural assignments of metabolites made are not definitive. Metabolic pathways, and rates and patterns of distribution and excretion may be different following oral exposure than following inhalation or dermal exposure. Differences in metabolism may account for differences in toxicity following exposure by these routes. Thus, further studies in animals of the rate and extent of absorption and excretion, of distribution, and of metabolism following exposure by all three routes, and *in vitro* studies to elucidate metabolic pathways, would provide the information to fully characterize the pharmacokinetics of 1,1,2,2-tetrachloroethane in animals.

Comparative Toxicokinetics. PBPK modeling of the kinetics of 1,1,2,2-tetrachloroethane in rats exposed by inhalation has been performed by Gargas and Andersen (1989). Data on comparative toxicokinetics in rats and mice exposed to 1,1,2,2-tetrachloroethane by intermediate-duration inhalation exposure are available (Mitoma et al. 1985). Mice metabolized 1,1,2,2-tetrachloroethane at roughly twice the rate of rats given similar doses, and the amount of protein bound equivalents were higher. Further studies in these and other species may provide information to account for differences in toxicity among animal species. There are limited human metabolism and excretion data. A single study has shown that 3% of inhaled 1,1,2,2-tetrachloroethane was excreted in the breath, and that the urinary excretion rate was 0.015% absorbed dose/minute (Morgan et al. 1970). Analysis of levels of metabolites in the urine of people with known exposure is a data need that could provide knowledge of metabolic pathways in humans. Additionally, biochemically viable human tissues, including liver, are now routinely available for metabolism studies. In this way, the metabolism of 1,1,2,2-tetrachloroethane in humans of differing genetic background and life style (e.g., consumers of alcohol or tobacco) can be determined in microsomes and precision-cut tissue slices. This information may allow accurate prediction of the metabolism of 1,1,2,2-tetrachloroethane in humans. Qualitative comparisons of human metabolites with those of animals could help to fill a data need by identifying the most appropriate animal species to serve as a model for predicting toxic effects in humans and studying the mechanism of action.

Methods for Reducing Toxic Effects. No studies were located regarding the mechanism of absorption in humans or animals after inhalation, oral, or dermal exposure to 1,1,2,2-tetrachloroethane. Carbon and castor oil have been shown to increase the survival times in rats administered oral doses of 1,1,2,2-tetrachloroethane (Laass 1973a, 1973b, 1974a, 1974b), but data are needed on the actual mechanisms of absorption and distribution of this chemical in the body. 1,1,2,2-Tetrachloroethane is metabolized to reactive toxic acyl chlorides and to free radicals. No treatments were described that

mitigate the health effects that result from exposure to the compound. However, alcohol and acetone, inducers of cytochrome P-450 isoenzyme 2E1 increased the metabolism of 1,1,2,2-tetrachloroethane and intensified the toxic effects (Gohlke and Schmidt 1972; Sato et al. 1980). Studies to determine methods for blocking the absorption or increasing the excretion of 1,1,2,2-tetrachloroethane would be helpful to better define methods to reduce the toxic effects of the chemical.

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

No information was located regarding potential age-related differences in susceptibility to 1,1,2,2-tetrachloroethane in humans or animals. A well-designed animal study would provide valuable information regarding the potential for age-related susceptibility to 1,1,2,2-tetrachloroethane.

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

3.12.3 Ongoing Studies

No ongoing studies pertaining to 1,1,2,2-tetrachloroethane were located in a search of the Federal Research in Progress database (FEDRIP 2006).