2. HEALTH EFFECTS

2.1 INTRODUCTION

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

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure 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 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 or exposure levels below which no adverse effects 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 tetrachloroethylene are indicated in Tables 2-B and 2-3 and Figures 2-l and 2-2.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for tetrachloroethylene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specific duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specified duration within a given route of exposure. MRLs are based on noncancer health effects only and do not reflect a consideration of carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques, Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be Iprotective for health effects that are delayed in development or result from repeated acute insults, such as hypersensitivity reactions, asthma, or

chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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

2.2.1 InhalationExposure

2.2.1.1 Death

At high vapor concentrations, tetrachloroethylene is both a potent anesthetic agent and a cardiac epinephrine sensitizer. Therefore, sudden death resulting from acute exposure to anesthetic vapor concentrations is presumed to result from either excessive depression of the respiratory center or the onset of a fatal cardiac arrhythmia induced by epinephrine sensitization. Human deaths caused by tetrachloroethylene inhalation have been reported. A 33-year-old man was found unconscious after performing work on a plugged line in a commercial dry cleaning establishment and died on the way to the hospital (Lukaszewski 1979). Exposure to tetrachloroethylene was presumably by inhalation since 'an autopsy revealed no tetrachloroethylene in the stomach contents but high levels of the compound in the blood and brain (4.4 mg/l00 mL and 36 mg/l00 g, respectively). In another report, a 53-year-old male dry cleaner died after being overcome by tetrachloroethylene fumes (Levine et al. 1981). Tetrachloroethylene concentrations were 66 mg/L in blood, and 79, 31, and 46 mg/kg in the brain, heart, and lungs, respectively, of a 2-year-old boy found dead 1.5 hours after he was placed in his room with curtains that had been incorrectly dry cleaned in a coin-operated dry cleaning machine (Gamier et al. 1996). In these reports, the level of tetrachloroethylene exposure was not reported.

Epidemiological studies of workers occupationally exposed to tetrachloroethylene have not consistently shown increased mortality. Although total mortality was not increased, Blair et al. (1979) found increased mortality from cancers of the lungs, cervix, uterus, and skin. This study is limited by a lack of control for alcohol and tobacco consumption. Other studies have not shown significantly increased mortality in workers occupationally exposed to tetrachloroethylene (Blair et al. 1990; Brown and Kaplan 1987; Katz and Jowett 1981; Spirtas et al. 1991).

2. HEALTH EFFECTS

There were no major differences between mice and rats in susceptibility to lethal effects of tetrachloroethylene following acute- or intermediate-duration exposure. In addition, no sex differences in response were detected. A 4-hour inhalation LC_{50} of 5,200 ppm for female albino mice has been reported. Data used to derive the LC_{50} show that the highest concentration of tetrachloroethylene for a 4-hour exposure that was not lethal to mice was 2,450 ppm; the lowest concentration that caused death was 3,000 ppm (Friberg et al. 1953). In another study, the highest concentration for a 4-hour exposure that did not result in death in $B6C3F_1$ mice or Fischer-344 rats of both sexes was 2,445 ppm; the lowest concentrations causing death were 2,613 ppm in mice and 3,786 ppm in rats (NTP 1986). A single 10- or 14-hour exposure of rats to 2,000 ppm and a single 4-hour exposure to 3,000 ppm did not produce death, while death occurred with exposure to 3,000 ppm for 5 hours or longer (Rowe et al. 1952).

Rats and mice were exposed to tetrachloroethylene by inhalation for 14 days or 13 weeks (NTP 1986). In the 14-day study, mortality occurred in rats exposed to 1,750 ppm tetrachloroethylene but not in mice. Compound-related mortality did not occur in either species at exposure concentrations of 875 ppm or lower. In the 13-week inhalation study, mortality occurred in rats and mice exposed to 1,600 ppm tetrachloroethylene but not to concentrations of 800 ppm or lower.

Mortality in rats exposed to 400 ppm tetrachloroethylene and mice exposed to 100 or 200 ppm tetrachloroethylene by inhalation in a 103-week carcinogenesis bioassay was a result of compoundrelated lesions and neoplasms (NTP 1986). This study is discussed in Sections 2.2.1.2 and 2.2.1.8.

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

2.2.1.2 Systemic Effects

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

No studies were located regarding dermal effects in humans or animals after inhalation exposure to tetrachloroethylene.

TABLE 2-1. Levels of Significant Exposure to Tetrachloroethylene - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
ACUTE EXPOSURE									
Death									
1	Rat (Fischer- 344)	4 hr					3786	(5/10 rats died)	NTP 1986
2	Rat (Fischer- 344)	2 wk 5d/wk 6hr/d					1750	(5/10 rats died)	NTP 1986
3	Mouse (NS)	4 hr					5200 F	(LC_{50})	Friberg et al. 1953
4	Mouse (B6C3F1)	4 hr					2613 F	(2/5 died)	NTP 1986
Systemic									
5	Human	3 hr	Cardio	87					Ogata et al. 1971
6	Human	0.05-2 hr	Resp	106	216	(irritation)	930	(severe irritation tolerated for ≤2 minutes)	Rowe et al. 1952
			Ocular		106	(slight ocular irritation)	930	(severe irritation tolerated for ≤2 minutes)	

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
7	Human	5 d 7.5hr/d	Resp	150 M			Stewart et al. 1981
			Cardio	150 M			
			Hemato	150 M			
			Hepatic	150 M			
			Renal	150 M			
8	Rat (Fischer- 344)	2 wk 5d/wk 6hr/d	Bd Wt	875		1750 M (body weight 28% lower than controls)	NTP 1986
9	Rat (Fischer- 344)	14 d 6hr/d	Hepatic		400 (hypertrophy)		Odum et al. 1988
			Renal	400			
10	Mouse (ddY)	5d 6hr/d	Resp		300 M (epithelial degeneration of olfactory mucosa, dilation of Bowman's glands, atrophy of olfactory nerves)		Aoki et al. 1994
11	Mouse (NS)	4 hr	Hepatic		200 F (fatty degeneration)		Kylin et al. 1963

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
12	Mouse (B6C3F1)	2 wk 5d/wk 6hr/d	Hepatic	425	875 (hepatic vacuolization)		NTP 1986
			Bd Wt	1750			
13	Mouse (B6C3F1)	14 d 6hr/d	Hepatic		400 (peroxisomal proliferation; fatty changes)		Odum et al. 1988
			Renal	400			
14	Dog (Beagle)	10 min	Resp	5000	10000 (upper respiratory tract irritation)		Reinhardt et al. 1973
			Cardio	10000			
Neurological							
15	Human	4 d 4hr/d		10 M	50 M (increased latency of pattern reversal visual-evoked potentials)		Altmann et al. 1990
16	Human	4 d 4hr/d		10[b]	50 M (increased latency of pattern reversal visual-evoked potential, significant performance deficits for vigilance and eye-hand coordination)		Altmann et al. 1992

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

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
17	Human	<3 hr		500	1000	(mood/personality changes)	2000	(anesthesia)	Carpenter 1937
18	Human	5 d 7.5hr/d		20	100	(cerebral cortical depression)			Hake and Stewart 1977; Stewart et al. 1981
19	Human	3 hr		87					Ogata et al. 1971
20	Human	0.05-2 hr		106	216	(dizziness/sleepiness)	280	(incoordination)	Rowe et al. 1952
21	Human	5 d 7hr/d			101	(mood/personality changes)			Stewart et al. 1970
22	Rat (Fischer- 344)	2 wk 5d/wk 6hr/d		875			1750	(hypoactivity; ataxia)	NTP 1986

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
23	Rat (Sprague-Dawley)	4 d 6hr/d			200	(increased open-field behavior, i.e., ambulation)			Savolainen et al. 1977
24	Mouse (B6C3F1)	2 wk 5d/wk 6hr/d		875			1750	(anesthesia)	NTP 1986
25	Mouse (B6C3F1)	4 hr					2328	(anesthesia)	NTP 1986
	Developmental								
26	Rat (Sprague-Dawley)	Gd 14-20 7hr/d		100	900	(transient decreased performance ascent test; decreased brain acetylcholinesterase; increased open-field activity)			Nelson et al. 1980
27	Rat (Sprague-Dawley)	Gd 6-15 7hr/d					300	(increased fetal resorptions)	Schwetz et al. 1975

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
28	Mouse (Swiss-Webster)	Gd 6-15 7hr/d			300	(decreased fetal weight; delayed ossification)			Schwetz et al. 1975
INTERMEDIATE EXPOSURE									
Death									
29	Rat (Fischer- 344)	13 wk 5d/wk 6hr/d					1600	(11/20 rats died)	NTP 1986
30	Mouse (B6C3F1)	13 wk 5d/wk 6hr/d					1600	(6/10 mice died)	NTP 1986
Systemic									
31	Rat (NS)	7 mo 5d/wk 8hr/d	Hepatic	70	230	(decreased glycogen)			Carpenter 1937
			Renal	230	470	(mild nephropathy)			
32	Rat (Fischer- 344)	28 d 6hr/d	Renal	400					Green et al. 1990

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
33	Rat (Sprague-Dawley)	90 d	Hepatic		320 M (increased liver weights)		Kyrklund et al. 1990
34	Rat (Fischer- 344)	13 wk 5d/wk 6hr/d	Resp	800	1600 (lung congestion)		NTP 1986
			Hepatic	200	400 (liver congestion)		
			Bd Wt	800		1600 M (body weight 20% lower than controls)	
35	Rat (Fischer- 344)	28 d 6hr/d	Hepatic		200 (hypertrophy)		Odum et al. 1988
			Renal	400			
36	Rat (Fischer- 344)	21 d 6hr/d	Hepatic		400 (hypertrophy)		Odum et al. 1988
			Renal	400			

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

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
37	Rat (Alpk:APfSD)	19wk: 11 wk, 5d/wk 6hr/d; daily during mating/ lactation	Hepatic	1000			Tinston 1995
			Renal	300	1000 M (minimal chronic progressive glomerulonephropathy; increased pleomorphism within proximal tubular nuclei)		
			Bd Wt	1000			
38	Mouse (B6C3F1)	28 d 6hr/d	Renal	400			Green et al. 1990
39	Mouse (NMRI)	30 d 24hr/d	Hepatic		9 (liver enlargement and vacuolization of hepatocytes)		Kjellstrand et al. 1984
			Bd Wt	150			
40	Mouse (NS)	8 wk 6d/wk 4hr/d	Hepatic		200 F (fatty degeneration)		Kylin et al. 1965
			Renal	200 F			
			Bd Wt	200 F			

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
41	Mouse (B6C3F1)	13 wk 5d/wk 6hr/d	Hepatic	200			400	(centrilobular liver necrosis)	NTP 1986
			Renal	100	200	(karyomegaly of renal tubular epithelial cells)			
			Bd Wt	1600					
42	Mouse (B6C3F1)	28 d 6hr/d	Hepatic		200	(peroxisomal proliferation; fatty changes)			Odum et al. 1988
			Renal	400					
43	Mouse (B6C3F1)	21 d 6hr/d	Hepatic		400	(peroxisomal proliferation; fatty changes)			Odum et al. 1988
			Renal	400					
	Neurological								
44	Rat (Sprague-Dawley)	30 or 90 d			320 M	(changes in the fatty acid composition of the brain)			Kyrklund et al. 1988, 1990

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
45	Rat (Alpk:APfSD)	19wk: 11 wk, 5d/wk 6hr/d; daily during mating/ lactation		300	1000 (decreased activity, reduced response to sound, increased salivation, piloerection)		Tinston 1995
46	Rat (Sprague-Dawley)	4 or 12 wk		300 M	600 M (decreased brain weight; decrease in cytoskeletal proteins)		Wang et al. 1993
47	Gerbil (Mongolian)	90 d 24hr/d			60 (decreased DNA levels in frontal cortex)		Karlsson et al. 1987
48	Gerbil (Mongolian)	3 mo 24hr/d			60 (decreased DNA content in the frontal cerebral cortex)		Rosengren et al. 1986

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Reproductive							
49	Rat (Alpk:APfSD)	19wk: 11 wk, 5d/wk 6hr/d; daily during mating/ lactation		300		1000 (significant reduction in the number of live born pups; decreased pup survival during lactation)	Tinston 1995
CHRONIC EXPOSURE							
Death							
50	Rat (Fischer- 344)	103 wk 5d/wk 6hr/d				400 M (reduced survival)	Mennear et al. 1986; NTP 1986
51	Mouse (B6C3F1)	103 wk 5d/wk 6hr/d				100 M (reduced survival)	Mennear et al. 1986; NTP 1986
Systemic							
52	Human	20 yr average	Hepatic		15.8 (diffuse parenchymal changes revealed by ultrasound)		Brodkin et al. 1995

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
53	Human	1-120 mo occupational	Hemato	20			Cai et al. 1991
			Hepatic	20			
			Renal	20			
54	Human	14 yr occupational	Renal		10 (increased urine β-glucuronidase and lysozyme)		Franchini et al. 1983
55	Human	6 yr occupational	Hepatic	21			Lauwerys et al. 1983
			Renal	21			
56	Human	10 yr average occupational	Renal		15 (nephrotoxicity)		Mutti et al. 1992
57	Human	12 yr average occupational	Renal	14			Solet and Robins 1991

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

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
58	Human	9 yr occupa-tional	Renal		23 F (increased urinary lysozyme activity)		Vyskocil et al. 1990
59	Rat (Fischer- 344)	103 wk 5d/wk 6hr/d	Resp		200 (thrombosis; squamous metaplasia of nasal cavity)		Mennear et al. 1986; NTP 1986
			Gastro	200	400 M (forestomach ulcers)		
			Renal		200 (renal tubular karyomegaly)		
			Endocr		200 M (adrenal medullary hyperplasia)		
			Bd Wt	400			
60	Mouse (B6C3F1)	103 wk 5d/wk 6hr/d	Resp		100 (acute passive congestion of the lungs)		Mennear et al. 1986; NTP 1986
			Hepatic		100 (hepatocellular degeneration)		
			Renal		100 (nephrosis)		
			Bd Wt	200			

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	Neurological						
61	Human	1-30 yr		0.2			Altmann et al. 1995
62	Human	1-120 mo occupational			20 (increase in subjective symptoms including dizziness)		Cai et al. 1991
63	Human	106 mo average			7.3 (color vision loss)		Cavalleri et al. 1994
64	Human	10 yr occupational			15[c] F (increased reaction times)		Ferroni et al. 1992
65	Human	6 yr occupational		21			Lauwerys et al. 1983
66	Human	occupational		15.3 M			Nakatsuka et al. 1992

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

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
67	Gerbil (Mongolian)	12 mo 24hr/d			120 M (phospholipid changes in the cerebral cortex and hippocampus)		Kyrklund et al. 1984
	Cancer						
68	Rat (Fischer- 344)	103 wk 5d/wk 6hr/d				200 (CEL: mononuclear cell leukemia)	Mennear et al. 1986; NTP 1986
69	Mouse (B6C3F1)	103 wk 5d/wk 6hr/d				100 (CEL: hepatocellular carcinoma)	Mennear et al. 1986; NTP 1986

[a]The numbers correspond to entries in Figure 2-1.

[b]The acute-duration inhalation minimal risk level (MRL) of 0.2 ppm was calculated from this concentration by expanding to continuous exposure (4/24 hours) and dividing by an uncertainty factor of 10 (for human variablility).

[c]The chronic-duration inhalation MRL of 0.04 ppm was calculated from this concentration by expanding to continuous exposure (8/24 hours, 5/7 days) and dividing by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); DNA = deoxyribonucleic acid; Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day; Hemato = hematological; hr = hour(s); LC_{50} = 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; Resp = respiratory; wk = week(s); yr = yr(s)

Figure 2-1. Levels of Significant Exposure to Tetrachloroethylene - Inhalation

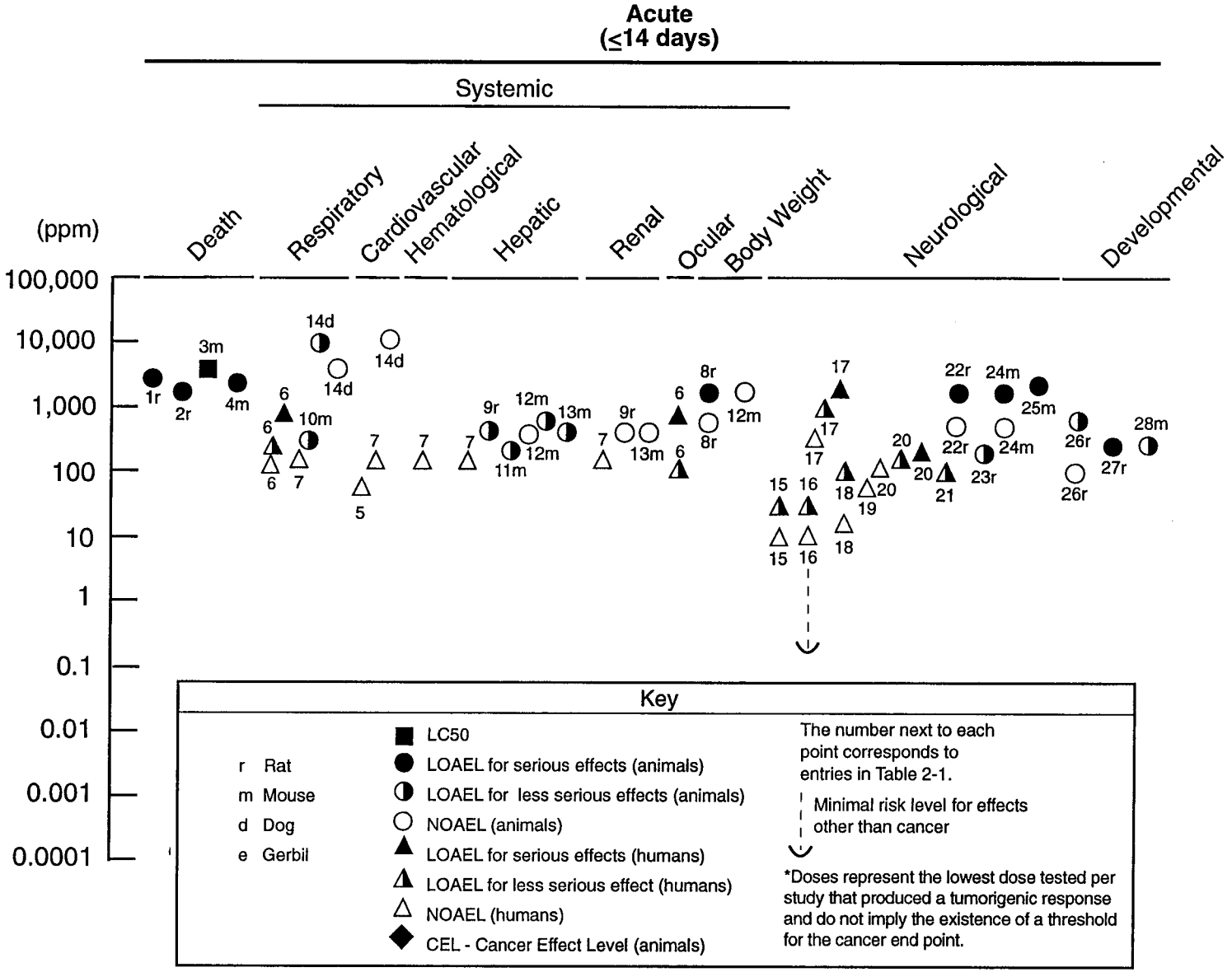


Figure 2-1. Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

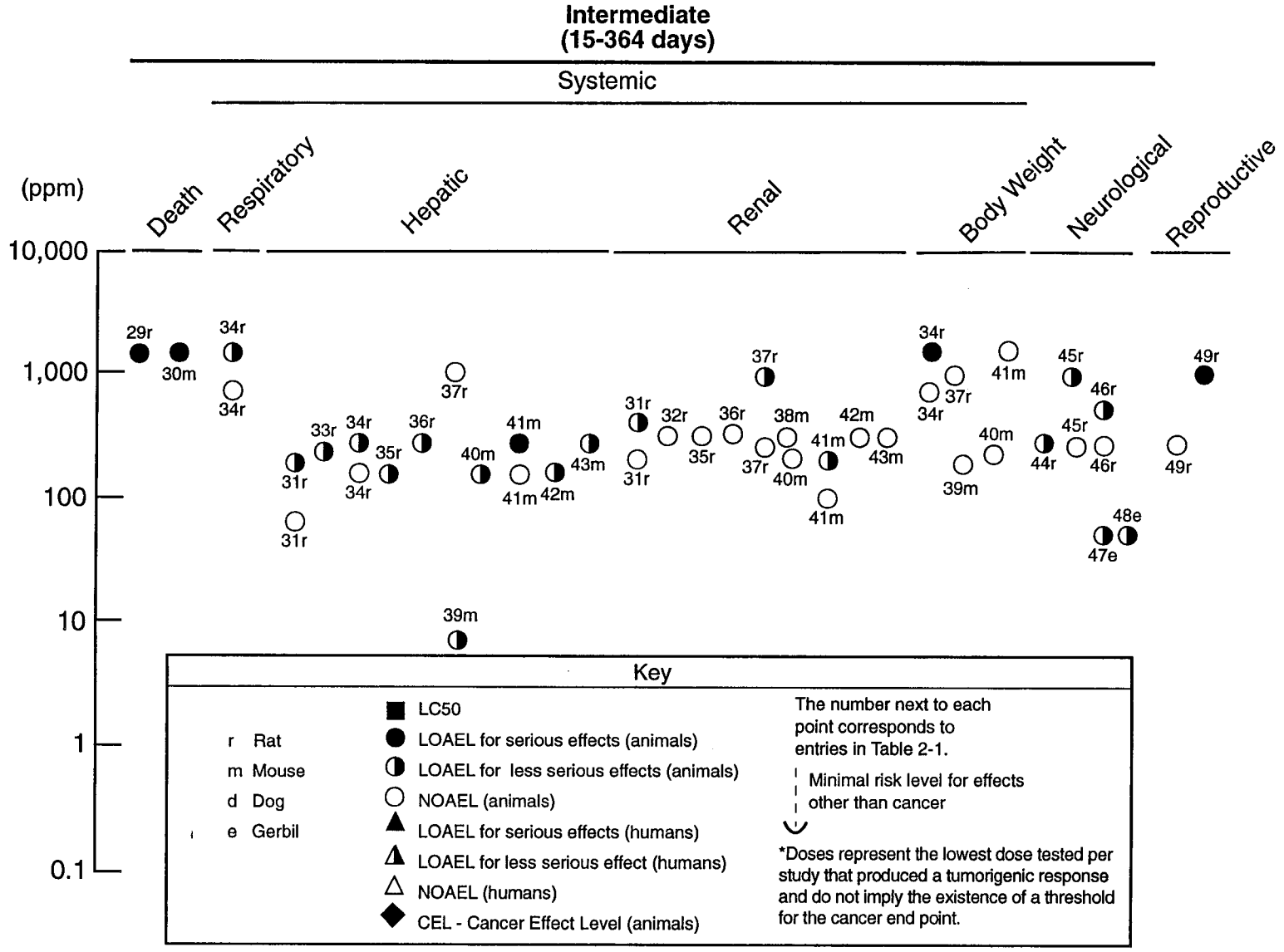
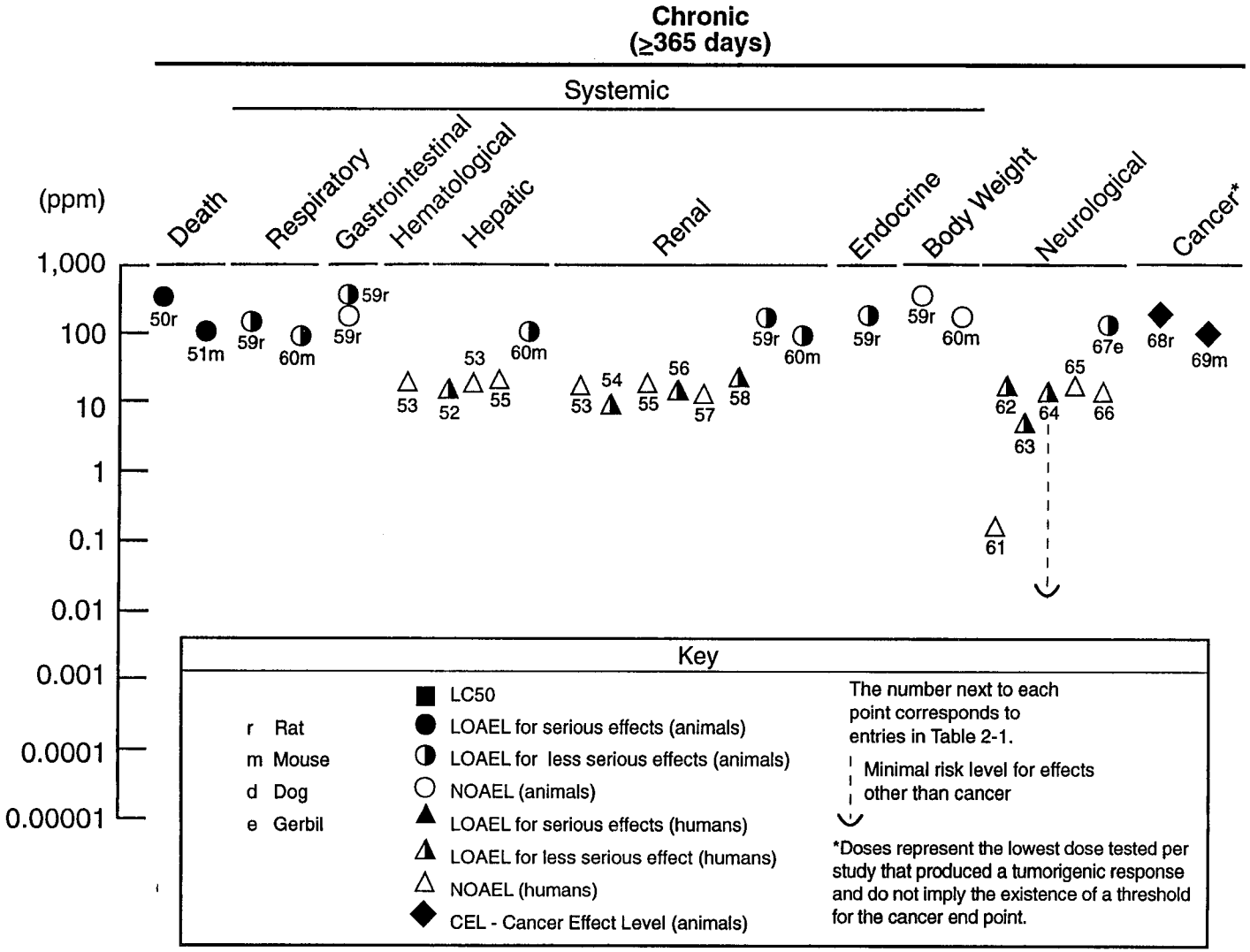


Figure 2-1. Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)



2. HEALTH EFFECTS

Respiratory Effects. Intense irritation of the upper respiratory tract was reported in volunteers exposed to high concentrations (>l,000 ppm) of tetrachloroethylene (Carpenter 1937; Rowe et al. 1952). These older acute inhalation studies in humans were limited by a small number of experimental volunteer subjects, incomplete characterization of subjects, variable concentrations of tetrachloroethylene, and reliance on symptomatology, which are subjective data. Despite these limitations, some of the end points identified at high concentrations provide important toxicological data on tetrachloroethylene effects in humans. Respiratory irritation (irritation of the nasal passages) was reported in workers exposed to tetrachloroethylene vapors at levels of 232-385 ppm in a degreasing operation (Coler and Rossmiller 1953) and in volunteers exposed to concentrations as low as 216 ppm for 45 minutes to 2 hours (Rowe et al. 1952). Volunteers exposed to concentrations as high as 1,060 ppm could tolerate no more than l-2 minutes of exposure before leaving the chamber (Rowe et al. 1952). Pulmonary edema occurred in a case of accidental exposure although this lesion may have been a secondary finding (Pate1 et al. 1973).

An experimental human exposure study titled *Tetrachloroethylene: Development of a biologic standard for the industrial worker by breath analysis,* completed by Stewart and colleagues, was first published by NIOSH in 1974. This publication can now be obtained from the National Technical Information Service (NTIS) with a 1981 date, and is cited as Stewart et al. (1981) throughout this Profile. In this study, four male volunteers were sequentially exposed to 0, 20, 100, or 150 ppm tetrachloroethylene vapor for 7.5 hours/day, 5 days/week (Stewart et al. 1981). The men were exposed to each concentration for 1 week. Once each week, pulmonary function was assessed at both rest and during two levels of exercise with forced maximum expiratory flow measurements, while alveolarcapillary gas exchange was measured by single breath carbon monoxide diffusion. The exposures to tetrachloroethylene at these vapor concentrations and time intervals had no effect on the pulmonary function measurements.

A l0-minute exposure of dogs to tetrachloroethylene at 10,000 ppm resulted in upper respiratory irritation (Reinhardt et al. 1973). This effect was not observed at 5,000 ppm. In a study designed to examine the effects of tetrachloroethylene on the respiratory mucosa, epithelial degeneration was observed in mice exposed to tetrachloroethylene at 300 ppm for 6 hours/day for 5 days (Aoki et al. 1994). The degeneration was more severe in the olfactory mucosa compared to other sites in the respiratory mucosa. Dilation of Bowman's glands and atrophy of olfactory nerves were also observed.

2. HEALTH EFFECTS

In a study in mice evaluating susceptibility to infection from inhaled *Streptococcus zooepidemicus* and pulmonary bacteriocidal activity to inhaled *Klebsiella pneumoniae*, exposure to 50 ppm tetrachloroethylene for 3 hours increased susceptibility to both bacteria. The primary adverse effect of tetrachloroethylene was hypothesized to be on alveolar macrophage activity, although other pulmonary and extrapulmonary defense mechanisms may also have been involved (Aranyi et al. 1986). However, because of variability in control group mortality and the lack of evaluation of specific immunological end points, the relevance of the findings is unclear.

Congestion of the lungs was reported in rats exposed intermittently to tetrachloroethylene at 1,600 ppm, but not 800 ppm, for 13 weeks (NTP 1986). Thrombosis and squamous metaplasia were observed in the nasal cavity of rats exposed intermittently at ≥200 ppm for 103 weeks (Mennear et al. 1986; NTP 1986). In mice exposed intermittently to tetrachloroethylene at ≥100 ppm for 103 weeks, acute passive congestion of the lungs was observed (Mennear et al. 1986; NTP 1986).

Cardiovascular Effects. No effects on heart rate or blood pressure were noted in four men exposed to tetrachloroethylene at 87 ppm for 3 hours (Ogata et al. 1971). Ten adult male volunteers and 10 adult female volunteers were exposed to 0, 20, 100, or 150 ppm tetrachloroethylene vapor for 1 hour, 3 hours, or 7.5 hours, 5 days/week for 1 week at each concentration (Stewart et al. 1981). During the exposure periods, blood pressure and pulse rate were measured every hour, while electrocardiograms were monitored continuously via telemetry. There was no deviation from the baseline measurements which were obtained preexposure or for the postexposure follow-up period (Stewart et al. 1981). These observations confirmed those of a separate study of six males and six females in which no effects on the electrical activity of the heart were observed following random exposure at 0, 25, and 100 ppm tetrachloroethylene vapor for 5.5 hours, 5 days/week (Stewart et al. 1977). The total study lasted 11 weeks, although the exposure concentrations varied daily throughout the study. A case report describes a 24-year-old man who experienced cardiac arrhythmia (frequent premature ventricular beats). The patient had been employed for 7 months in a dry cleaning facility where he used tetrachloroethylene (Abedin et al. 1980). Plasma tetrachloroethylene was-measured at 0.15 ppm on his 5th day of hospitalization. The patient was discharged the next day but returned in 2 weeks for outpatient evaluation with a recurrence of skipping of heartbeats, headache, and dizziness. At that time, plasma tetrachloroethylene was measured at 3.8 ppm. Since the biological exposure index associated with an 8-hour exposure of 25 ppm is 0.5 mg/L tetrachloroethylene in blood (ACGIH

1995), this subject was exposed to relatively high concentrations. The patient was reported to be asymptomatic 1 month after finding different employment.

Epinephrine-induced cardiac arrhythmia was not induced in beagle dogs exposed by face mask to 5,000 or 10,000 ppm tetrachloroethylene (Reinhardt et al. 1973). This study was complicated by the dogs' struggling, which could represent irritant effects of these high tetrachloroethylene concentrations on the upper respiratory tract.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to tetrachloroethylene. Forestomach ulcers were observed in male rats exposed intermittently to tetrachloroethylene at 400 ppm for 103 weeks (NTP 1986). Ulcers were not observed at 200 ppm.

Hematological Effects. Ten adult male volunteers and 10 adult female volunteers were exposed to 0, 20, 100, or 150 ppm tetrachloroethylene vapor for 1 hour, 3 hours, or 7.5 hours, 5 days/week for 1 week at each vapor concentration (Stewart et al. 1981). A complete blood count was obtained once a week and compared to the preexposure and postexposure values. No deviation from baseline was observed. Six males and six females were randomly exposed to 0, 25, or 100 ppm tetrachloroethylene vapor for 5.5 hours, 5 days a week, over an 1l-week period (Stewart et al. 1977). A complete blood count was obtained once a week and compared to the preexposure and postexposure values; no deviations from baseline were observed. Relative to unexposed controls, changes in hemoglobin levels and white blood cell counts were not observed in workers exposed to tetrachloroethylene at a geometric mean time-weighted average (TWA) concentration of 20 ppm (Cai et al. 1991).

A decrease in erythrocyte δ-aminolevulinate dehydratase activity was observed in rats exposed to 200 but not 50 ppm tetrachloroethylene for 4 weeks (Soni et al. 1990). It is not clear if exposure was intermittent or continuous. Rats exposed to 230 or 470 ppm tetrachloroethylene for up to 160 days had splenic congestion and increased hemosiderin deposits (Carpenter 1937). Study limitations include the use of sick animals (parasites, pneumonia), nonstandard study protocols, rats of undefined strain, and inadequate controls. A transient increase in reticulocytes was observed in mice exposed to tetrachloroethylene at 135 and 270 ppm during the first few weeks of an 11.5-week study (Seidel et al. 1992). Microscopic examination of bone marrow revealed no effect on pluripotent stem cells and only

a small reduction in erythroid committed cells. Because of a lack of statistical analysis, NOAELs and LOAELs were not clearly identified in the Seidell et al. (1992) study.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to tetrachloroethylene. Histological changes were not observed in the limb muscles of rats exposed to tetrachloroethyliene at 50, 200, or 800 ppm 6 hours/day, 5 days/week, for 13 weeks (Mattsson et al. 1992).

Hepatic Effects. The liver is a target organ in humans accidentally exposed to high concentrations of tetrachloroethylene. Hepatocellular damage was documented by biopsy in a case study of a woman exposed occupationally to tetrachloroethylene fumes for 2.5 months (Meckler and Phelps 1966). Liver damage also has been diagnosed by the presence of hepatomegaly, icterus, and elevations of serum glutamic oxaloacetic transaminase (SGOT), bilirubin, and urinary urobilinogen (Coler and Rossmiller 1953; Hake and Stewart 1977; Saland 1967; Stewart et al. 1961a). These effects were generally observed several days after an acute exposure resulting in nervous system effects. There was one case report of diffuse fatty liver in a dry cleaner who died shortly after being exposed to tetrachloroethylene fumes (Levine et al. 1981). Because of the brief interval between exposure and death, this liver lesion may have been preexistent.

Ten adult male volunteers and 10 adult female volunteers were sequentially exposed to 0, 20, 100, or 150 ppm tetrachloroethylene vapor for 1 hour, 3 hours, or 7.5 hour periods, 5 days/week for one week at each exposure concentration. No ethanol consumption was permitted during the exposure sequence. A complete panel of clinical chemistries was obtained each week. The tests completed included a serum alkaline phosphatase, a serum ghrtamic pyruvic transaminase (SGPT), an SGOT, and a serum bilirubin. These results were compared to the preexposure and postexposure values. No deviation from baseline was observed (Stewart et al. 1981). Six males and six females were randomly exposed to 0, 25, or 100 ppm tetrachloroethylene vapor for 5.5 hours, 5 days a week, over an 11-week period (Stewart et al. 1977). A complete panel of clinical chemistries was obtained each week,-which included a serum alkaline phosphatase, an SGPT, an SGOT, and a serum bilirubin. These results were compared to preexposure and postexposure values; no deviations from baseline were observed.

Hepatic effects as measured by SGPT elevations were not detected in 22 dry cleaning workers in Belgium exposed to a TWA concentration of 21 ppm tetrachloroethylene over an average of 6 years

(Lauwerys et al. 1983). SGOT, SGPT, and serum alkaline phosphatase were not increased in workers exposed to tetrachloroethylene at a geometric mean TWA concentration of 20 ppm for l-120 months (Cai et al. 1991). Differences in the isoenzyme fractionation of serum gamma-glutamyltransferase (GGT) enzymes were observed in 141 workers exposed to tetrachloroethylene at an average concentration of 11.3 ppm relative to 130 unexposed controls (Gennari et al. 1992). Both exposed and control subjects were chosen on the basis of normal liver function tests (SGOT, SGPT, serum alkaline phosphatase, lactate dehydrogenase, and 5'-nucleotidase). In exposed workers, total GGT was significantly (1.4-fold; $p<0.01$) increased, principally as a result of an increase in GGT-2. Small amounts of GGT-4 were only observed in exposed workers. No correlation between serum GGT levels and worker tetrachloroethylene exposure level or duration was found. The investigators indicated that GGT-4 is associated with hepato-biliary impairment and that further investigation is required to determine why low-level exposure to tetrachloroethylene is associated with changes in the GGT isoenzyme profile in workers without any other evidence of liver disease.

Changes in serum levels of liver enzymes may not be the most sensitive marker of liver damage following exposure to tetrachloroethylene. In dry cleaning workers exposed to an average of 15.8 ppm tetrachloroethylene, ultrasound revealed diffuse parenchymal changes in the livers of 18/27 (67%) compared with10/26 (39%) unexposed laundry workers (Brodkin et al. 1995). This difference was statistically significant ($p<0.05$). An exposure-related trend was also noted, with parenchymal changes observed in all 5 subjects with exposures above 15 ppm, in 6 of the 12 subjects with exposures below 15 ppm, and in 38% of unexposed laundry workers. No changes in serum markers of liver damage (SGOT, SGPT, γ-glutamyl transferase, alkaline phosphatase, total and direct bilirubin) were noted in these workers. The workers in this study stated that they had not drunk an average of more than two alcoholic beverages a day for six months and had no history of alcoholism or hepatitis. Dry cleaners were included in the study only if tetrachloroethylene was used exclusively in the past 5 years. The average duration of employment was 20 years for the dry cleaning workers and 5 years for the laundry workers.

Hepatic lesions are also induced in experimental animals during inhalation exposure to tetrachloroethylene. Mice are the species most sensitive to this effect. Hepatocellular vacuolization occurred after a single 4-hour exposure of mice to 200 ppm or greater concentrations of tetrachloroethylene (Kylin et al. 1963). This lesion was also reported in male $B6C3F_1$ mice exposed to

875 or 1,750 ppm tetrachloroethylene for 14 days and in females exposed to the highest concentration. Vacuolization was not present at 425 ppm (NTP 1986).

Liver lesions differed markedly between mice and rats after longer duration exposure. In a 13-week study, male mice exposed to 200 ppm and higher concentrations of tetrachloroethylene exhibited mitotic alterations in the liver while both sexes had leukocytic infiltrations, centrilobular necrosis, and bile stasis at 400 ppm and higher concentrations (800 and 1,600 ppm). Dose-related liver congestion was observed in rats, with 8/20, 10/20, and 15/19 rats affected at 400, 800, and 1,600 ppm tetrachloroethylene, respectively, with no liver effects observed at 200 ppm (NTP 1986). In a reproductive study, hepatic effects were not observed in parental male and female rats exposed to 1,000 ppm of tetrachloroethylene 6 hours/day, 5 days/week for 1l-19 weeks (Tinston 1995).

Another inhalation study in mice and rats correlated light microscopic and ultrastructural liver effects with liver levels of cyanide-insensitive palmitoyl CoA oxidase, a marker for peroxisomal β-oxidation (Odum et al. 1988). Animals were exposed to 200 ppm of tetrachloroethylene for 28 days or 400 ppm for 14, 21, or 28 days. Centrilobular hepatocellular vacuolization was induced in mice by tetrachloro-ethylene exposure. Electron microscopy revealed that this effect corresponded to lipid accumulation. Centrilobular hepatocytes with cytoplasmic eosinophilia on light microscopy had marked proliferation of cytoplasmic peroxisomes at the ultrastructural level, and there was a significant increase in the marker enzyme. These changes occurred in mice at both doses and all exposures and were most pronounced in male mice. Exposed male rats in both dose groups and female rats exposed to 400 ppm developed centrilobular hepatocellular hypertrophy, which ultrastructurally consisted of proliferation of smooth endoplasmic reticulum. There was no increase in peroxisomes (Odum et al. 1988).

NMRI mice were exposed to 0, 9, 37, 75, or 150 ppm tetrachloroethylene continuously for 30 days (Kjellstrand et al. 1984). Exposed mice developed hepatocellular vacuolization and enlargement. Lesions were observed at 37 ppm and were noted to be most pronounced at exposures to 75 and 150 ppm tetrachloroethylene. It was not possible to determine if a dose-response relationship existed for this effect because the nature and extent of the lesions at each dose were not reported. Relative liver weights were not calculated; however, absolute liver weights were significantly elevated at exposure concentrations of 9 ppm and higher. Liver weights were still increased (10%) 120 days following 30 days of continuous exposure to 150 ppm. Plasma butyrylcholinesterase (BuChe) also was elevated in some exposed mice, but the significance of this increase is unclear for two reasons:

there was wide variability in BuChe activity in the controls, and plasma BuChe can be modulated by nonhepatic factors (Kjellstrand et al. 1984).

The hepatic effects of tetrachloroethylene in guinea pigs have also been evaluated (Rowe et al. 1952). Changes reported were increased liver weight (≥200 ppm) and cirrhosis (400 ppm). These data are of questionable value because of the use of an undefined strain of guinea pigs, lack of standardized protocols, small numbers of animals per exposure group, incomplete necropsy examination, inadequate controls, selective histopathological evaluation, and lack of quantitative supporting data.

Hepatocellular degeneration and necrosis occurred in male mice exposed to 100 and 200 ppm tetrachloroethylene for 103 weeks and in females exposed to 200 ppm. Liver effects were not reported in rats exposed chronically to 200 or 400 ppm tetrachloroethylene, but the effects of mononuclear cell leukemia infiltrates may have obscured subtle compound-induced changes (NTP 1986). Both sexes of mice also had increased incidences of hepatocellular tumors at both exposure concentrations. This study is discussed further in Section 2.2.1.8.

Renal Effects. Ten adult male volunteers and 10 adult female volunteers were exposed to 0, 20, 100, or 150 ppm tetrachloroethylene vapor for 1 hour, 3 hours, or 7.5 hours, 5 days/week, for 1 week at each concentration, during which time urinalysis and blood urea nitrogen (BUN) analysis were completed. These results were compared to the preexposure and postexposure values. No deviation from baseline was observed (Stewart et al. 1981). Six males and six females were randomly exposed to 0, 25, or 100 ppm tetrachloroethylene vapor for 5.5 hours, 5 days a week, over an 1 l-week period (Stewart et al. 1977). Urinalysis and BUN analysis were completed each week. These results were compared to preexposure and postexposure values; no deviations from baseline were observed. Symptoms of renal dysfunction, including proteinuria and hematuria, have been associated with accidental exposure to anesthetic concentrations of tetrachloroethylene vapor (Hake and Stewart 1977). Weak or no renal effects, depending on the parameters evaluated, were reported in people with chronic occupational exposure. Workers in dry cleaning shops exposed for an average of 14 years to an estimated TWA concentration of 10 ppm of tetrachloroethylene had increased urinary levels of lysozyme and β-glucuronidase suggestive of mild tubular damage (Franchini et al. 1983).

Urinary lysozyme activity was also increased in workers exposed to an average of 23 ppm for about 9 years (Vyskocil et al. 1990). At unspecified exposure concentrations and durations, an increase in

urinary fibronectin was observed in workers exposed to tetrachloroethylene (Bundschuh et al. 1993). No effects on urinary proteins (high and low molecular weight) or n-acetyl-glucosaminidase (NAG) were observed. No effects on BUN or serum creatinine were observed in workers exposed at an average concentration of 20 ppm for l-120 months (Cai et al. 1991), and occupational exposure to tetrachloroethylene at an average concentration of 14 ppm for an average of 12 years had no effects on total urinary protein, albumin, NAG, and creatinine (Solet and Robins 1991). In another report, serum creatinine and urinary albumin, β_2-microglobulin, and retinol-binding protein levels were normal in dry cleaning workers exposed to a TWA concentration of 21 ppm of tetrachloroethylene for 6 years (Lauwerys et al. 1983).

In a more comprehensive examination of kidney function, urinary markers were measured in 9 men and 41 women occupationally exposed to tetrachloroethylene from trace levels to 85 ppm and in 50 controls (Mutti et al. 1992). Both exposure levels and measurements of kidney function were taken over a long period of time to account for variability in the working cycle or seasonal fluctuations. The total duration of the study was not stated. The results showed an increase in markers suggesting an increase in the shedding of epithelial membrane components from tubular cells. The following urinary markers were increased in exposed workers relative to unexposed workers: albumin; transferrin; brush-border antigens BBA, BB50, and HF5; and tissue nonspecific alkaline phosphatase. Urinary fibronectin was also significantly increased. Serum antiglomerular basement membrane antibodies and serum laminin levels were significantly increased in exposed workers compared to controls. No effects on serum β_2-microglobulin, creatinine, or urinary prostaglandins, glycosaminoglycans, NAG, or intestinal alkaline phosphatase were noted. The investigators (Mutti et al. 1992) indicated that the significance of the findings was unclear, and they suggested that the changes could be a physiological adaptation to exposure or may represent an early state of potentially progressive renal disease. Relative to age- and sex-matched unexposed controls, laminin fragments in the serum (n=37) and urine (n=50) of tetrachloroethylene-exposed workers were significantly increased, suggesting glomerular dysfunction (Price et al. 1995). The exposure concentrations and the duration of exposure were not stated.

In animal studies, adverse renal effects have been observed in rodents exposed to tetrachloroethylene. Hyaline droplets in proximal tubules but no tubular damage or cell proliferation occurred in male rats exposed to 1,000 ppm by inhalation for 10 days (Green et al. 1990). Male rats exposed to 400 ppm tetrachloroethylene (the same concentration used in the NTP [1986] chronic study) for 28 days did not

develop kidney lesions (Green et al. 1990). Minimal chronic progressive glomerulonephropathy and increased pleomorphism within the proximal tubular nuclei were noted in male but not female rats exposed to tetrachloroethylene at 1,000 ppm for up to 19 weeks (Tinston 1995). Kidney effects were not observed at 300 ppm. In other intermediate-duration studies, rats exposed to 470 ppm for 150 days or to 7,000 ppm for 40 or more exposures had intratubular casts and swelling and desquamation of tubular epithelium (Carpenter 1937). On the other hand, abnormal renal function or histopathological findings were not observed in rats or guinea pigs exposed to tetrachloroethylene vapor concentrations of 0, 100, 200, or 400 ppm for about 6 months (Rowe et al. 1952). Guinea pigs that received 18 exposures of 7 hours each to 2,500 ppm tetrachloroethylene over a period of 20 days had increased kidney weights with slight-to-moderate cloudy swelling of tubular epithelium.

Renal tubular karyomegaly (nuclear enlargement) occurred in both sexes of mice exposed to 200, 400, 800, and 1,600 ppm tetrachloroethylene for 13 weeks but did not occur in mice exposed to 100 ppm. Kidney lesions did not occur in rats exposed to 1,600 ppm; kidneys from lower dose groups were not examined microscopically (NTP 1986).

Peroxisomal proliferation induced in hepatocytes by tetrachloroethylene exposure appeared to be correlated with hepatotoxicity and cell proliferation However, peroxisomal proliferation in renal tubular epithelium of rats or mice was not induced by exposure to 200 or 400 ppm tetrachloroethylene for up to 28 days (Odum et al. 1988). Intermittent exposure of rats to 200 ppm tetrachloroethylene for 4 weeks induced renal P-450 enzymes (Soni et al. 1990).

In the chronic inhalation toxicity/oncogenicity study of tetrachloroethylene, Fischer-344 rats of each sex were exposed to 0, 200, or 400 ppm tetrachloroethylene, and B6C3F_1 mice were exposed to 0, 100, or 200 ppm tetrachloroethylene for 103 weeks (NTP 1986). Dose-related renal tubular cell karyomegaly occurred in both species and sexes at all exposure concentrations. This alteration was accompanied by low incidences of renal tubular cell hyperplasia in male rats.

Endocrine Effects. Ferroni et al. (1992) measured prolactin levels in 30 controls and in 60 women occupationally exposed to tetrachloroethylene at a median concentration of 15 ppm. Although they noted a significant increase in prolactin levels in the exposed women relative to the controls during the proliferative phase of the menstrual cycle, values of both groups were in the normal range. Therefore, it is unlikely that the observed effect has biological significance.

Medullary hyperplasia of the adrenal glands was observed in male rats, and cortical hyperplasia of the adrenal glands was observed in female rats, when both groups were exposed to tetrachloroethylene at 200 or 400 ppm for 103 weeks (NTP 1986). Histological changes were not observed in the pituitaries of rats exposed to tetrachloroethylene at 50, 200, or 800 ppm 6 hours/day, 5 days/week, for 13 weeks (Mattsson et al. 1992).

Ocular Effects. Intense irritation of the eyes of humans was noted following acute exposure to high concentrations (930 ppm) of tetrachloroethylene vapors (Carpenter 1937; Rowe et al. 1952). Burning or stinging sensations in the eyes occurred after exposure to 600 or 280 ppm; very mild irritation was reported by four subjects at exposure to 216 or 106 ppm (Rowe et al. 1952); and transient eye irritation was noted in six subjects during the first few minutes of exposure at 75-80 ppm (Stewart et al. 196lb). The Rowe et al. (1952) and Carpenter (1937) studies are limited by small numbers of subjects, variable concentrations of tetrachloroethylene, and lack of measured clinical changes. Although no loss of color vision was noted in workers exposed to tetrachloroethylene at average concentrations of 15.3 and 10.7 ppm for men and women, respectively (Nakatsuka et al. 1992), loss of color vision was reported in dry cleaners exposed to an average concentration of 7.3 ppm for an average of 106 months (Cavalleri et al. 1994). Because this effect may be a neurological effect rather than a direct effect on the eyes, it is also presented in Section 2.2.1.4.

Histological changes were not observed in the eyes of rats exposed to tetrachloroethylene at 50, 200, or 800 ppm 6 hours/day, 5 days/week, for 13 weeks (Mattsson et al. 1992).

Body Weight Effects. Rats appear to be more sensitive to effects on body weight than mice. Following intermittent exposure to tetrachloroethylene for 2 weeks, body weights of rats but not mice were significantly reduced at 1,750 ppm (NTP 1986). Following intermediate-duration exposure to tetrachloroethylene, body weights of rats were significantly reduced at 1,600 ppm (NTP 1986), with no changes greater than 10% noted in rats exposed at 800 ppm (Mattsson et al. 1992) or 1,000 ppm (Tinston 1995). No effects on body weight were noted in mice intermittently exposed to tetrachloroethylene for intermediate durations at concentrations as high as 1,600 ppm (Kjellstrand et al. 1985; Kylin et al. 1965; NTP 1986). Body weight effects were not observed in rats exposed to tetrachloroethylene at 400 ppm, or in mice exposed at 200 ppm for 103 weeks (NTP 1986).

In intermediate-duration studies, guinea pigs exposed to tetrachloroethylene at 2,500 ppm for 24 days lost weight, and guinea pigs exposed to 200 ppm for 158 days showed a significant depression in body weight gain (Rowe et al. 1952). Limitations of this study include a lack of quantitative data, the use of small numbers of animals, and intercurrent infection

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after inhalation exposure to tetrachloroethylene.

There are also no reliable data to assess immunological effects in animals following inhalation exposure. However, in a mouse study (see the discussion on respiratory effects in Section 2.2.1.2), there was increased host susceptibility to pulmonary bacterial infection after a 3-hour inhalation exposure to 50 ppm tetrachloroethylene (Aranyi et al. 1986). The specific mechanism of the increased susceptibility is unknown. The significance of the study is unclear because of variability in control group mortality and lack of evaluation of specific immunological end points.

2.2.1.4 Neurological Effects

The nervous system is a major target organ in humans exposed to tetrachloroethylene by inhalation. Acute exposure, depending on concentration, can result in reversible mood and behavioral changes, impairment of coordination, or anesthetic effects.

The anesthetic and preanesthetic central nervous system effects of tetrachloroethylene were documented in four volunteer subjects (one male, sex not specified for the other three) exposed acutely to concentrations ranging from 500 to 2,000 ppm. Mood changes, slight ataxia, faintness, and dizziness occurred with exposure to concentrations of l,000-1,500 ppm for <2 hours. At exposure to 2,000 ppm for 5-7 minutes, subjects experienced a sensation of impending collapse (Carpenter 1937). Slight lightheadedness was reported by six male volunteers exposed to tetrachloroethylene at a concentration of 210-240 ppm for over 30 minutes (Stewart et al. 1961b). Dizziness has been reported after brief accidental exposure to high concentrations of tetrachloroethylene fumes (Saland 1967) while longer exposures resulted in collapse, coma, and seizures (Hake and Stewart 1977; Morgan 1969; Pate1 et al. 1973; Stewart 1969; Stewart et al. 196la).

2. HEALTH EFFECTS

There have been several experimental studies of acute neurological effects in adult humans exposed to tetrachloroethylene. In one study, symptoms of neurological impairment were not reported after exposure to 106 ppm for 1 hour (Rowe et al. 1952). Neurological symptoms of dizziness and drowsiness occurred at exposure to 216 ppm for 45 minutes to 2 hours; loss of motor coordination occurred at exposure to 280 ppm for 2 hours or 600 ppm for 10 minutes. Volunteers in this study were allowed to leave the exposure chamber when they experienced discomfort. Consequently, exposure times varied and ranged from 3 minutes to 2 hours (Rowe et al. 1952). In another study, exposure to 100 ppm for 7 hours produced symptoms such as headache, dizziness, difficulty in speaking, and sleepiness (Stewart et al. 1970). Of five objective tests of central nervous system performance in humans exposed for 7 hours, none showed any abnormality except the Romberg test of balance, which was abnormal for three of the five subjects exposed for 7 hours a day for 5 consecutive days. Only one exposure level (100 ppm) was used in this study, and no control subjects were included (Stewart et al. 1970).

Hake and Stewart (1977) describe a study in which four male volunteers were exposed to concentrations of 0, 20, 100, and 150 ppm tetrachloroethylene for 7.5 hours/day. Exposure at each concentration lasted for 5 days. Subjective evaluation of electroencephalographic scores suggested cortical depression in subjects exposed to 100 ppm. Coordination, as measured by the Flanagan coordination test, was significantly decreased at some time points during exposure to 100 or 150 ppm. No effects on flash visual-evoked responses, equilibrium tests, math skills, time discrimination, and reaction times were noted.

In contrast to the Hake and Stewart (1977) study, Altmann et al. (1990) found a statistically significant ($p<0.05$) increase in latency of pattern reversal visual-evoked potentials in 10 male volunteers exposed to tetrachloroethylene at 50 ppm for 4 hours/day for 4 days, relative to 12 subjects exposed at 10 ppm. No effects on brainstem auditory-evoked potentials were noted. Tests of visual contrast measured in a few individuals showed a tendency for loss of contrast in the low and intermediate spatial frequencies at 50 ppm. In this study, measurements were also completed the day before exposure so each individual served as his own control. The lo-ppm group was considered the control group, and this concentration was used because it is well above the odor threshold of tetrachloroethylene so that there was at least an attempt to blind the subjects to the exposure concentrations. Blood tetrachloroethylene concentrations were measured before, in the middle, and at the end of each day's exposure, and an association between the effect on pattern reversal visual-evoked potentials and blood tetrachloro-

ethylene concentrations was observed ($p<0.03$). The lack of effect on flash visual-evoked potentials in the Hake and Stewart (1977) study at concentrations up to 100 ppm compared to an effect on pattern reversal visual-evoked potentials at 50 ppm in the Altmann et al. (1990) study may reflect the greater inter- and intrasubject variability of waveforms for flash visual-evoked potentials (Otto et al. 1988).

In a second study completed by Altmann et al. (1992) in which baseline measurements were completed 72 hours before exposure, 16 male volunteers were exposed to 50 ppm, and 12 male volunteers were exposed to 10 ppm, 4 hours/day for 4 days. A faint odor was reported by 33% of the subjects at 10 ppm and 29% of the subjects at 50 ppm on the first day of testing, and by 15% of the subjects at 10 ppm and 36% of the subjects at 50 ppm on the last day of testing, leading the investigators to conclude that only a few subjects could identify their exposure condition. This study confirmed the effect on pattern reversal visual-evoked potentials at 50 ppm and the lack of effect on brainstem auditory-evoked potentials. In addition, Altmann et al. (1992) completed a battery of neurological tests including finger tapping; eye-hand coordination using a sine wave tracking task; simple reaction time; continuous performance test; symbol-digit test; visual retention; pattern recognition; digit learning; paired associates learning and retention; vocabulary test; and mood scales. Analysis of covariance, with preexposure baseline values as covariates, revealed significant performance deficits for vigilance ($p=0.04$) and eye-hand coordination ($p=0.05$) at 50 ppm. A borderline ($p=0.09$) effect on simple reaction times was also noted at 50 ppm. Based on the NOAEL of 10 ppm, an acute-duration inhalation MRL of 0.2 ppm was calculated as described in the footnote to Table 2-l.

An investigation was conducted with 19 volunteers (10 males and 9 females) exposed 5 days/week for 1 month to tetrachloroethylene vapor concentrations of 0, 20, 100, or 150 ppm (Stewart et al. 1981). The subjects were exposed 7.5 hours/day and were exposed to each concentration for 1 week. Electroencephalogram (EEG) results indicated that major changes in the EEG of three of four male subjects and four of five female subjects occurred during exposure to 100 ppm. In the majority of subjects, the EEG changes were characterized by a reduction in overall wave amplitude and frequency, most strikingly evident in the occipital leads. The study authors stated that the altered EEG pattern was similar to that seen in healthy adults during drowsiness, light sleep, and the first stages of anesthesia.

Long-term neurotoxic effects may be a sequel of organic solvent exposure as indicated by studies of dry cleaning workers. While acute work-related symptoms, such as headache, seemed to improve after

cessation of exposure of workers to solvents, symptoms suggestive of chronic encephalopathy, particularly memory and concentration impairment, persisted after cessation of exposure. These latter symptoms remained unchanged even after workers had been free of organic solvent exposure for 6.6 years and continued in workers still being exposed (Gregersen 1988). Limitations of this 10-year follow-up study of solvent-exposed workers include the combining of workers exposed to organic solvents other than tetrachloroethylene (white spirit, toluene, and styrene) with dry cleaners for purposes of analysis, unknown exposure concentrations and durations, possible skewed recruitment of the study population when the study was started in 1975, different methods employed in the two follow-up studies, and failure to confirm symptoms of chronic encephalopathy by a neuropsychological investigation.

In a study of 22 dry cleaning workers (primarily women) in Belgium exposed to a TWA concentration of 21 ppm tetrachloroethylene over an average of 6 years, no significant alterations were detected in neurological symptoms or psychomotor performances compared to 33 unexposed controls (Lauwerys et al. 1983). However, 17 of 22 subjective neurologic symptoms were more prevalent in the exposed group, particularly memory loss and difficulty in falling asleep. Exposure assessment included measurement of urinary trichloroacetic acid daily for 1 week, measurement of air tetrachloroethylene concentrations with personal air samplers and badges, and measurement of breath and blood concentrations of tetrachloroethylene. All measurements were completed during 1 work week. Cai et al. (1991) also reported an increase in subjective symptoms including dizziness and forgetfulness in workers exposed to tetrachloroethylene at a geometric mean concentration of 20 ppm for l-120 months relative to unexposed controls. Exposure was measured using a diffusive sampling with carbon cloth. Additional details, including frequency of measurements were not reported.

In a study of 65 dry cleaning workers exposed to tetrachloroethylene for at least 1 year, behavioral tests that measured short-term memory for visual designs showed deficits in the high-exposure group (40.8 ppm) relative to the low-exposure group (11.2 ppm) (Echeverria et al. 1995). Exposure was assessed by a breath sample, and by 15-minute air samples from the breathing zone of a-clerk, a pressor, and an operator in 19 of the 23 shops studied. Individuals were then placed in the high-, moderate-, or low-exposure groups based on work history. These authors (Echeverria et al. 1995) also describe four cases referred for neuropsychologic assessment of possible tetrachloroethylene encephalopathy. The subjects performed below expectation on tasks assessing memory, motor, visuospatial, and executive functions, with milder attentional deficits. The authors suggest that

tetrachloroethylene may affect the functioning of the frontal lobes (mediating complex organizational behavior, attention executive functioning, and reasoning) and the limbic system (mediating mood and memory).

There are conflicting reports on the effect of tetrachloroethylene on color vision. No effect on blue-yellow color vision was noted in 30 men or 34 women occupationally exposed to tetrachloroethylene at average concentrations of 15.3 and 10.7 ppm, respectively (Nakatsuka et al. 1992). The average duration of exposure for these subjects was not stated. When compared to unexposed controls (matched for sex, age, alcohol consumption and cigarette use), 22 dry cleaners exposed to an average concentration of 7.3 ppm tetrachloroethylene for an average of 106 months showed a significant decrease ($p=0.007$) in color vision, primarily in the blue-yellow range (Cavalleri et al. 1994). Because the exposure concentrations were measured on a single day, it is not clear how well they represent long-term exposure. The mechanism of color vision loss and the contribution of peak exposure to this effect are not known.

Dry cleaning workers exposed to a TWA concentration of 12 or 54 ppm tetrachloroethylene had significantly impaired perceptual function, attention, and intellectual function compared to a control population when evaluated by a battery of psychological tests and questionnaires (Seeber 1989). The workers were exposed chronically, but the specific duration of exposure is unclear as no units for duration of exposure were stated. The study showed no dose response (no significant differences between high- and low-exposure groups), no correlation between test results and individual exposure levels as measured by blood tetrachloroethylene and urinary TCA levels, and variable deviations between exposed and control populations. Compared to 30 unexposed women, significantly prolonged reaction times (simple reaction times, $p<0.000l$; shape comparison to test vigilance and to test stress, $p<0.005$) were reported in 60 women occupationally exposed to tetrachloroethylene at a median concentration of 15 ppm for an average of 10 years (Ferroni et al. 1992). Exposure levels were determined by measuring tetrachloroethylene in the blood collected during the workday and in air samples collected during 4-hour periods in the workweek. The sampling was completed-during the winter and summer to account for seasonable variability. No significant association between measures of exposure and neurobehavioral tests was noted. Based on the LOAEL of 15 ppm, a chronic-duration inhalation MRL of 0.04 ppm was calculated as described in the footnote to Table 2-l.

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A study of 14 persons living above or next to dry cleaning facilities for l-30 years relative to 23 controls suggests that further studies of a large population exposed to very low levels of tetrachloroethylene would be useful. In this study, no significant differences were observed in the absolute values of tests of a neurological battery (pattern reversal visual-evoked potentials continuous performance test, hand-eye coordination, finger tapping, simple reaction time, visual memory) (Altmann et al. 1995). When analyzed using multivariate analysis to adjust for age, gender, and education, response time in the continuous performance test and simple reaction time were increased ($p<0.05$), and a smaller number of stimuli were identified correctly by the exposed subjects ($p<0.05$). The median concentrations of tetrachloroethylene were 0.2 and 0.003 ppm in the apartments of exposed and control subjects, respectively, and blood concentrations measured in the examination room were 17.8±46.9 μg/L in exposed subjects and below the 0.5-μg/L detection limit in controls. Because there were no significant effects on the absolute values of the neurological tests, the 0.2ppm concentration is considered a NOAEL for neurological effects in humans.

Neurological effects and biochemical changes in the brain have been reported in animals exposed to tetrachloroethylene. Many experimental studies did not correlate biochemical with behavioral effects or either parameter with morphologic changes in the brain. The significance of many of these studies regarding neurotoxicity is therefore unclear.

Neurological signs typical of an anesthetic effect of inhaled tetrachloroethylene have been reported in numerous animal studies (see Table 2-l). These clinical signs consist of hyperactivity (excitability), ataxia, hypoactivity, and finally loss of consciousness (Friberg et al 1953; NTP 1986; Rowe et al. 1952). In one study, mice inhaling tetrachloroethylene for 4 hours showed signs of anesthesia at concentrations of 2,328 ppm (NTP 1986). Mice exposed to concentrations of 0, 100, 200, 425, 875, and 1,750 ppm (6 hours per day, 5 days per week, for 2 weeks) experienced dyspnea, hypoactivity, hyperactivity, anesthesia, and ataxia at the highest concentration (NTP 1986). In another study, anesthesia was observed in mice within 2.5 minutes of breathing air containing 6,800 ppm tetrachloro-ethylene (Friberg et al. 1953). Rats exposed to 0, 100, 200, 425, 875, and 1,750 ppm tetrachloro-ethylene (6 hours per day, 5 days per week, for 2 weeks) were observed to have dyspnea, hypoactivity, and ataxia at the highest concentrations (NTP 1986). In additional studies, rats exposed to 3,000 ppm tetrachloroethylene became anesthetized in several hours, while those exposed to 6,000 ppm were anesthetized in minutes (Rowe et al. 1952). Rats became ataxic following exposure to 2,300 ppm for 4 hours (Goldberg et al. 1964). Dogs exposed to 5,000 ppm tetrachloroethylene by face mask for less

than 10 minutes became excited and struggled (Reinhardt et al. 1973). This response may have represented irritant respiratory effects of tetrachloroethylene.

Albee et al. (1991) reported electrophysiological changes in male rats exposed to tetrachloroethylene at 800 ppm 4 hours/day for 4 days. The changes included altered shape, reduced amplitude, and decreased latency of flash-evoked potentials and decreased latency of somatosensory evoked potentials. EEG changes were also observed. A 13-week study in which rats were exposed to 50, 200, or 800 ppm tetrachloroethylene (6 hours/day, 5 days/week) reported no effect on gait, posture, muscle tone, sensory response, and hind and forelimb grip performance (Mattsson et al. 1992). At 800 ppm, minimal changes were noted in flash-evoked potentials measured 1 week after the last exposure. The investigators considered the effect nonadverse and indicated that changes in flash-evoked potential can occur in rats exposed to enriched environment (paired housing, access to an exercise wheel, and handling twice a day by study personnel). Histological changes were not observed in the optic tract, brain, spinal cord, or peripheral nerves. According to the investigators, this study indicates that intermediate-duration exposure of rats to tetrachloroethylene at 800 ppm does not cause serious permanent damage and suggests that if minor acute changes in flash-evoked potentials are prevented, more serious neurological effects will not occur However, it is not possible to draw a conclusion on the reversibility of the effects without data on the post-exposure time course of these effects.

A multigeneration study in rats suggests that animals may adapt to some of the neurological effects of tetrachloroethylene. Exposure at 1,000 ppm, 6 hours/day, 5 days/week, for 11-19 weeks resulted in decreased activity, reduced response to sound, salivation, breathing irregularities, and piloerection (Tinston 1995). The effects were observed only during the first 2 weeks in each generation, and recovery from these effects was noted about 30 minutes before the end of each exposure.

Behavioral alteration has been observed in rodents after inhalation exposure to tetrachloroethylene. Open-field behavior (ambulation) was elevated in groups of 10 male rats exposed to 200 ppm tetrachloroethylene of unspecified purity for 6 hours a day for 4 days (Savolainen et al. 1977). Ambulation was significantly increased 1 hour, but not 17 hours, after the last exposure. Biochemical changes in the brains following several additional exposures were reduced ribonucleic acid (RNA) content and increased nonspecific cholinesterase content. There was no histologic examination of brain tissue, so these findings could not be correlated with brain structural damage.

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Biochemical changes were reported in brains of rats and Mongolian gerbils exposed by inhalation to tetrachloroethylene. Gerbils exposed to 320 ppm continuously for 3 months followed by a 4-month exposure-free period had changes in levels of S-100 protein, a marker for astrocytes as well as other cells in the peripheral nervous system and skin (Rosengren et al. 1986). Rats exposed to 320 ppm continuously for 30 days had changes in brain cholesterol, lipids, and polyunsaturated fatty acids (Kyrklund et al. 1988). Changes in the fatty acid composition of the brain were also observed in rats continuously exposed to tetrachloroethylene at 320 ppm for 90 days (Kyrklund et al. 1990). Gerbils exposed to 60 or 320 ppm had decreased deoxyribonucleic acid (DNA) content in portions of the cerebrum (Karlsson et al. 1987; Rosengren et al. 1986). Gerbils exposed to 120 ppm continuously for 12 months had altered phospholipid content (phosphatidylethanolamine) in the cerebral cortex and hippocampus (Kyrklund et al. 1984). In another study, gerbils with a similar exposure regimen had decreased taurine content and increased glutamine content in areas of subcortical brain tissue (Briving et al. 1986). These studies are limited by failure to examine nervous tissue histologically in order to correlate biochemical changes with behavioral alterations or with morphologic evidence of brain damage. In addition, all but the Rosengren et al. (1986) study involved exposure to only one concentration of tetrachloroethylene.

In a study designed to examine tetrachloroethylene effects on different regions and different cell types of the brain, Wang et al. (1993) measured brain weight and neuronal and glial markers in rats exposed continuously at 300 or 600 ppm for 4 or 12 weeks. Brain weight was significantly reduced at 600 ppm following both 4 and 12 weeks of exposure. Measurement of neuron-specific enolase, a cytosolic neuronal protein in the frontal cerebral cortex, hippocampus, and brainstem did not show any changes. The cytosolic marker of glial cells, glial S-100, was significantly reduced in all three brain regions following exposure at 600 ppm for 12 weeks, with the greatest reduction observed in the frontal cerebral cortex. Cytoskeletal elements of neuronal cells (neurofilament 68 kD polypeptide) and glial cells (glial fibrillary acid protein) were significantly reduced in the frontal cerebral cortex at 600 ppm. The neuronal marker was reduced at both 4 and 12 weeks, while the glial marker was reduced only at 12 weeks. In the hippocampus and brainstem, only the glial cytoskeleton protein was significantly reduced following 12 weeks of exposure at 600 ppm. The investigators (Wang et al. 1993) concluded that the frontal cerebral cortex is more sensitive to tetrachloroethylene than other regions of the brain, that cytoskeletal elements are more sensitive than cytosolic proteins, and that in addition to neural cells, glial cells are vulnerable to the effects of tetrachloroethylene.

Histologic lesions in the central nervous system have not been observed in chronic inhalation studies in rats and mice (NTP 1986).

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

2.2.1.5 Reproductive Effects

Some adverse reproductive effects in women have been reported to be associated with occupational exposure to tetrachloroethylene in dry cleaning operations. These effects include menstrual disorders and spontaneous abortion. However, no definitive conclusions can be made because of the limitations associated with these studies.

A small-scale exploratory study described menstrual disorders in dry cleaning workers (Zielhuis et al. 1989). Limitations of the study are lack of exposure measurement data, methodologic problems (self-administered questionnaire with no follow-up and failure to account for various confounding factors such as smoking, alcohol consumption, and medicinal drugs), and a relatively small study population.

Several case-control studies of women occupationally exposed to tetrachloroethylene in dry cleaning operations suggested that exposed women had increased risk of spontaneous abortion (Ahlborg 1990; Kyyriinen et al. 1989; Windham 1991). Limiting factors include a low number of pregnancies among exposed women (Ahlborg 1990), a small group of exposed affected workers, biological monitoring not concurrent with the first trimester of pregnancy (Kyyrönen et al. 1989), and exposure assessed through telephone interviews (Windham et al. 1991). In another small study, spontaneous abortions and birth defects occurred at a higher incidence in Italian dry cleaning workers than in housewives, but this difference was not statistically significant (Bosco et al. 1986). No increase in spontaneous abortion rates for laundry and dry cleaning workers in Canada was detected in a cross-sectional study (McDonald et al. 1986). In a case-control study of 214 cases of low birth weight, congenital malformations, perinatal mortality, or spontaneous abortions identified in a cohort of dry cleaning workers in Scandinavia, no consistent effect on pregnancy outcome was observed (Olsen et al. 1990). Study limitations include incomplete participation of all dry cleaning facilities, limited controls for lifestyle factors, and limited exposure information

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In a study of semen quality among dry cleaners (n=34), the overall percentages of abnormal sperm were similar in the dry cleaners and 48 unexposed laundry workers (Eskenazi et al. 1991b). However, the sperm cells of dry cleaners were significantly more likely to be round and less likely to be narrow. Men with the highest exposure levels had sperm with less progressive linear movement and more lateral movement. No effects on sperm counts were noted. A study of the reproductive outcome of 17 of the dry cleaners and 32 of the laundry workers showed that there is some evidence that it may take slightly longer for the wives of dry cleaners to become pregnant and that they seek help for infertility problems more often (Eskenazi et al. 1991a). Spontaneous abortions were not increased in wives of dry cleaners (Eskenazi et al. 1991a). In 20 women occupationally exposed to unspecified concentrations of tetrachloroethylene, a nonsignificant increase in time-to-pregnancy was observed compared to 92 unexposed controls (Sallmen et al. 1995). Exposure concentrations were not provided in this study.

Adverse effects on reproductive performance were not detected in rats exposed by inhalation to 70, 230, or 470 ppm tetrachloroethylene for 28 weeks, as judged by the number of pregnancies, number of litters conceived, and number of offspring per litter (Carpenter 1937). This older study has numerous limitations including intercurrent disease, nonstandard protocols, rats of undefined strain, and inadequate controls.

In a multi-generation study, groups of rats were exposed to tetrachloroethylene at 0, 100, 300, or 1,000 ppm for 6 hours/day, 5 days/week, for 11 weeks before mating (Tinston 1995). After mating, the males were exposed at all concentrations daily until termination, and the females were exposed at all concentrations daily until gestation day 20 when they were removed from exposure. One litter was produced in the first generation, and the dams and litters were exposed to all concentrations daily from day 6 to day 29 post partum. The F_1 generation parents were exposed to tetrachloroethylene at 0, 100, 300, or 1,000 ppm for at least 11 weeks before mating. Three litters were produced in the second generation. Dams and F_2A litters of the control and l00-ppm exposure groups were exposed daily from day 6 to day 29 post partum, and dams and F_2A litters of the 300-ppm exposure group were exposed daily from day 7 to day 29 postpartum. Dams and F_2A litters of the l,000-ppm group were not exposed during lactation. For all exposure concentrations, dams and F_2B litters were not exposed during lactation. The F_2C litters were produced by mating unexposed females with male controls and the males exposed to 1,000 ppm.

Exposure at 1,000 ppm resulted in sedation of dams and pups. Decreased body weight gain in the parental animals was noted at 1,000 ppm during the pre-mating and lactation periods but was generally less than 10%. The proportion of pups born live at 1,000 ppm was significantly lower in the F_1A, F_2A, and F_2B litters. The incidence of pup mortality during lactation was also significantly increased at 1,000 ppm in the F_1A, F_2A, and F_2B litters. The effects on survival were observed with and without pup exposure suggesting an *in utero* effect rather than a direct effect of tetrachloroethylene. Relative to controls, growth of offspring was reduced during lactation, with the reduction most marlced at 1,000 ppm. At the beginning of the pre-mating period for the F_1 parents, body weights of males and females were 26% and 24% lower than controls, respectively. After adjustment for initial body weights, growth of females was similar to controls, although growth of the l,000-ppm males was less than controls. Body weights of offspring in the l00- and 300-ppm groups were generally within 10% of control values. In the F_2C litters, there were no statistically significant changes in the proportion of pups born live, pup survival, or growth suggesting that the effects were not male mediated. No effects on reproductive outcome were noted at 300 ppm. The investigators describe treatment-related chronic progressive glomerulonephropathy in the kidneys of adult rats at 1,000 ppm (Tinston 1995). The report indicates that other organs were removed for histological examination, but it is not clear if they were examined, and if they were examined, details of the results are not provided. The l,000-ppm concentration is considered a serious LOAEL for reproductive effects resulting in a decrease in the number of livebom pups, and the 300-ppm concentration is considered a NOAEL.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to tetrachloroethylene.

A slight but significant increase in maternal and fetal toxicity occurred in Sprague-Dawley rats and Swiss Webster mice exposed to 300 ppm tetrachloroethylene by inhalation on days 6-15 of gestation (Schwetz et al. 1975). Maternal or fetal toxicity or teratogenicity was not, however, reported for rats exposed on days 1-19 or rabbits on days l-24 of gestation by inhalation to 500 ppm tetrachloroethylene (Hardin et al. 1981). Limitations of this study include use of only one dose level, the use of summary and nonquantitative data, and conduct of portions of the study at two separate laboratory facilities.

In a behavioral teratology study, pregnant Sprague-Dawley rats were exposed to 0, 100, or 900 ppm tetrachloroethylene on days 14-20 of gestation and to 0 or 900 ppm tetrachloroethylene on days 7-13 (Nelson et al. 1980). Effects occurred after exposure to 900 ppm for both exposure periods, but not after exposure to 100 ppm. Dams had reduced feed consumption and weight gain, without liver or kidney histological alterations. Pups of dams exposed to 900 ppm on gestation days 7-13 had decreased performance during tests of neuromuscular ability (ascent on a wire mesh screen and rotarod balancing) on certain days. Offspring (before weaning) from dams exposed to 900 ppm on days 14-20 performed poorly on the ascent test on test day 14 only, but later in development their performance in the rotarod balancing test was superior to the controls, and they were more active in an open-field test. Brains of 21-day-old offspring exposed to 900 ppm prenatally had significant decreases in neurotransmitters (dopamine in those exposed on gestation days 14-20 and acetylcholine in those exposed on days 7-13 or 14-20). The lower concentration (100 ppm) produced no significant differences from controls. There were no microscopic brain lesions. Changes in brain fatty acid composition were observed in the offspring of guinea pigs exposed to tetrachloroethylene at 160 ppm during gestation days 33-65 (Kyrklund and Haglid 1991). Measurements of brain lipids did not show any effects. The investigators concluded that changes in fatty acid composition in the brains of developing animals were not greater than in adult animals exposed to tetrachloroethylene.

The highest NOAEL values and all reliable LOAEL values for developmental effects in rats and mice following acute exposure to tetrachloroethylene are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.7 Genotoxic Effects

Assays of clastogenic effects in humans following occupational exposure to tetrachloroethylene via inhalation have shown inconsistent results. Increases in chromosome aberrations and sister chromatid exchanges were not detected in lymphocytes from 10 workers who were occupationally exposed to tetrachloroethylene (Ikeda et al. 1980). The exposure concentrations for these workers were estimated to be between 10 and 220 ppm for 3 months to 18 years. The small number of workers-and the wide range of exposure concentrations and durations limit the generalizations that can be made from this study. Twenty-seven workers exposed to an 8-hour TWA concentration of 10 ppm tetrachloroethylene were compared to unexposed occupational controls with respect to incidence of sister chromatid exchanges (Seiji et al. 1990). Although the study authors had found no significant effect of cigarette smoking alone in either the exposed workers or the controls, the difference in sister chromatid

exchange frequency between tbe exposed workers who smoked and the nonsmoking controls was statistically significant. The authors proposed a synergistic effect of chemical exposure and cigarette smoking. The number of workers examined was small (12 smokers and 2 nonsmokers among the exposed men; 9 smokers and 3 nonsmokers among the controls). The lack of any effect of cigarette smoking alone on the frequency of sister chromatid exchange is somewhat surprising, as this is a recognized effect that is well documented in the literature (Hook 1982).

No studies were located regarding genotoxic effects in animals after inhalation exposure to tetrachloroethylene.

Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

There have been a number of epidemiology studies of dry cleaning and laundry workers. Many of these studies are complicated by potential exposure to other petroleum solvents.

The only investigation of dry cleaning workers with no known exposure to petroleum solvents was a retrospective mortality study of a subcohort of 615 workers employed only in shops where tetrachloroethylene was the principal solvent (Brown and Kaplan 1987). Excess risk for cancer at any site was not identified in this subcohort. In the entire cohort, whicR was composed of 1,690 workers (including workers who had potential occupational exposure to petroleum solvents), there were significant excesses of mortality from kidney, bladder, and cervical cancer. The authors state that the increased incidence of cervical cancer may reflect the lower socioeconomic status of the cohort, as other studies have reported a correlation between lower socioeconomic status and increased risk of cervical cancer (Brown and Kaplan 1987; Hoover et al. 1975). A limitation of this study was lack of evaluation of smoking habits of the study cohort, since cigarette smoking has been associated with an increased risk of kidney, bladder, and cervical cancers (Newcomb and Carbone 1992).

A follow-up of the Brown and Kaplan (1987) cohort further examined the vital status of the workers without updating the work histories (Ruder et ah 1994). Statistically significant excesses were observed for bladder cancer (standardized mortality ratio [SMR] = 2.54), esophageal cancer (SMR =

2.14) and intestinal cancer (SMR = 1.56). Increased mortality from pancreatic cancer was also noted in the subcohort with the longest latency period.

Additional epidemiological studies of dry cleaning and laundry workers have shosvn significant excesses in mortality resulting from cancers of the lung, cervix, esophagus, kidney, skin, lymphatic/hematopoietic system, and/or colon (Blair et al. 1979, 1990; Duh and Asal 1984; Katz and Jowett 1981). Lynge and Thygesen (1990) reported a small excess risk of liver cancer among female (7 observed, 2.1 expected) but not male laundry and dry cleaning workers. A nested-case-control study of this population, which distinguished between laundry and dry cleaning workers, indicated that all of the liver cancers were found among laundry workers (Lynge et al. 1995). Renal cell carcinoma was also not increased among dry cleaners relative to laundry workers. The investigators concluded that the excess risk of liver cancer among women working in laundries and dry cleaning shops was not explained by exposure to dry cleaning solvents.

Non-significant increases in lymphosarcoma/reticulosarcoma, bladder cancer, and cervical cancer have also been reported (Blair et al. 1990). Although these studies suggest a possible association between chronic occupational exposure to tetrachloroethylene and increased cancer risk, the evidence must be regarded as inconclusive for the following reasons. First, workers were exposed to petroleum solvents and other dry cleaning agents as well as tetrachloroethylene. Second, other confounding factors such as smoking, alcohol consumption, and low socioeconomic status were not considered in the analyses. Third, the numbers of deaths from cancer of specific organs or involving the hematopoietic system were low. Fourth, in several of these studies, attempts were not made to distinguish between laundry and dry cleaning workers.

In a study of Finnish workers (292 men and 557 women) exposed primarily to tetrachloroethylene, non-significant increases in non-Hodgkin’s lymphoma, cervical cancer, and pancreatic cancer were noted (Anttila et al. 1995). The total number of cancer cases in this study was 31. Blood concentrations of tetrachloroethylene measured in random samples taken from these workers averaged 116 μg/L in men and 66 μg/L in women. As the biological exposure index associated with an 8-hour exposure of 25 ppm is 500 μg/L tetrachloroethylene in blood (ACGIH 1995), these workers were probably exposed to concentrations of tetrachloroethylene below 25 ppm.

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Two other epidemiological studies of laundry and dry cleaning workers did not identify an occupational risk of bladder cancer compared to control subjects (Chapman et al. 1981; Smith et al. 1985). In the epidemiological study conducted by Smith et al. (1985), smoking status was examined to evaluate confounding or interactive effects, and smoking was found to be associated with an increased risk of bladder cancer. While an increased risk of bladder cancer specifically in laundry or dry cleaning workers of both sexes was not detected by Chapman et al. (1981), these authors found that women exposed to solvents as a group were in the high-risk category.

A cohort of white male chemical workers in Louisiana exposed to a variety of chemicals including tetrachloroethylene did not have an increased risk for total mortality or cancer (Olsen et al. 1989). This nonpositive study was confounded by the healthy worker effect, defined as the observation that employed persons have lower mortality rates than the general population. Blacks and women were not analyzed in this study because of the small numbers of representatives from these groups.

A case-control study in New Jersey identified an increased risk of primary liver cancer in male workers categorized as craftsman or operators in laundry or dry cleaning operations (Stemhagen et al. 1983). The specific solvents to which the workers were exposed and exposure levels were not identified. The study controlled for alcohol consumption and smoking. A case control study of astrocytic brain cancer among white males in Louisiana, New Jersey, and Pennsylvania showed a trend for increased brain tumors with high tetrachloroethylene exposure (Heineman et al. 1994). This result was based on only three cases and is limited in that exposure information was not available. This study may also be confounded by exposure to methylene chloride. The study authors concluded that the association between tetrachloroethylene and brain cancer requires further study.

A retrospective cohort study of 14,457 aircraft maintenance workers at Hill Air Force Base, Utah, was undertaken by Spirtas et al. (1991) to determine if occupational exposure to over 20 solvents, including trichloroethylene and tetrachloroethylene, posed an increased risk of mortality. Deaths due to multiple myeloma or non-Hodgkin's lymphoma were elevated in female workers exposed to tetrachloroethylene for at least 1 year. However, confidence in these data is low primarily because multiple and overlapping exposure to more than one chemical was considerable. In addition, the levels of tetrachloroethylene to which the workers were exposed were not provided, and lifestyle factors such as smoking and alcohol consumption were not assessed.

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An association between exposure to tetrachloroethylene and increased risk of developing cancer has been suggested in results from animal experiments A 103-week inhalation toxicity/carcinogenicity study of tetrachloroethylene was conducted using male and female Fischer-344 rats and $B6C3F_1$ mice. Exposure levels were 0, 200, or 400 ppm tetrachloroethylene for rats and 0, 100, or 200 ppm tetrachloroethylene for mice (NTP 1986). In rats, there were significant and dose-related increases in the incidences of mononuclear cell leukemia in exposed male and female rats (males: 28/50 control, 37/50 low dose, 37/50 high dose; females: 18/50 control, 30/50 low dose, 29/50 high dose). This neoplasm occurs spontaneously in Fischer-344 rats, and incidences of mononuclear cell Peukemia in control groups (56% for males, 36% for females) for this study were higher than for historical chamber controls for the laboratory or for untreated controls from the NTP database. However, NTP's Board of Scientific Counselors considered the incidence of rat leukemias to be a valid finding despite high background frequencies because there was a decreased time to the onset of the disease and the disease was more severe in treated animals than in control animals.

Low incidences of renal tubular cell adenomas or adenocarcinomas (l/49, 3149, 4/50) occurred in male rats (NTP 1986). Although the incidence of these tumors was not statistically significant, the fact that there was any increase was itself significant because these tumors are considered uncommon in untreated male rats. In mice of both sexes exposed to 100 or 200 ppm, there were significantly increased incidences of hepatocellular neoplasms (Table 2-2). Study limitations include numerous instances of rats and mice loose from their cages within the exposure chambers, with the potential for aberrations in exposure and animal identification, as well as a very high incidence of mononuclear cell leukemia in control rats, and liver tumors in mice.

In summary, a number of epidemiology studies of dry cleaning workers have shown increases in cancer, especially esophageal and bladder cancers. After reviewing the data, Weiss (1995) concluded that confounding of esophageal cancer by cigarette smoking and heavy alcohol consumption was only partially taken into account in these studies. He also suggested that bladder cancers may be a result of exposure to other solvents used in dry cleaning. Following inhalation exposure to tetrachloroethylene, mononuclear cell leukemia was observed in rats and hepatic tumors were observed in mice (NTP 1986). Because both mononuclear cell leukemia and hepatic tumors are common in rats and mice, respectively, the relevance of these tumors to humans is not clear. Further discussion of the relevance of tumors in animals exposed to tetrachloroethylene to humans is presented in Section 2.5. The cancer effect levels (CELs) for rats and mice are recorded in Table 2-I and plotted in Figure 2- 1.

TABLE 2-2. Hepatocellular Neoplasms in B6C3F$_1$ Mice Exposed to Tetrachloroethylene for 103 Weeks by Inhalation[a,b]

	Control		100 ppm		200 ppm	
	Male	Female	Male	Female	Male	Female
Hepatocellular adenoma	12/49 (24%)	3/48 (16%)	8/49 (12%)	6/50 (12%)	19/50 (38%)	2/50 (4%)
Hepatocellular carcinoma	7/49 (14%)	1/48 (2%)	25/49 (51%)	13/50 (26%)	26/50 (58%)	36/50 (72%)
Hepatocellular adenoma or carcinoma	17/49 (35%)	4/48 (8%)	31/49 (63%)	17/50 (34%)	41/50 (82%)	38/50 (76%)

[a]NTP 1986

[b]Data are presented as the number of neoplasms found per total number of animals in each exposure group. Percentages are given in parentheses.

2.2.2 Oral Exposure

2.2.2.1 Death

One human death has been reported following oral treatment with 3 mL (152 mg/kg) of tetrachloroethylene for hookworm infestation (Chaudhuri and Mukerji 1947). This individual was a severely emaciated "street beggar" with preexistent chronic malnutrition and septic cholecystitis; thus, it is difficult to determine the specific cause of his death and the relevance of this death to healthy humans.

Single-dose LD_{50}, values of 3,835 and 3,005 mg/kg were determined for male and female rats given tetrachloroethylene by gavage in 4% Emulphor in water. Death occurred within 24 hours after dosing and was preceded by tremors, ataxia, and central nervous system depression (Hayes et al. 1986). When given in corn oil, half the female rats treated with a single dose of 5,000 mg tetrachloroethylene/kg died (Berman et al. 1995). An oral LD_{50} of 8,139 mg/kg was reported for mice treated with undiluted tetrachloroethylene (Wenzel and Gibson 1951).

Osborne-Mendel rats of each sex received tetrachloroethylene in corn oil by gavage at doses of 316, 562, 1,000, 1,780, or 3,160 mg/kg 5 days/week for 6 weeks. Deaths (number unspecified) occurred in both males and females at the two highest doses but not at 1,000 mg/kg or lower (NCI 1977).

In a bioassay of tetrachloroethylene administered by gavage to rats and mice, compound-related mortality occurred as a result of toxic nephropathy in both species and hepatocellular tumors in mice (NCI 1971). Increased deaths occurred in groups of male and female rats exposed to 471 and 474 mg/kg/day tetrachloroethylene, respectively, 5 days per week for 78 weeks. Similarly exposed mice had increased numbers of deaths at doses of 536 and 386 mg/kg/day for males and females, respectively. This study is discussed in Sections 2.2.2.2 and 2.2.2.8.

All reliable LOAEL and LD_{50} values for death in each species are recorded in Table 2-3 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-2. No studies were located regarding musculoskeletal or ocular effects in humans or animals after oral exposure to tetrachloroethylene.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to tetrachloroethylene. In a chronic bioassay, microscopic examination of the lungs did not reveal any effects in rats treated by gavage with tetrachloroethylene at doses up to 941 mg/kg/day or in mice at doses up to 1,072 mg/kg/day, doses which were associated with increased mortality (NCI 1977).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to tetrachloroethylene. However, cardiovascular effects from chronic ingestion of solvent-contaminated (including tetrachloroethylene) drinking water were investigated in family members of patients with leukemia in Woburn, Massachusetts (Byers et al. 1988). Fourteen adults in a group of 25 complained of cardiac symptoms of tachycardia at rest, palpitations, or near syncope. Eleven of these were selected for detailed testing that included resting and exercise tolerance electrocardiograms, Holter monitoring, echocardiograms, and serum lipid levels. Of these 11, 8 had serious ventricular dysfunctions, 7 had multifocal premature ventricular beats, and 6 required cardiac medication. None of the subjects had clinically significant coronary artery disease. No rationale was given as to the factors that were involved in the selection of the 11 given extensive testing. No background information on family history of heart disease, smoking habits, or occupational history was given for any of the 25 family members.

In a chronic bioassay, microscopic examination of the heart did not reveal any effects in rats treated by gavage with tetrachloroethylene at doses up to 941 mg/kg/day or in mice at doses up to 1,072 mg/kg/day, both of which were doses associated with increased mortality (NCI 1977).

Gastrointestinal Effects. Vomiting has been reported in boys treated with unspecified oral doses of tetrachloroethylene to remove intestinal worms (Wright et al. 1937). Histological changes in the gastrointestinal tract were not observed in rats or mice treated by gavage with tetrachloroethylene for 78 weeks at doses that increased mortality (NCI 1977).

TABLE 2-3. Levels of Significant Exposure to Tetrachloroethylene - Oral

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
	ACUTE EXPOSURE						
	Death						
1	Rat (Fischer- 344)	once (GO)				5000 F (50% died)	Berman et al. 1995
2	Rat (Sprague-Dawley)	once (G)				3005 F (LD_{50})	Hayes et al. 1986
						3835 M (LD_{50})	
3	Mouse (Swiss-Webster)	once (G)				8139 M (LD_{50})	Wenzel and Gibson 1951

TABLE 2-3. Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Systemic						
4	Rat (Fischer- 344)	14 d (GO)	Hepatic	500 F	1500 F (increased relative liver weights; increased alanine aminotransferase; hepatocellular hypertorphy)		Berman et al. 1995
			Renal	1500 F			
			Endocr	1500 F			
5	Rat (Fischer- 344)	10 d 1x/d (GO)	Hepatic		1000M (increased liver to body weight ratio)		Goldsworthy and Popp 1987
			Bd Wt	1000 M			
6	Rat (Wistar)	5d (GO)	Hepatic	500 M	1000M (significantly increased liver weights; induction of CYP2B P450 enzymes; induction of phase II drug-metabolizing enzymes)		Hanioka et al. 1995
			Bd Wt	1000 M	2000M (body weights 16% lower than controls)		

TABLE 2-3. Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
7	Rat (Fischer- 344)	Gd 6-19 (GO)	Bd Wt			900 F (about 25% decrease in body weight gain)	Narotsky and Kavlock 1995
8	Rat (Fischer- 344)	11 d (GO)	Hepatic	1000 M			Schumann et al. 1980
			Bd Wt	500 M		1000 M (22% decrease in body weight gain)	
9	Mouse (B6C3F1)	10 d 1x/d (G)	Hepatic		1000M (increased liver to body weight ratios; peroxisomal proliferation)		Goldsworthy and Popp 1987
			Renal		1000M (peroxisomal proliferation)		
			Bd Wt	1000 M			
10	Mouse (B6C3F1)	11 d (GO)	Hepatic		100M (hepatocellular swelling)		Schumann et al. 1980
			Bd Wt	1000			

TABLE 2-3. Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Immuno/Lymphor						
11	Rat (Fischer- 344)	14 d (GO)		1500 F			Berman et al. 1995
12	Rat (Wistar)	5d (GO)		1000 M	2000M (atrophy of the spleen and thymus)		Hanioka et al. 1995
	Neurological						
13	Human	once (C)				116 M (amnesia; dizziness; hallucinations)	Haerer and Udelman 1964
14	Human	once				108 (unconsciousness)	Kendrick 1929
15	Rat (Fischer- 344)	once		500 F		1500 F (lacrimation and gait score significantly increased; motor activity significantly decreased)	Moser et al. 1995
16	Rat (Fischer- 344)	Gd 6-19 (GO)				900 F (ataxia that lasted about 4 hours after dosing)	Narotsky and Kavlock 1995

TABLE 2-3. Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Reproductive						
17	Rat (Fischer- 344)	Gd 6-19 (GO)				900 (significant increase in resorptions)	Narotsky and Kavlock 1995
	Developmental						
18	Rat (Fischer- 344)	Gd 6-19 (GO)				900 (increased postnatal deaths; increased micro/anophthalmia)	Narotsky and Kavlock 1995
19	Mouse (NMRI)	7 d (GO)			5[b] M (increased activity at 60 days of age)		Fredriksson et al. 1993
	INTERMEDIATE EXPOSURE						
	Death						
20	Rat (Osborne-Mendel)	6 wk 5d/wk (GO)				1780 (number of deaths not specified)	NCI 1977

TABLE 2-3. Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Systemic						
21	Rat (Sprague-Dawley)	90 d (W)	Hemato	1400			Hayes et al. 1986
			Hepatic	400	1400 (increased liver/body weight ratio)		
			Renal	14	400M (increased kidney/body weight ratio)		
			Bd Wt	14	400 F (18% decrease in body weight gain)	1400 F (24% decrease in body weight gain)	
22	Rat (Osborne-Mendel)	6 wk 5d/wk (GO)	Bd Wt	1000			NCI 1977
23	Rat (Osborne-Mendel)	7 wk 5d/wk (GO)	Hepatic		995 (increased liver weight; increased Type II GGT and foci with or without an initiator)		Story et al. 1986

TABLE 2-3. Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
24	Mouse (Swiss-Cox)	6 wk 5d/wk (GO)	Hepatic	20	100 (increased relative liver weight; increased liver triglycerides)	200 (hepatic necrosis)	Buben and O'Flaherty 1985
25	Mouse (B6C3F1)	6 wk 5d/wk (GO)	Bd Wt			562 F (30% decrease in body weight gain)	NCI 1977
	CHRONIC EXPOSURE						
	Death						
26	Rat (Osborne-Mendel)	78 wk 5d/wk (GO)				471 M (decreased survival) 474 F (decreased survival)	NCI 1977
27	Mouse (B6C3F1)	78 wk 5d/wk (GO)				386 F (reduced survival) 536 M (reduced survival)	NCI 1977

TABLE 2-3. Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Systemic						
28	Rat (Osborne-Mendel)	78 wk 5d/wk (GO)	Resp	941			NCI 1977
			Cardio	941			
			Gastro	941			
			Hepatic	941			
			Renal			471 M (nephropathy) 474 F (nephropathy)	
			Endocr	941			
			Derm	941			
			Bd Wt	941			
29	Mouse (B6C3F1)	78 wk 5d/wk (GO)	Resp	1072			NCI 1977
			Cardio	1072			
			Gastro	1072			
			Hepatic	1072			
			Renal			386 F (nephropathy) 536 M (nephropathy)	
			Endocr	1072			
			Derm	1072			
			Bd Wt	1072			

TABLE 2-3. Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
	Cancer						
30	Mouse (B6C3F1)	78 wk 5d/wk (GO)				386 F (CEL: hepatocellular 536 M carcinomas)	NCI 1977

[a]The numbers correspond to entries in Figure 2-2.

[b]The acute duration oral MRL of 0.05 mg/kg/day was calculated by dividing the 5 mg/kg/day dose by an uncertainty factor of 100 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 1 for human variability).

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm = dermal; Endocr = endocrine; F = female; Gastro = gastrointestinal; (G) = gavage -- vehicle not specified; Gd = gestation day; GGT = gamma glutamyl transpeptidase; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; •LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s)

Figure 2-2. Levels of Significant Exposure to Tetrachloroethylene - Oral

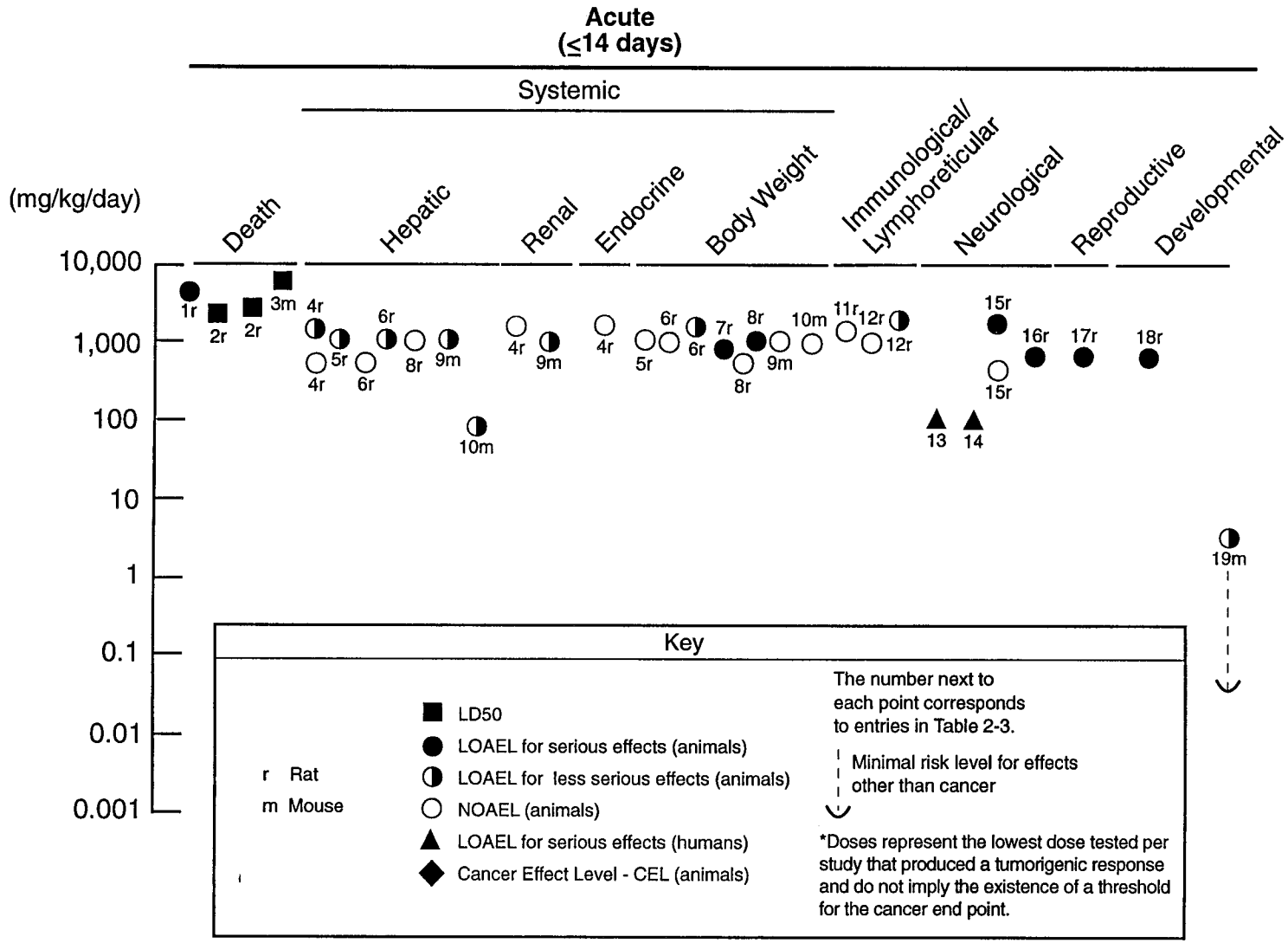


Figure 2-2. Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

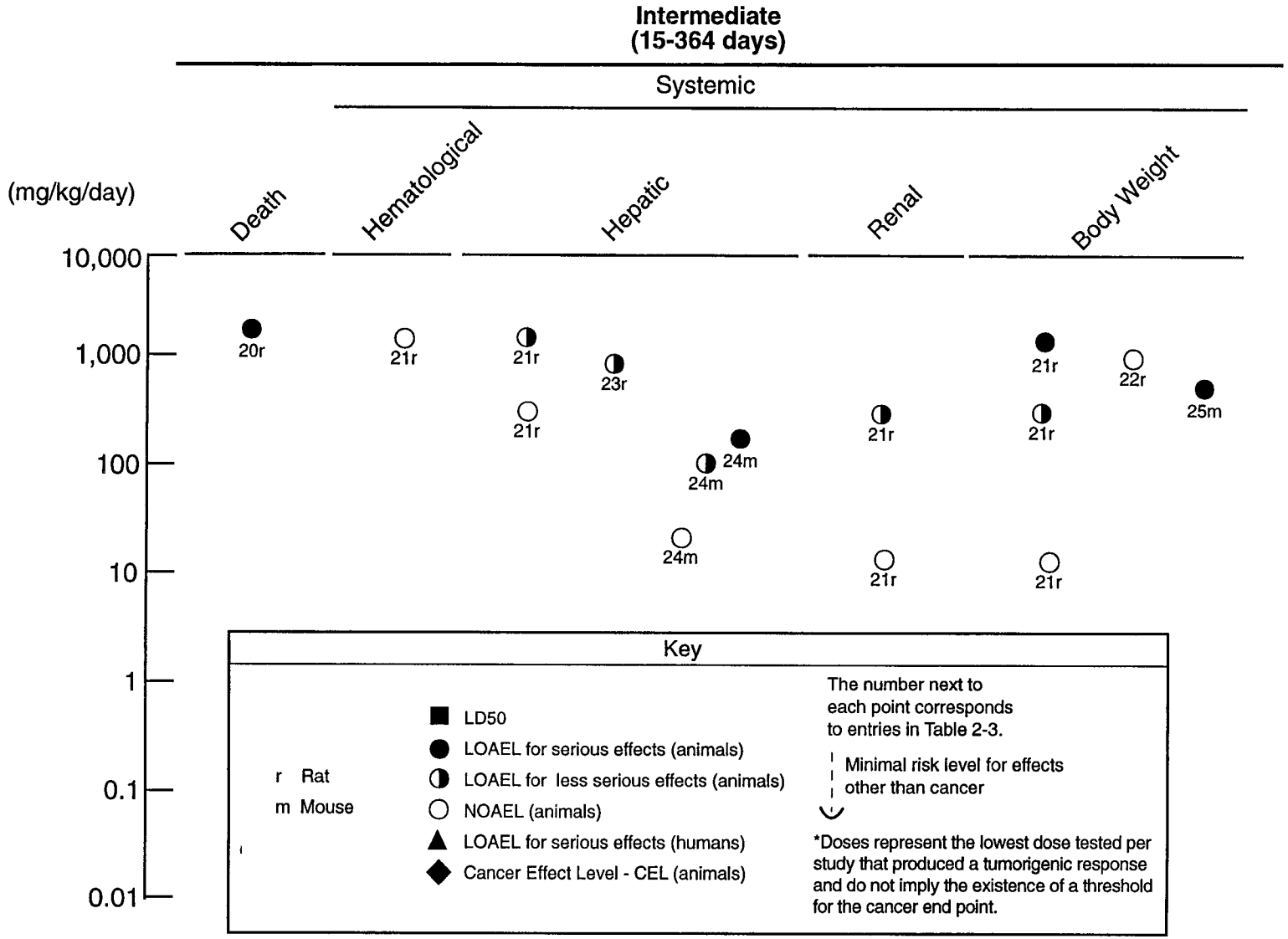
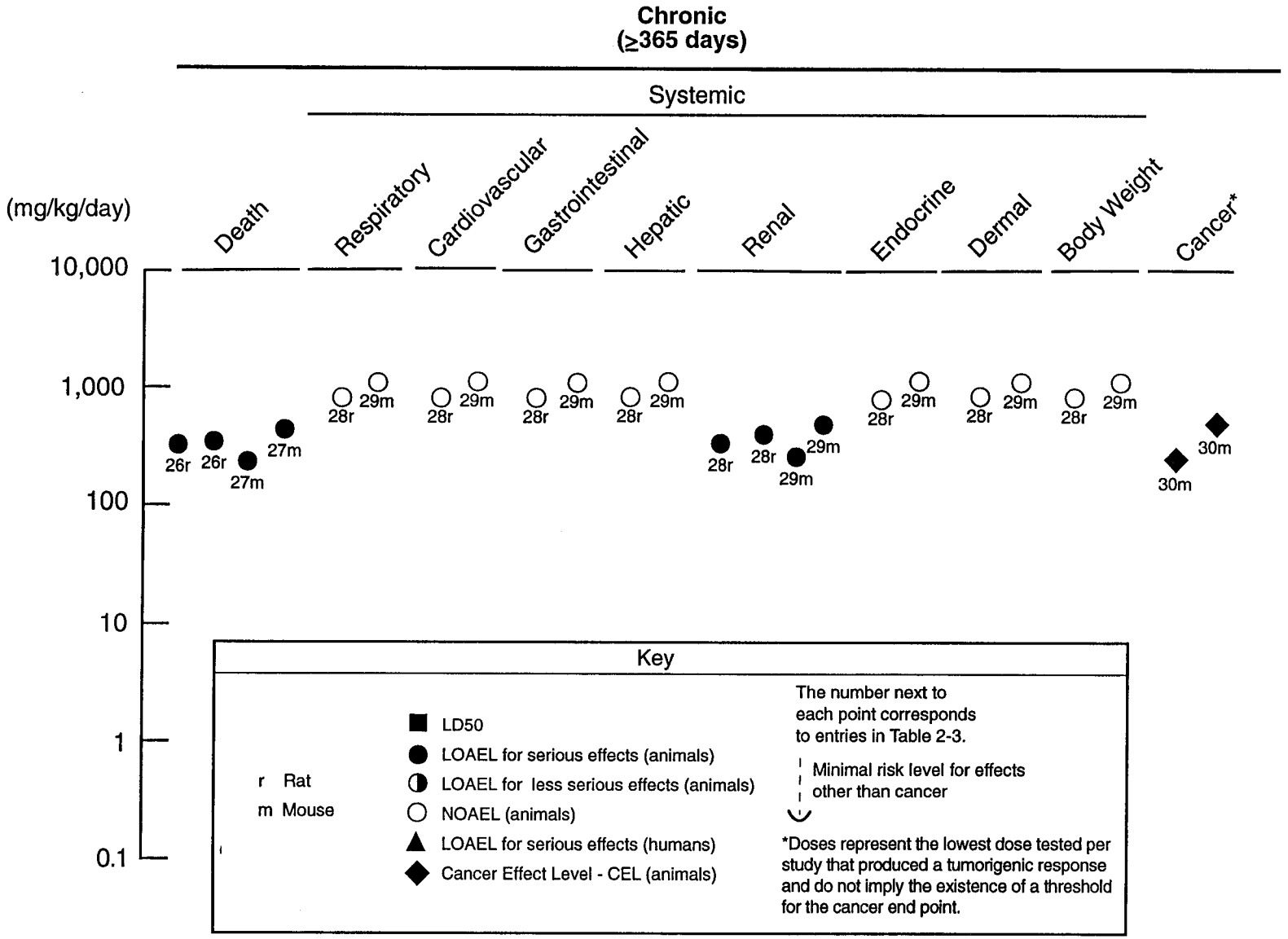


Figure 2-2. Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)



Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to tetrachloroethylene.

Hemoglobin, hematocrit, and cell counts were not affected in rats exposed to tetrachloroethylene in drinking water (4% emulphor) at doses up to 1,400 mg/kg/day for 90 days (Hayes et al. 1986). Mice exposed to 0.1 mg/kg/day tetrachloroethylene in drinking water for 7 weeks had high relative concentrations of tetrachloroetbylene in the spleen, increased spleen weight, increased hemosiderin deposits and congestion of red pulp, increased serum lactic dehydrogenase (LDH) isozyme I, which was interpreted as being indicative of erythrocyte hemolysis, and a relative decrease in bone marrow erythropoiesis (Marth 1987). Milder or no hematological effects, depending on the parameters evaluated, occurred at exposures to 0.05 mg/kg/day. All hematological effects were reversible within an S-week recovery period. There are several limitations of this study. First, only one sex of mouse was evaluated. Second, splenic hemosiderosis, one of the parameters evaluated, is present in normal mouse spleens; therefore, the presence of this pigment in the spleen is not necessarily an indicator of hemolysis unless it is more widespread and severe compared to control spleens. Third, grading of lesions by distribution and severity for either spleen or bone marrow was not documented in the paper. Fourth, the study author did not provide documentation that LDH isozyme I is the isozyme found in mouse erythrocytes.

Mild microcytic anemia and bone marrow and immune function changes occurred in $B6C3F_1$ mice exposed via drinking water to tetrachloroethylene plus 24 other groundwater contaminants (Germolec et al. 1989). The observed changes in bone marrow consisted of suppression of granulocytemacrophage progenitor cells accompanied by a decrease in bone marrow cellularity. A dose-related suppression of antigen-induced antibody forming cells was also observed. This study is discussed in more detail in Section 2.2.2.3.

Hepatic Effects. The liver has not been shown to be a target organ in humans exposed to tetrachloroethylene by the oral route except a single case report of obstructive jaundice and hepatomegaly reported in a 6-week-old infant exposed to tetrachloroethylene (1 mg/dL) via breast milk (Bagnell and Ellenberger 1977). After breast feeding was ended, a rapid improvement was observed.

2. HEALTH EFFECTS

The liver is a principal target organ in rodents exposed orally to tetrachloroethylene. Hepatic effects in rodents from oral exposure to tetrachloroethylene are similar to those produced by inhalation exposure. Mice are more sensitive than rats to tetrachloroethylene-induced toxic effects; these effects are related to tetrachloroethylene metabolism-particularly the formation of TCA-as discussed in Section 2.3.

Liver weights were significantly increased and CYP2B P-450 enzymes were significantly induced in rats treated by gavage with tetrachloroethylene in corn oil at 1,000 and 2,000 mg/kg/day for 5 days (Hanioka et al. 1995). The P-450 enzymes were also significantly induced at 500 mg/kg/day, although no change in liver weight was noted at this dose. Phase II drug metabolizing enzymes were also induced with significant increases in DT-diaphorase activity at 2,000 mg/kg/day, significant increases in glutathione *S*-transferase activity at 1,000 and 2,000 mg/kg/day, and significant increases in UDP-glucuronyltransferase activity at all doses tested (≥125 mg/kg/day). Increased relative liver weights, increased serum alanine aminotransferase, and hepatocellular hypertrophy were observed in female rats treated by gavage with tetrachloroethylene in corn oil at a dose of 1,500 mg/kg/day for 14 days (Berman et al. 1995). Hepatic effects were not observed at 500 mg/kg/day.

Tetrachloroethylene administered by gavage at a dose of 1,000 mg/kg/day for 10 days to male $B6C3F_1$ mice increased relative liver weights and elevated cyanide-insensitive palmitoyl CoA oxidase levels, indicative of peroxisomal proliferation (Goldsworthy and Popp 1987). The same dose administered to Fischer-344 rats did not elevate cyanide-insensitive palmitoyl CoA oxidase levels significantly above controls, although relative liver weights were increased. Schumann et al. (1980) reported hepatocellular swelling in mice given 11 daily gavage doses of 100 mg tetrachloroethylene/kg. A similar effect was not observed in rats exposed at doses up to 1,000 mg/kg/day.

Toxic effects induced in male Swiss Cox mice given tetrachloroethylene by gavage at doses of 0, 20, 100, 200, 500, 1,000, 1,500, or 2,000 mg/kg/day for 6 weeks were increased relative liver weight and triglycerides beginning at 100 mg/kg/day, decreased glucose-6-phosphate and increased SGPT at 500 mg/kg, and hepatocellular lesions at ≥100 mg/kg/day. Lesions consisted of centrilobular hepatocellular hypertrophy, karyorrhexis, centrilobular necrosis, polyploidy, and hepatocellular vacuolization. All these effects were present in the two dose groups examined histologically (200 and 1,000 mg/kg/day) (Buben and O'Flaherty 1985). Centrilobular necrosis and increased levels of protein

and protein-bound carbohydrates were observed in the livers of rats treated by gavage with tetrachloroethylene in sesame oil at 3,000 mg/kg/day for 42 days (Ebrahim et al. 1995).

Elevated liver weights, relative to body weight but not brain weight, occurred in both sexes of Sprague-Dawley rats given 1,400 mg/kg/day tetrachloroethylene in drinking water for 13 weeks. While the serum enzyme, 5'-nucleotidase, was increased in females given 1,400 mg/kg/day and in males given 400 or 1,400 mg/kg/day, results of other biochemical measurements did not suggest a hepatotoxic effect. In addition, gross necropsy examination did not reveal any abnormalities in selected organs including the liver (Hayes et al. 1986). The major limitation of this study was lack of microscopic examination of livers.

Tetrachloroethylene has been tested for initiating and promoting activity in a rat liver foci assay (Story et al. 1986). Mean liver weights and/or liver-to-body weight ratios were significantly increased relative to the controls in partially hepatectomized adult male Osborne-Mendel rats (l0/group) administered 995 mg/kg/day tetrachloroethylene by gavage in corn oil. In both the presence and absence of an initiator (30 mg/kg diethylnitrosamine), tetrachloroethylene (995 mg/kg/day) induced an increase in enzyme-altered foci (foci with increased γ-glutamyltranspeptidase activity).

Chemically related nonneoplastic liver lesions were not reported for Osborne-Mendel rats or $B6C3F_1$ mice given tetrachloroethylene by gavage in a chronic bioassay (NCI 1977). This study, including its limitations, is discussed in Section 2.2.2.8.

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to tetrachloroethylene.

Daily gavage administration of 1,000 mg/kg tetrachloroethylene to male Fischer-344 rats for 10 days produced an increase in protein droplet accumulation and cell proliferation in the P2 segment of the kidney. This effect, not seen in female rats, was correlated with an increased presence of α-2μ-globulin in the proximal convoluted epithelial cells (Goldsworthy et al. 1988). Results from an earlier study by the same investigators indicated that peroxisomal proliferation in the rat kidney was not associated with administration of 1,000 mg/kg/day tetrachloroethylene (Goldsworthy and Popp 1987). Peroxisomal proliferation was the only end point investigated in this experiment. Male rats exposed to 1,500 mg/kg tetrachloroethylene by gavage for 42 days developed typical α-2μ-globulin nephropathy

(Green et al. 1990). Male rats, but not female rats, also developed α-2μ-globulin nephropathy following daily gavage treatment with tetrachloroethylene at 500 mg/kg/day (Bergamaschi et al. 1992). Kidney effects were not observed in female rats treated by gavage with tetrachloroethylene in corn oil at a dose of 1,500 mg/kg/day for 14 days (Berman et al. 1995). Male $B6C3F_1$ mice exposed to 1,000 mg/kg per day by gavage for 10 days had peroxisomal proliferation as evidenced by elevated cyanide-insensitive palrnitoyl CoA oxidase levels (Goldsworthy and Popp 1987).

Hypercellular glomeruli and congestion of the convoluted tubules were observed in the kidneys of rats treated by gavage with tetrachloroethylene (3,000 mg/kg/day) in sesame oil for 42 days (Ebrahim et al. 1995). Significant increases in the levels of protein and protein-bound carbohydrates in the kidneys were also observed. No other doses of tetrachloroethylene were used in this study. Increased kidney/body weight ratios were observed in male rats treated with tetrachloroethylene in the drinking water at 400 mg/kg/day for 90 days (Hayes et al. 1986). No effects on the kidneys were observed at a dose of 14 mg/kg/day.

Osborne-Mended rats and $B6C3F_1$ mice of each sex were exposed to tetrachloroethylene in corn oil by gavage for 78 weeks, followed by observation periods of 32 weeks (rats) and 12 weeks (mice) in a carcinogenicity bioassay (NCI 1977). TWA doses for the study were 536 and 1,072 mg/kg/day for male mice, 386 and 772 mg/kg/day for female mice, 471 and 941 mg/kg/day for male rats, and 474 and 949 mg/kg/day for female rats; untreated and vehicle control groups were included. Study limitations are discussed in Section 2.2.2.8. Toxic nephropathy occurred at all dose levels in both sexes of rats and mice, as did increased mortality. The nephropathy in both species was characterized by degenerative changes in the proximal convoluted tubules at the junction of the cortex and medulla, with cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium and hyalin intralurninal casts. Rat kidneys also had occasional basophilic tubular cytomegaly, chronic inflammation, and mineralization.

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to tetrachloroethylene. Histopathological changes in the adrenal glands were not observed in female rats treated by gavage with tetrachloroethylene in corn oil at a dose of 1,500 mg/kg/day for 14 days (Berman et al. 1995). In a chronic bioassay, histological changes were not observed in the adrenal glands, thyroid, parathyroid, pancreas, or pituitary of rats and mice treated by gavage with tetrachloroethylene at doses that resulted in increased mortality (NCI 1977).

Dermal Effects. In family members of patients with leukemia from the Woburn study, 13 of 25 adults who had been chronically exposed to solvent-contaminated drinking water (including tetrachloroethylene) developed skin lesions. These were maculopapular rashes that occurred approximately twice yearly and lasted 2-4 weeks. These skin conditions generally disappeared within l-2 years after cessation of exposure to contaminated water (Byers et al. 1988). There is no evidence that skin lesions were related to solvent exposure in general or to tetrachloroethylene specifically.

In a chronic bioassay, histological changes were not observed in the skin of rats and mice treated by gavage with tetrachloroethylene at doses that resulted in increased mortality (NCI 1977).

Body Weight Effects. At the end of a 5-day study, body weights of male rats treated by gavage with tetrachloroethylene at 2,000 mg/kg/day were 16% lower than controls (Hanioka et al. 1995). Body weight gain was decreased 22% in male Fischer-344 rats treated by gavage with tetrachloroethylene at 1,000 mg/kg/day for 11 days (Schumann et al. 1980). A decrease in body weight gain of approximately 25% was observed in pregnant rats treated by gavage with tetrachloroethylene in corn oil at 900 mg/kg/day on gestation days 6-19 (Narotsky and Kavlock 1995). No effect on body weight was observed in Fischer-344 rats treated by gavage with tetrachloroethylene at 1,000 mg/kg/day for 10 days (Goldsworthy and Popp 1987) or in $B6C3F_1$ mice treated by gavage with tetrachloroethylene at 1,000 mg/kg/day for 10 or 11 days (Goldsworthy and Popp 1987; Schumann et al. 1980). An explanation for the difference in effect on body weight in rats in the studies was not readily apparent.

Changes in body weight in longer term oral studies are also not consistent. Hayes et al. (1986) reported 18% and 24% decreases in body weight gain in female rats treated with tetrachloroethylene in the drinking water at 400 and 1,400 mg/kg/day, respectively, for 90 days. Body weight gain was significantly decreased (15%) in males only at 1,400 mg/kg/day. A 30% reduction in body weight gain was observed in female mice treated by gavage with tetrachloroethylene at 562 mg/kg/day for 90 days (NCI 1977), but no effect on body weight gain in male mice was noted at this dose. Changes in body weight were not observed in rats treated by gavage with tetrachloroethylene at doses of ≤1,000 mg/kg/day for 6 weeks or in rats or mice in a chronic bioassay at doses associated with increased mortality (up to 941 mg/kg/day for rats and 1,072 mg/kg/day for mice) (NCI 1977).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to tetrachloroethylene.

There was, however, a study suggesting immunological effects in humans with chronic exposure to a solvent-contaminated domestic water supply. Several wells in Wobum, Massachusetts, were contaminated by a variety of solvents. The two main volatile chlorinated hydrocarbons measured before well closure were trichloroethylene (267 ppb) and tetrachloroethylene (21 ppb) (Byers et al. 1988). A potential association between water contamination in Woburn and cases of childhood leukemia is discussed in Section 2.2.2.8.

Some immunological abnormalities were found in 23 adults in Wobum who were exposed to contaminated water and who were family members of children with leukemia. These immunological abnormalities, tested for 5 years after well closure, were persistent lymphocytosis, increased numbers of T lymphocytes, and depressed helper:suppressor T cell ratio. A follow-up test 18 months later revealed reductions in lymphocyte counts, decreased numbers of suppressor T cells, and increased helper:suppressor ratio. Auto-antibodies, particularly anti-nuclear antibodies, were detected in 48% (1 l/23) of the adults tested. In the Wobum population, there was also a suggestion of an association between cumulative exposure to contaminated wells and increased urinary tract infections and respiratory disorders (asthma, bronchitis, pneumonia) in children (Lagakos et al. 1986).

Interpretation of the results reported by Byers et al. (1988) and Lagakos et al. (1986) is limited because of the possible bias in identifying risk factors for immunological abnormalities in a small, nonpopulation-based group identified through probands with leukemia. There is evidence that some genetic factor or factors may predispose persons to both altered immunologic parameters as well as an increased risk of developing leukemia. Other limitations of this study are described in Section 2.2.2.8.

Atrophy of the spleen and thymus, indicated by significantly decreased organ weights, was noted in rats treated by gavage with tetrachloroethylene in corn oil at 2,000 mg/kg/day for 5 days (Hanioka et al. 1995). This effect was not observed at 1,000 mg/kg/day. Histopathological changes in the spleen and thymus were not observed in female rats treated by gavage with tetrachloroethylene in corn oil at 1,500 mg/kg/day for 14 days (Berman et al. 1995).

Immunological effects were detected in a study exposing female $B6C3F_1$ mice to drinking water containing tetrachloroethylene (maximum concentration 6.8 ppm) and 24 other contaminants frequently found in groundwater for 14 or 90 days (Germolec et al. 1989). Mice exposed to the highest concentration of this laboratory-prepared stock solution had a dose-related suppression in antibody plaque-forming units to sheep red blood cells and increased host susceptibility to infection by the protozoan, *Plasmodium yoelii.* There were no changes in lymphocyte number or T cell subpopulations, no alterations of T cell, NK cell or macrophage activities, and no effect on host susceptibility to challenge with intravenous *Listeria monocytogenes* (bacteria) or PYB6 tumor cells. These findings indicate an immunotoxic effect on B cells/humoral immunity (Germolec et al. 1989). These effects cannot be attributed to tetrachloroethylene alone.

In a chronic bioassay, microscopic examination of the spleen, lymph nodes, and thymus of rats and mice exposed by gavage to tetrachloroethylene at doses that resulted in increased mortality did not reveal any adverse immunological or lymphoreticular effects (NCI 1977).

The highest NOAEL values and all LOAEL values from each reliable study for immunological and lymphoreticular effects identified in rats for each duration category are recorded in Table 2-3 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

Acute neurological effects in humans after ingesting tetrachloroethylene are similar to those seen after inhalation. A 6-year-old child who ingested 12-16 g of tetrachloroethylene was conscious upon admission to a hospital 1 hour after ingestion, but his level of consciousness deteriorated to somnolence and subsequently coma (Koppel et al. 1985). Other symptoms included drowsiness, vertigo, agitation, and hallucinations. The boy recovered completely.

The oral administration of tetrachloroethylene as an anthelminthic in humans was common at one time; however, newer therapeutic agents have since replaced tetrachloroethylene. Narcotic effects, inebriation, perceptual distortion, and exhilaration, but not death, were observed in patients receiving doses ranging from 2.8 to 4 mL (about 4.2-6 g) of tetrachloroethylene orally as an anthelminthic (Haerer and Udelman 1964; Kendrick 1929; Sandground 1941; Wright et al. 1937).

Ataxia was observed in pregnant rats treated by gavage with tetrachloroethylene in corn oil at 900 mg/kg/day on gestation days 6-19 (Narotsky and Kavlock 1995). The ataxia lasted about 4 hours after dosing. Four hours after female rats were given a single gavage dose of 1,500 mg tetrachloroethylene/kg, lacrimation and gait scores were significantly increased and motor activity was significantly decreased (Moser et al. 1995). The study authors indicated that the effects were less 24 hours after dosing, but specific data were not provided. A battery of neurological tests which examined autonomic, neuromuscular, and sensorimotor function, as well as activity and excitability did not show any significant effects at 4 or 24 hours after a single gavage dose of 500 mg/kg, or 24 hours after the last of 14 daily doses of 1,500 mg tetrachloroethylene/kg (Moser et al. 1995).

In a chronic bioassay, microscopic examination of the brains of rats and mice exposed by gavage to tetrachloroethylene at doses that resulted in increased mortality did not reveal any adverse effects (NCI 1977).

The serious LOAELs for nervous system effects identified in human and animal studies, and the NOAEL in rats are indicated in Table 2-3 and Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to tetrachloroethylene.

Resorptions were significantly increased in rats treated by gavage with tetrachloroethylene in corn oil at doses of 900 and 1,200 mg/kg/day on gestation days 6-19 (Narotsky and Kavlock 1995). At 1,200 mg/kg/day, no live pups were delivered by gestation day 22, while the number at 900 mg/kg/day (5.2±1.5 pups/litter) was significantly ($p<0.01$) reduced compared to controls (7.7±0.7 pups/litter). The implantation sites required ammonium sulfide staining for detection, suggesting that the embryos died early in the treatment period. The 900-mg/kg/day dose also resulted in maternal ataxia and body weight gain approximately 25% less than controls.

In a chronic bioassay, microscopic examination of the testes and ovaries of rats and mice exposed by gavage to tetrachloroethylene at doses that resulted in increased mortality did not reveal any adverse effects (NCI 1977).

The serious LOAEL for reproductive effects in rats is recorded in Table 2-3 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

In the Woburn, Massachusetts, study of residents exposed to drinking water contaminated with solvents, including 21 ppb tetrachloroethylene, there was a suggestion that eye/ear anomalies and central nervous system/chromosomal/oral cleft anomalies were associated with exposure (Lagakos et al. 1986). However, several scientists have questioned the biological relevance of grouping these anomalies for purposes of statistical analysis (Lagakos et al. 1986). The association between birth outcome and drinking water contamination has also been examined in 75 towns in New Jersey (Bove et al. 1995). Based on four cases, oral cleft defects were increased (odds ratio 3.54; 90% confidence interval 1.28-8.78) in the group with the highest exposure (>10 ppb). Because of possible exposure misclassification, and limits in the number of possible confounders that were examined (maternal occupational exposures, smoking, medical history, height, gestational weight gain), the study authors note that this study alone cannot resolve whether some of the relationships between drinking water contaminants and adverse outcome are causal or a result of chance or bias.

At 900 mg/kg/day, a dose that resulted in maternal toxicity (ataxia and body weight gain approximately 25% less than controls), increased numbers of postnatal deaths and increased micro/anophthalmia were observed in offspring of rats treated by gavage with tetrachloroethylene in corn oil on gestation days 6-19 (Narotsky and Kavlock 1995). On postnatal day 6, the number of pups/litter that were alive was 7.7±0.7 in the control litters, and 4.9±1.2 in the 900-mg/kg/day group ($\rho<0.001$) Additional data about malformations were not provided.

In a study regarding late stages of nervous system development, male mouse pups were treated by gavage with tetrachloroethylene at 5 and 320 mg/kg/day for 7 days beginning at 10 days of age (Fredriksson et al. 1993). Throughout the dosing period, no clinical signs of toxicity were observed. Measures of activity (locomotion, rearing, and total activity) were completed in mice at 17 and 60 days of age. No significant effects were observed in mice at 17 days of age, while at 60 days of age a significant increase in locomotion ($p<0.05$ or <0.0l) and total activity ($p<0.01$) was observed at both doses. Based on this LOAEL of 5 mg/kg/day for evidence of developmental neurotoxicity, an acute oral MRL of 0.05 mg/kg/day was calculated as described in the footnote to Table 2-3.

All reliable LOAELs values identified in rats and mice are recorded in Table 2-3 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to tetrachloroethylene.

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

A case-control study was completed to examine the relationship between bladder cancer, kidney cancer, and leukemia with exposure to tetrachloroethylene in public drinking water in an area in Massachusetts where many pipes were lined with a tetrachloroethylene containing resin (Aschengrau et al0 1993). Exposure was estimated as a relative delivered dose using a model described by Webler and Brown (1993). Based on a small number of cancer patients with tetrachloroethylene exposure (7), the investigators indicated that there was a tendency for an increased risk of leukemia among patients (2) who were most highly exposed. Because of the small number of patients, and the potential for drinking water contaminated with other chemicals, the association between leukemia and tetrachloroethylene noted in this study is not definitive. In a study in New Jersey, tetrachloroethylene contamination of the drinking water was associated with an increased incidence of non-Burkitt's highgrade non-Hodgkin's lymphoma in females (Cohn et al. 1994). Many of the water supplies were also contaminated with trichloroethylene, making it difficult to assess the relative contribution of each chemical. The investigators also noted that the conclusions of their study are limited by potential misclassification of exposure because of lack of information on individual long-term residence and water consumption

After tri- (212 μg/L) and tetrachloroethylene (180 μg/L) were identified in the drinking water supply of two towns in Finland, the incidence rates of total cancer, Biver cancer, non-Hodgkin's lymphoma, mnltiple myeloma, and leukemia were compared with the rest of the country (Vartianinen et al. 1993). No significant difference was found. This study is limited in that people who might not have been exposed were included in the exposed group, and it is not clear how long the people were exposed.

2. HEALTH EFFECTS

The contamination was discovered in 1992, and new sources of drinking water were supplied shortly after the discovery. A controversial study of a population in Woburn, Massachusetts, reported a potential association between ingestion of drinking water contaminated with solvents and increased risk of childhood leukemia, particularly acute lymphocytic leukemia (Lagakos et al. 1986). Numerous investigators (MacMahon 1986; Prentice 1986; Rogan 1986; Swan and Robins 1986; Whitmore 1986) have evaluated the data and have identified a number of shortcomings in the study. The two wells in question began pumping in 1964-1967. Measurements of well contaminants before their closure in 1979 revealed numerous volatile organic compounds in the drinking water, with the highest concentrations being trichloroethylene (267 ppb) and tetrachloroethylene (21 ppb) (Byers et al. 1988). Of particular importance is the fact that no more than 6 of the 20 cases of leukemia could be linked to drinking water from the contaminated wells; several cases occurred in children with no access to these wells. The extent and duration of the contamination in the wells of concern are also not known. Geophysical modeling has suggested that the contamination had probably been present before the measurements of the contaminants were taken. Therefore, it is not possible to determine when exposure to the chemicals first occurred or whether the level of exposure varied over time. Two approaches were used in classifying exposures in the study by Lagakos et al. (1986). The use of continuous measurement based on estimates of the use and distribution of water from the contaminated wells actually showed less significance than the cruder measurement which accounted for water consumed from other sources, such as schools or workplaces. This toxicological profile attempts, where possible, to identify exposures to the specific chemical under discussion. The contamination of the two wells at Wobum involved more than one measurable contaminant.

The study by Lagakos et al. (1986) used family members of children affected with leukemia and other community members as interviewers, introducing possible interviewer bias. In addition, the study was performed following considerable publicity about the well contamination and the possible health effects that could follow these exposures, thus contributing to recall bias of the participants.

Cancer has been reported in experimental animals after oral exposure to tetrachloroethylene. Osborne-Mendel rats and B6C3F_1 mice of each sex were exposed to tetrachloroethylene in corn oil by gavage for 78 weeks, followed by observation periods of 32 weeks (rats) and 12 weeks (mice) in an NCI (1977) carcinogenicity bioassay. Because of numerous dose adjustments during the study, doses had to be represented as TWAs. TWA doses were 471 and 941 mg/kg/day for male rats, 474 and 949 mg/kg/day for female rats, 536 and 1,072 mg/kg/day for male mice, and 386 and 772 mg/kg/day

for female mice. The elevated early mortality, which occurred at both doses in both sexes of rats and mice, was related to compound-induced toxic nephropathy (see Section 2.2.2.2). Because of reduced survival, this study was not considered adequate for evaluation of carcinogenesis in rats. Statistically significant increases in hepatocellular carcinomas occurred in the treated mice of both sexes. Incidences in the untreated control, vehicle control, low-dose, and high-dose groups were 2/17, 2/20, 32/49, and 27/48 in male mice, and 2/20, 0/20, 19/48, and 19/48 in female mice. Study limitations included control groups smaller than treated groups (20 versus 50), numerous dose adjustments during the study, early mortality related to compound-induced toxic nephropathy suggesting that a maximum tolerated dose was exceeded, and pneumonia due to intercurrent infectious disease (murine respiratory mycoplasmosis) in both rats and mice.

Because of its carcinogenic activity in mouse liver, tetrachloroethylene has been tested for initiating and promoting activity in a rat liver foci assay. Tetrachloroethylene administered by gavage in corn oil at 995 mg/kg/day did not exhibit initiating activity as indicated by an increase in γ-glutamyltrans-peptidase-positive type I altered foci. Tetrachloroethylene did promote the appearance of type II altered foci, both in the presence and in the absence of an initiator (in this case, diethylnitrosamine) (Story et al. 1986).

All reliable CELs are recorded in Table 2-3 and plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to tetrachloroethylene.

All five rabbits treated with a single dermal dose of 3,245 mg/kg tetrachloroethylene that was occluded for 24 hours survived (Kinkead and Leahy 1987). Additional studies regarding death following dermal exposure in animals were not located.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, gastrointestinal, hematological, or musculoskeletal effects in humans or animals after dermal exposure to tetrachloroethylene.

Cardiovascular Effects. Hypotension was reported in a male laundry worker found lying in a pool of tetrachloroethylene (Hake and Stewart 1977). In this case, the worker was exposed to tetrachloroethylene by both inhalation and dermal routes of exposure, and the exact contribution of dermal exposure is unknown. The patient fully recovered from the effects of tetrachloroethylene.

No studies were located regarding cardiovascular effects in animals after dermal exposure to tetrachloroethylene.

Hepatic Effects. Elevated serum enzymes (not further described) indicative of mild liver injury were observed in an individual found lying in a pool of tetrachloroethylene (Hake and Stewart 1977). Exposure in this case was by both the inhalation and dermal routes, and the exact contribution of dermal exposure is unknown.

No studies were located regarding hepatic effects in animals after dermal exposure to tetrachloroethylene.

Renal Effects. Proteinuria, which lasted for 20 days, was observed in an individual found lying in a pool of tetrachloroethylene (Hake and Stewart 1977). Exposure in this case was by both the inhalation and dermal routes, and the exact contribution of dermal exposure is unknown.

No studies were located regarding renal effects in animals after dermal exposure to tetrachloroethylene.

Dermal Effects. Five volunteers placed their thumbs in beakers of tetrachloroethylenefor 30 minutes (Stewart and Dodd 1964). Within 5-10 minutes, all subjects had a burning sensation. After the thumb was removed from the solvent, the burning decreased during the next 10 minutes. Marked erythema, which cleared l-2 hours after exposure, was present in all cases. Chemical burns characterized by severe cutaneous erythema, blistering, and sloughing have resulted from prolonged

(more than 5 hours) accidental contact exposure to tetrachloroethylene used in dry cleaning operations (Hake and Stewart 1977; Ling and Lindsay 1971; Morgan 1969).

Rabbits were exposed dermally to pure tetrachloroethylene (2 mL/kg body weight) which was covered by an occlusive dressing for 24 hours to prevent evaporation of the chemical. The animals did not develop toxic signs, and skin lesions were not reported (Kinked and Leahy 1987).

Ocular Effects. Intense ocular irritation has been reported in humans after acute exposure to tetrachloroethylene vapor at concentrations greater than 1,000 ppm (Carpenter 1937; Rowe et al. 1952). Vapors of tetrachloroethylene at 5 or 20 ppm were irradiated along with nitrogen dioxide in au environmental chamber in order to simulate the atmospheric conditions of Los Angeles County. These conditions did not produce appreciable eye irritation in volunteers exposed to the simulated atmosphere (Wayne and Orcutt 1960).

No studies were located regarding ocular effects in animals after dermal exposure to tetrachloroethylene including direct application to the eye.

2.2.3.3 Immunological and Lymphoreticuiar Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals following dermal exposure to tetrachloroethylene.

2.2.3.4 Neurological Effects

A male laundry worker found lying in a pool of tetrachloroethylene was in a coma (Hake and Stewart 1977). The exposure to tetrachloroethylene in this case was by both the inhalation and dermal routes, and the exact contribution of dermal exposure is unknown. The patient fully recovered from the effects of tetrachloroethylene.

No studies were located regarding neurological effects in animals after dermal exposure to tetrachloroethylene.

No studies were located regarding the following health effects in humans or animals after dermal exposure to tetrachloroethylene:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans after dermal exposure to tetrachloroethylene.

In a mouse skin initiation-promotion assay, tetrachloroethylene applied at amounts of 18 or 54 mg did not produce skin tumors over a 440-594-day study duration when applied either as an initiator or a promoter (Van Duuren et al. 1979).

2.3 TOXICOKINETICS

Tetrachloroethylene is readily absorbed following inhalation and oral exposure as well as direct exposure to the skin. Pulmonary absorption of tetrachloroethylene is dependent on the ventilation rate, on the duration of exposure, and at lower concentrations, on the proportion of tetrachloroethylene in the inspired air. Compared to pulmonary exposure, uptake of tetrachloroethylene vapor by the skin is minimal. Once tetrachloroethylene is absorbed, its relatively high lipophilicity results in distribution to fatty tissue. The fat/blood partition coefficient in humans is in the range of 125-159. Because of its affmity for fat, tetrachloroethylene is found in milk, with greater levels in milk with a higher fat content. Tetrachloroethylene has also been shown to cross the placenta and distribute to the fetus.

Regardless of the route of exposure, only l-3% of the absorbed tetrachloroethylene is metabolized to trichloroacetic acid (TCA) by humans, and the metabolism of tetrachloroethylene is saturable. Compared to humans, rodents, especially mice, metabolize more tetrachloroethylene to TCA. Geometric mean V_{max} values for the metabolism of tetrachloroethylene of 13, 144, and

710 nmol/(minkg) have been reported for humans, rats, and mice, respectively. TCA produced from tetrachloroethylene is excreted in the urine, and in humans, TCA excretion is linearly related to concentrations of tetrachloroethylene in air at levels up to about 50 ppm. Unmetabolized tetrachloroethylene is exhaled. The half-lives of tetrachloroethylene in vessel-rich tissue, muscle, and adipose tissue of humans have been estimated to be 12-16 hours, 30-40 hours, and 55 hours, respectively.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

The primary route of exposure to tetrachloroethylene is inhalation. In humans, tetrachloroethylene is readily absorbed into the blood through the lungs. Fulmonary uptake of tetrachloroethylene is proportional to ventilation rate, duration of exposure, and at lower atmospheric concentrations of tetrachloroethylene, to the concentration of tetrachloroethylene in the inspired air (Hake and Stewart 1977; Stewart et al. 1981). Absorption was measured in male volunteers exposed to concentrations between 72 and 144 ppm for 4 hours (Monster et al. 1979). The data indicated that uptake was influenced more by lean body mass than by ventilation rate or the amount of adipose tissue. In addition, uptake decreased as a function of exposure time, so that after 4 hours, it was 75% of its initial value. This latter finding may be attributable to a large percentage uptake of tetrachloroethylene during the first few minutes of exposure, or the decreased uptake may result from a decrease in retention of tetrachloroethylene with exposure time.

Six volunteers were exposed by inhalation to 0.02-44 mmol/m^3 (0.5-9.8 ppm) tetrachloroethylene for durations of l-60 minutes (Opdam and Smolders 1986). The concentration of tetrachloroethylene in alveolar air was determined for residence times (i.e., the time interval between the beginning of inhalation and the end of the next exhalation) in the lung ranging from 1 to 50 seconds. Measurements were made both during and after exposure periods. During exposures, the concentrations of tetrachloroethylene in alveolar air decreased as a function of the residence time. The concentration seemed to stabilize at residence times of 10-12 seconds but decreased even more rapidly at residence times longer than 12 seconds. In the postexposure period, the alveolar concentration of tetrachloroethylene increased for residence times of 5-10 seconds. The decreasing concentration of tetrachloroethylene in alveolar air for times less than 10 seconds could be explained by absorption by

mixed venous blood. Furthermore, the alveolar air concentration of tetrachloroethylene measured during exposures for residence times of 1%12 seconds provided a valid estimate of the concentration of the chemical in mixed venous blood in the pulmonary artery. This study is discussed further in Section 2.3.4.1.

In another study (Pezzagno et al. 1988), 15 volunteers were exposed to tetrachloroethylene during periods of rest and during periods of rest alternated with periods of exercise. The experiments were designed to assess the relationship between pulmonary uptake and urinary concentration of tetrachloroethylene, and between pulmonary uptake and ventilation and/or retention of the chemical. Urinary concentration of tetrachloroethylene was positively correlated with uptake of the chemical. The retention index decreased with increasing ventilation at rest and during exercise. The urinary concentration of tetrachloroethylene was ventilation and retention index-dependent, increasing when either of these two parameters increased. In the same study, a group of workers occupationally exposed to tetrachloroethylene (occupation not specified) were also monitored to determine if urinary concentration of tetrachloroethylene correlated with environmental exposure. A close relationship between the environmental TWA concentration and urinary concentration after a 4-hour exposure was found. These results suggest that physical activity affects the absorption of tetrachloroethylene and that these variations in absorption are reflected in urinary concentrations of the chemical.

Inhalation experiments in animals indicate that tetrachloroethylene is readily absorbed through the lungs into the blood. The amount of tetrachloroethylene absorbed in male Sprague-Dawley rats exposed for 6 hours increases as atmospheric tetrachloroethylene concentrations increase from 10 to 600 ppm (Pegg et al. 1979). Radioactivity has been detected in the urine, feces, expired air, and carcasses of $B6C3F_1$ mice following inhalation exposure to 10 ppm of ^{14}C-labeled tetrachloroethylene for 6 hours (Schumann et al. 1980). Dallas et al. (1994c) examined the uptake of tetrachloroethylene in Sprague-Dawley rats during nose-only exposure to tetrachloroethylene at 50 or 500 ppm for 3 hours. At 500 ppm, minute volumes and respiratory rates were lower than at 50 ppm. Near steadystate breath concentrations in exhaled air were achieved within about 20 minutes and were proportional to concentration (2.1-2.4 μg/mL at 500 ppm and 0.2-0.22 μg/mL at 50 ppm). The percentage of tetrachloroethylene taken up following inhalation exposure was relatively constant after the first 20 minutes and averaged 40% at 500 ppm and 50% at 50 ppm. The total uptake of tetrachloroethylene during the 3-hour exposure was 79.9 mg/kg at 500 ppm and 11.2 mg/kg at 50 ppm indicating that cumulative uptake was not proportional to inhaled concentration. The investigators suggest that

the greater uptake at 50 ppm relative to 500 ppm provides further evidence that tetrachloroethylene metabolism is saturable. The metabolism of tetrachloroethylene is discussed further in Section 2.3.3.

2.3.1.2 Oral Exposure

Tetrachloroethylene was found in the blood of a g-year-old boy who ingested 12-16 g of the compound, indicating that tetrachloroethylene is absorbed following oral exposure in humans (Koppel et al. 1985). The blood tetrachloroethylene level was 21.5 µg/mL 1 hour after ingestion.

Results from several studies (Dallas et al. 1994a, 1995; Frantz and Watanabe 1983; Pegg et al. 1979; Schumann et al. 1980) indicate that tetrachloroethylene is rapidly and virtually completely absorbed following oral administration to rats, mice, and dogs. A peak blood tetrachloroethylene concentration of 40 µg/mL was measured 1 hour following administration of the chemical by gavage (500 mg/kg) to Sprague-Dawley rats (Pegg et al. 1979). The analytical technique used in this study lacked the sensitivity for precisely measuring blood levels of tetrachloroethylene following administration of 1 mg/kg of the compound. Radioactivity was found in the liver, kidney, and fat, but not the brain. In Sprague-Dawley rats and Beagle dogs given a single oral dose of tetrachloroethylene (10 mg/kg) by gavage in polyethylene glycol 400, the absorption constants were estimated to be 0.025/minute for rats and 0.34/minute for dogs (Dallas et al. 1994a). After rats and dogs were treated with a single oral dose of tetrachloroethylene (1, 3, or 10 mg/kg), maximum blood concentrations of tetrachloroethylene were reached in 20-40 minutes and 15-30 minutes after dosing in rats and dogs, respectively.

2.3.1.3 Dermal Exposure

Dermal absorption in humans following exposure to vapors of tetrachloroethylene is apparently not as important as absorption via inhalation. Dermal and pulmonary absorption of tetrachloroethylene vapor was compared by exposing subjects to the vapor (600 ppm) after they had been fitted with a full-facepiece respirator to prevent inhalation (Riihimaki and Pfaffli 1978). After an exposure period of 3.5 hours, absorption of tetrachloroethylene by the dermal route was found to be 1% of that expected had no respirator been worn. Dermal absorption of tetrachloroethylene has also been measured by immersing one thumb of experimental subjects (about 0.1% of the total body surface area) into a liquid sample (99% pure tetrachloroethylene) and then measuring the concentration of tetrachloroethylene in the exhaled air (Stewart and Dodd 1964). To prevent inhalation exposure, the

beaker of tetrachloroethylene was placed under a hood and was covered with Saran wrap, leaving only enough room for immersing a thumb into the solvent. A peak concentration of 0.31 ppm in exhaled air was reached after 40 minutes of exposure.

Animal studies also indicate that dermal uptake of tetrachlorethylene following vapor exposure is Minimal. For example, the skin absorption rate of tetrachloroethylene in nude Balb/cAnNCrj mice exposed to 200 ppm while wearing respirators was 0.002 mg/cm^2/hour (Tsuruta 1989). Skin absorption of tetrachloroethylene occurred by passive diffusion as defined by Fick's law and increased to 0.007 and 0.02 mg/cm^2/hour following exposure at 1,000 and 3,000 ppm, respectively. Tetrachloroethylene exposure (12,500 ppm) of Fischer-344 rats that were wearing respirators, and whose fur was closely clipped indicated that <10% of a mixed inhalation dermal exposure to tetrachloroethylene vapor was taken up by the skin (McDougal et al. 1990).

Uptake of tetrachloroethylene following direct application to the skin is greater than uptake following vapor exposure. Absorption following application of the undiluted compound to the shaved backs of guinea pigs (strain not specified) yielded peak blood concentration of 1.1 μg/mL after 30 minutes of exposure. It then decreased to 0.63 μg/mL after 6 hours of exposure (Jakobson et al. 1982). The decline in tetrachloroethylene blood levels with duration of exposure was attributed to local vasoconstriction of the exposed skin or rapid transport of the compound from the blood to adipose tissue. The decrease in blood concentration with exposure time was not attributed to rapid metabolism of the compound. Little of the absorbed dose was expected to be metabolized in this species because at concentrations well below 100 ppm, the metabolites TCA and trichloroethanol reach a plateau (Jakobson et al. 1982).

Tetrachloroethylene applied to a patch of abdominal skin of ICR mice for 15 minutes/week resulted in an *in vivo* absorption rate of 0.24 mg/cm^2/hour (Tsuruta 1975). An *in vitro* study using excised rat (SD-JCL) skin demonstrated that the rate of penetration by tetrachloroethylene was much slower than that of several other halogenated hydrocarbons (i.e., 2,070 times slower than that of the fastest compound, dichloromethane), and the measured rate for tetrachloroethylene penetration was 0.005 mg/cm^2/hour. The penetration rate observed in the *in vitro* method was 44 times slower than that observed in the *in vivo* method. The difference may result from the solubility of the substance in 0.9% sodium chloride and its solubility in body fluids (Tsuruta 1977).

Bogen et al. (1992) immersed anesthetized female hairless guinea pigs in water containing 27-64 ppb tetrachloro[^{14}C]ethylene for 70 minutes, and the disappearance of radioactivity was determined. The guinea pigs were immersed up to their shoulders, and the top of the container was sealed around them to help prevent evaporation. About 20% of the radioactivity was lost in an hour. When an animal was not present in the chamber, about 1.3% of the radioactivity was lost. Therefore, it was assumed that most of the lost radioactivity was absorbed by the guinea pig. Over the concentration range studied, no difference in the dermal absorption of tetrachloroethylene was noted. From their results using low concentrations, the investigators (Bogen et al. 1992) estimated that a 70-kg human with a surface area of 18,000 cm^2, 80% immersed, would take up the tetrachloroethylene in 2 L of water (of the total amount of water in which the person was immersed) in 20 minutes. These results suggest that dermal exposure to tetrachloroethylene in domestic water supplies could be an important route of exposure.

2.3.2 Distribution

Examples of partition coefficients determined in four species by four different methods are shown in Table 2-4. Both Ward et al. (1988) and Gearhart et al. (1993) used a vial equilibration method in which tetrachloroethylene was added to a closed vial containing blood or tissue, and partitioning was determined by estimating the amount of chemical that disappeared from the head space after equilibration at 37°C. Gear-hart et al. (1993) and Byczkowski and Fisher (1994) used a modification of the vial equilibration method; the tissue was homogenized and smeared onto the inside of a vial. Dallas and colleagues determined partition coefficients in Sprague-Dawley rats given a single bolus injection of tetrachloroethylene through an arterial cannula (Dallas et al. 1994b) or in Sprague-Dawley rats and beagle dogs given a single oral dose of tetrachloroethylene (Dallas et al. 1994a). After treatment, groups of animals were sacrificed at various timepoints after dosing. Following all methods, partitioning into fat was the greatest. A marked difference between species is the partition coefficients for milk/blood, which were 12 in Sprague-Dawley rats and 2.8 in humans (Byczkowski and Fisher 1994). The difference between rats and humans probably reflects a greater fat content in the rat milk that was tested compared to the human milk that was tested. The partition coefficients for human perinatal blood are lower than adult and perinatal rat values (Byczkowski and Fisher 1994). Details on the infant tissues that were obtained and the age of rat pups at sacrifice were not provided.

Table 2-4. Partition Coefficients for Tetrachloroethylene in Mice, Rats, Dogs, and Humans

Partition[a] Coefficients	Mouse	Rat	Dog	Human	Method[b]	Reference
Blood/Air	16.9	18.9		10.3	Vial equilibration	Ward et al. 1988
	21.5			11.6	Smear method	Gearhart et al. 1993
		33.5		19.8	Smear method	Byczkowski and Fisher 1994
		19.8			Intraarterial dosing	Dallas et al. 1994b
		19.6	40.5		Oral dosing	Dallas et al. 1994a
Liver/Air	70.3	70.3		70.3	Vial equilibration	Ward et al. 1988
		62			Vial equilibration	Gearhart et al. 1993
	48.8	50.2		61.1	Smear method	
Fat/Air	2060	2300		1638	Vial equilibration	Ward et al. 1988
		1237			Vial equilibration	Gearhart et al. 1993
	1510	1437		1450	Smear method	
Vessel-rich/Air	70.3	70.3		70.3	Vial equilibration	Ward et al. 1988
Muscle/Air	20.0	20.0		20.0	Vial equilibration	Ward et al. 1988
		18.1			Vial equilibration	Gearhart et al. 1993
	79.1	21.7		70.5	Smear method	
Kidney/Air		51.7			Vial equilibration	Gearhart et al. 1993
	79.1	51.3		58.6	Smear method	
Liver/Blood	2.3			5.28	Smear method	Gearhart et al. 1993
		1.9		6.83	Smear method	Byczkowski and Fisher 1994
		5.3			Intraarterial dosing	Dallas et al. 1994b
		5.0	2.4		Oral dosing	Dallas et al. 1994a
Fat/Blood	70.4			125	Smear method	Gearhart et al. 1993
		42.4		159	Smear method	Byczkowski and Fisher 1994
		152			Intraarterial dosing	Dallas et al. 1994b
		150.5	71.4		Oral dosing	Dallas et al. 1994a
Muscle/Blood	3.69			6.11	Smear method	Gearhart et al. 1993
		3.0			Intraarterial dosing	Dallas et al. 1994b
		2.4	2.4		Oral dosing	Dallas et al. 1994a
Kidney/Blood	2.3			5.1	Smear method	Gearhart et al. 1993

Table 2-4. Partition Coefficients for Tetrachloroethylene in Mice, Rats, Dogs, and Humans (*continued*)

Partition[a] Coefficients	Mouse	Rat	Dog	Human	Method[b]	Reference
Kidney/Blood		4.5			Intraarterial dosing	Dallas et al. 1994b
		3.2	2.1		Oral dosing	Dallas et al. 1994a
Lung/Blood		2.5			Intraarterial	Dallas et al. 1994b
		1.9	1.3		Oral dosing	Dallas et al. 1994a
Brain/Blood		4.4			Intraarterial dosing	Dallas et al. 1994b
		4.1	4.1		Oral dosing	Dallas et al. 1994a
Heart/Blood		2.7			Intraarterial dosing	Dallas et al. 1994b
		2.4	2.4		Oral dosing	Dallas et al. 1994a
Milk/Blood		12		2.80	Smear method	Byczkowski and Fisher 1994
Slowly perfused/ Blood		0.93		7.8	Smear method	Byczkowski and Fisher 1994
Rapidly perfused/ Blood		1.7		6.8	Smear method	Byczkowski and Fisher 1994
Perinatal (pups or infant)						
Blood/Air		24.3		8	Smear method	Byczkowski and Fisher 1994
Other tissues/Blood		4.5		6.6	Smear method	Byczkowski and Fisher 1994

[a]Determined in tissue from adults except as noted

[b]Examples of partition coefficients for tetrachloroethylene determined by four methods: (1) vial equilibration method—tetrachloroethylene was added to a closed vial containing blood or tissue and partitioning was determined by estimating the amount of chemical that disappeared from the head space after equilibration at 37°C; (2) smear method (modification of the vial method)—homogenized tissue was smeared onto the inside of a vial; (3) intraarterial dosing—rats were given a single bolus injection of tetrachloroethylene through an arterial cannula. After treatment, groups of four rats were sacrificed at 1, 5, 10, 15, 30, and 60 minutes and at 2, 4, 6, 12, 36, 48, and 72 hours after dosing. (4) oral dosing—rats and dogs were given a single oral dose of tetrachlorethylene. After treatment, groups of four rats were sacrificed at 1, 5, 10, 15, 30, and 60 minutes, and 2, 4, 6, 12, 8, 36, 48, and 72 hours after dosing, and groups of 3 dogs were sacrificed 1, 4, 12, 24, 48, and 72 hours after dosing.

2.3.2.1 Inhalation Exposure

Repeated inhalation exposure to tetrachloroethylene results in the accumulation of this compound in the body, especially in fatty tissue as indicated by the partition coefficients. Data indicating that tetrachloroethylene is accumulated in the body is provided by the study of Stewart et al. (1977). Experimental subjects were exposed by inhalation to 100 ppm tetrachloroethylene 7 hours a day for 5 days. During the 5-day exposure period, the concentration of tetrachloroethylene in exhaled breath increased as the 5-day week progressed, indicating an increase in the body burden with repeated daily exposures. Following termination of exposure, a slight but definite accumulation of the compound was indicated by a long decay (greater than 14 days) of the concentration of tetrachloroethylene in exhaled air. The study authors concluded that tetrachloroethylene's affinity for fat tissue probably accounts for the protracted period of excretion via the lungs. Altmann et al. (1990) measured blood concentrations of tetrachloroethylene in volunteers before, during, and after four daily 4-hour exposures to 10 or 50 ppm. Tetrachloroethylene levels in the blood were also measured the day after exposure. Even at relatively low concentrations, with exposures of 4 hours/day, tetrachloroethylene levels in the blood measured at all time points increased from one exposure day to the next. Blood levels in ug/L measured before exposure, on exposure days l-4, and the day after cessation of exposure are shown below.

Exposure day	10 ppm (n=12)	50 ppm (n=l0)
Day 1	<0.5	<0.5
Day 2	36 ± 49	59 ± 25
Day 3	38 ± 37	109 ± 50
Day 4	52 ± 48	127 ±47
One day after cessation of exposure	56 ± 56	153 ±49

The observation of tetrachloroethylene in the blood (1.8-31.8 umol/L) and TCA in the urine (0.71-15.8 mmol/mol creatinine) on Monday before work in dry cleaners suggests that the weekend is not long enough to clear the tetrachloroethylene that has accumulated during the week (Skender et al. 1987).

2. HEALTH EFFECTS

Several case studies provide some information on concentrations of tetrachloroethylene in various tissues following inhalation exposure. In one human fatality following exposure to the chemical, the highest concentrations were found in the brain (36 mg/kg) and lowest concentrations in the lung (3 mg/kg) (Lukaszewski 1979). These were the only two tissues examined. Tetrachloroethylene was detected in the liver (240 mg/kg), kidney (71 mg/kg), brain (69 mg/kg), and lung (30 mg/kg) of a dry cleaner who died following exposure to high concentrations of the chemical (Levine et al. 1981). Tetrachloroethylene concentrations were 66 mgiL in blood, and 79, 31, and 46 mg/kg in the brain, heart, and lungs, respectively, in a 2-year-old boy found dead shortly after he was placed in his room with curtains that had been incorrectly dry cleaned (Gamier et al. 1996).

Hattis et al. (1993) reviewed a number of experimental studies of humans exposed to tetrachloroethylene and calculated ratios of arm blood to alveolar air tetrachloroethylene concentrations following inhalation exposure. These ratios suggest that the blood/air partition coefficient should be 15-18. Among the human blood/air partition coefficients estimated by *in vitro* methods (Table 2-4), the *in vivo* values are closest to the human blood/air partition coefficient of 19.8 estimated by Byczkowski and Fisher (1994) using the smear method.

Animal data support the theory that tetrachloroethylene is distributed readily to fatty tissue. The distribution of the compound in Sprague-Dawley rats following exposure to 200 ppm tetrachloroethylene vapor for 5 days was characterized by Savolainen et al. (1977). Seventeen hours after the fourth daily exposure, tetrachloroethylene was found to have distributed primarily to adipose tissue and especially the perirenal fat. Tetrachloroethylene levels were 145 times greater in the perirenal fat than in the blood. Dallas et al. (1994b) exposed Sprague-Dawley male rats to tetrachloroethylene at 500 ppm for up to 2 hours. At 15, 30, 60, 90, and 120 minutes during the exposure and 0.25, 0.5, 1, 2, 4, 6, 12, 36, 48, and 72 hours after the exposure, five rats were sacrificed and tetrachloroethylene residues in the blood, brain, liver, kidneys, lung, heart, perirenal fat, and skeletal muscle were measured. The maximum tetrachloroethylene concentration of 1,536 μg/g was found in the fat, which contained 9-18 times more of the chemical than nonfat tissues. The maximum concentration in the blood was 44 μg/g, and of the tissues examined, skeletal muscle contained the lowest concentration, 87.3 μg/g. Half-lives ranged from 322 minutes in the blood to 578 minutes in fat.

Tetrachloroethylene can cross the placenta and distribute to the fetus and amniotic fluid. Unmetabolized tetrachloroethylene was found in the fetoplacental unit following inhalation exposure of pregnant

657BL/6N mice to radioactive tetrachloroethylene for 10 minutes or 1 hour (Ghantous et al. 1986). High uptake of radioactivity in maternal tissues was found in the body fat, brain, nasal mucosa, blood, and in well-perfused organs such as the liver, kidneys, and lungs.

2.3.2.2 Oral Exposure

Pertinent data regarding the distribution of tetrachloroethylene in humans following oral administration were not found in the available literature.

Following dietary administration of tetrachloroethylene to pigs, the chemical was concentrated mainly in subcutaneous fat (Vemmer et al. 1984). Male Fischer-344 rats given a daily oral dose of 1,500 mg/kg tetrachloroethylene for 42 days had evidence of kidney damage. In addition, radiolabelled material included with the doses given on days 1, 17, and 42 was detected in bile and urine. These data indicated that tetrachloroethylene was distributed to the liver and kidneys (Green et al. 1990). Following oral exposure of Sprague-Dawley rats to a single dose of tetrachloroethylene (10 mg/kg), the highest concentrations were found in the fat (360 minutes after dosing), liver (10 minutes after dosing), kidney (10 minutes after dosing), and brain (15 minutes after dosing) (Dallas et al. 1994a). In Beagle dogs given a single oral dose of tetrachloroethylene, the highest concentrations were found in the fat, brain, liver, heart, and kidneys. Except for the fat in which the peak concentrations were noted at 720 minutes, peak concentrations in the other organs were observed at 60 minutes, the first measurement time, so that true maximum concentrations may have actually occurred earlier.

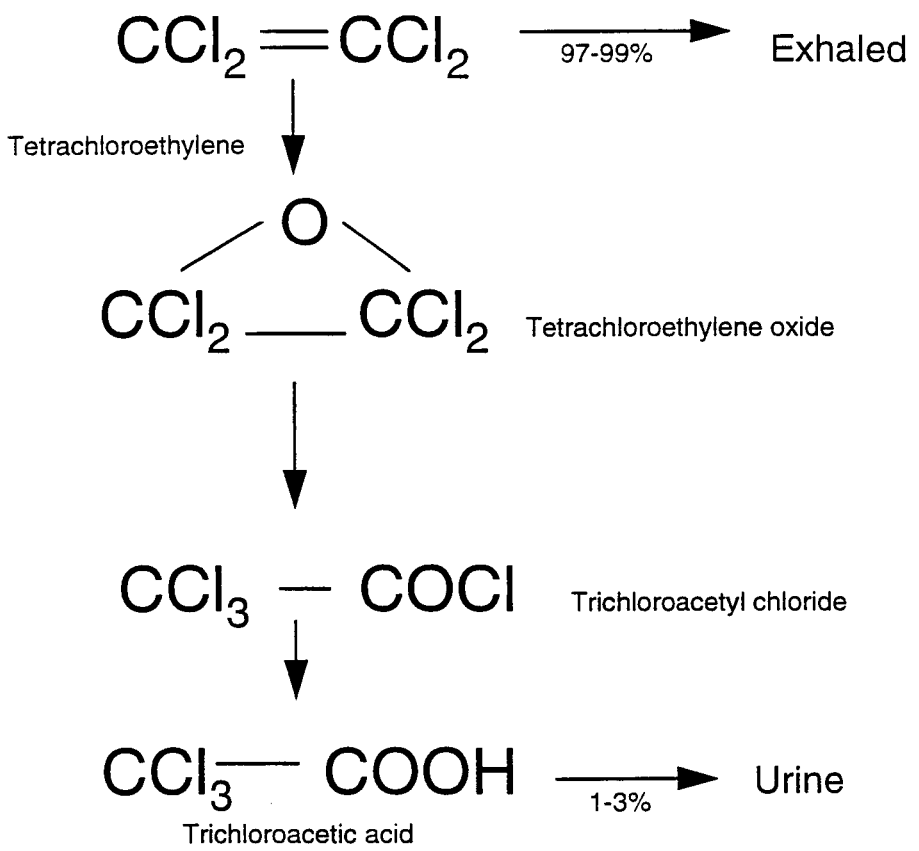
2.3.2.3 Dermal Exposure

Pertinent data regarding the distribution of tetrachloroethylene in humans and animals following dermal exposure to the compound were not found in the available literature.

2.3.3 Metabolism

The metabolism of tetrachloroethylene by humans is shown in Figure 2-3. Irrespective of the route of exposure, only l-3% of the absorbed tetrachloroethylene is metabolized to trichloroacetic acid (TCA) by humans (ACGIH 1991). The remaining absorbed tetrachloroethylene is exhaled unchanged. Small

FIGURE 2-3. Metabolism of Tetrachloroethylene by Humans*



*Modified from ACGIH 1991

amounts of trichloroethanol have also been detected in the urine of workers exposed to tetrachloroethylene (Bimer et al. 1996; Monster 1986). Skender et al. (1991) indicate that trichloroethanol is not generally found following experimental exposure of humans to pure tetrachloroethylene and suggest that the trichloroethanol found in urine of workers exposed to tetrachloroethylene is a result of trichloroethylene contamination of tetrachloroethylene. Although trichloroethylene was not detected in the air of workers exposed to tetrachloroethylene, trichloroethanol was found in the urine of two of the four workers studied (Birner et al. 1996). The study authors could not provide a reasonable mechanism for the formation of trichloroethanol. Further research is required to determine if trichloroethanol is a metabolite of tetrachlorethylene, or is produced from trichloroethylene which can contaminate tetrachloroethylene.

The metabolism of tetrachloroethylene is saturable in humans. Total measured trichloro-compounds in the urine of tetrachloroethylene-exposed workers in dry cleaning and textile-processing plants reached a plateau in the urine at tetrachloroethylene exposure concentrations of >l00 ppm in workroom air (Ohtsuki et al. 1983). Another study of dry cleaning workers showed that the urinary level of trichloro-compounds was linearly related to exposure at concentrations below 112 ppm (Seiji et al. 1989). Thioethers have also been detected in the urine of dry cleaning workshop employees, but the significance of this finding is unclear (Lafuente and Mallol 1986).

The amount of tetrachloroethylene metabolized varies among different ethnic human populations. Seiji et al. (1989) reported that the relationship between total urinary trichloro-compounds and the concentration of tetrachloroethylene in breath air was 0.063 mg TCA/L per ppm tetrachloroethylene in Chinese workers, while the value was 0.7 mg TCA/L per ppm tetrachloroethylene in Japanese workers. Jang et al. (1993) determined that the biological exposure index in Korean workers exposed to 50 ppm tetrachloroethylene was 1.6 mg tetrachloroethylene/ in blood and 2.9 mg TCA/L in urine compared to the ACGIH values of 1 mg tetrachloroethylene/L in blood and 7 mg TCA/L in urine for exposure to 50 ppm (ACGIH 1991).

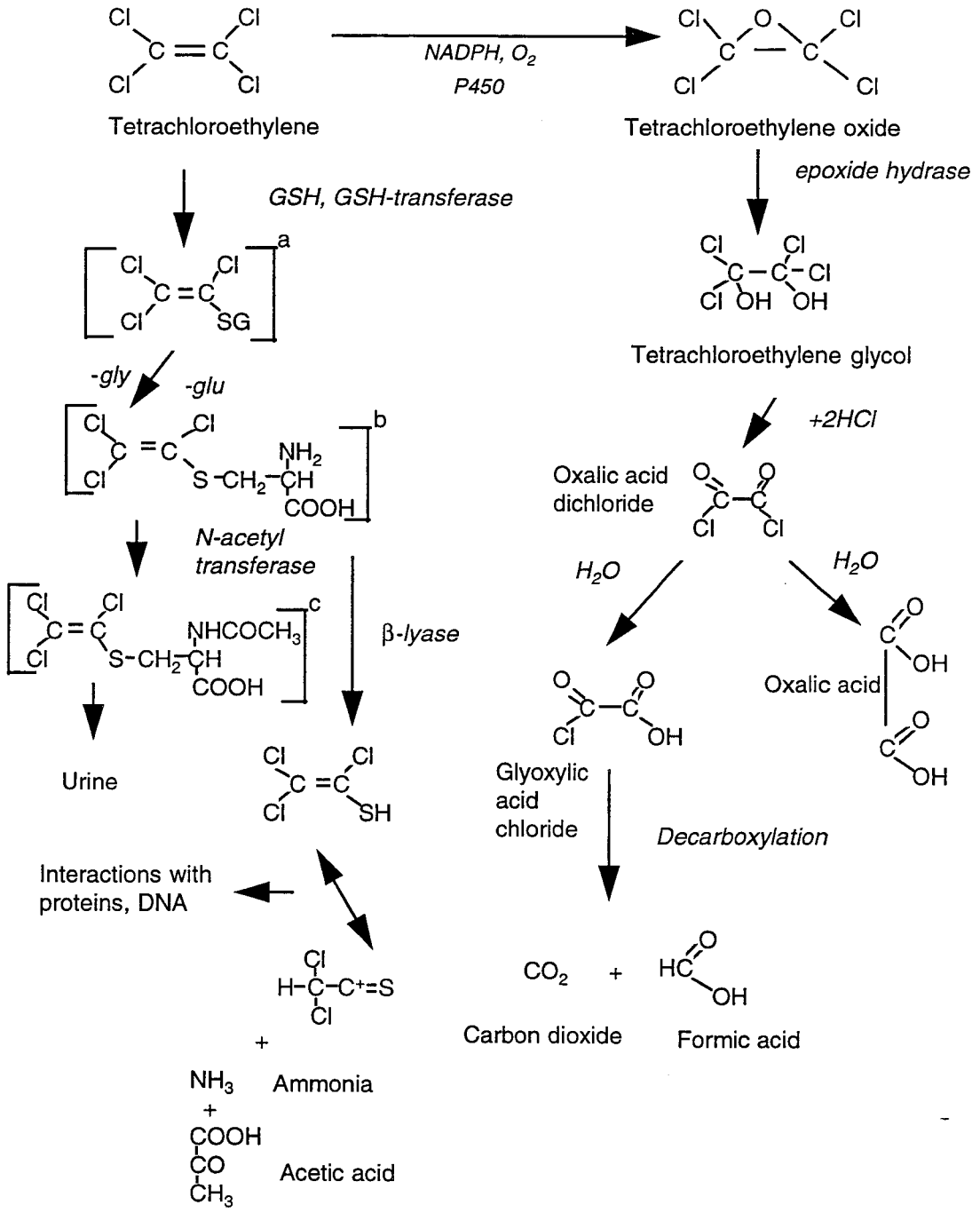
The variability of tetrachloroethylene metabolism among humans is reflected by a wide range of V_{max} and K_m values that have been reported in the literature. These values, summarized by Hattis et al. (1990), are shown in Table 2-5. Also shown in the table are the values for rats and mice. Following exposure to tetrachloroethylene, metabolism to TCA is the principal route of metabolism in these

rodents. As indicated by the V_{max} values, rats metabolize tetrachloroethylene at a greater rate than humans, and mice metabolize tetrachloroethylene at a much greater rate than rats.

Metabolism of tetrachloroethylene to TCA in animals is also limited. Swiss-Cox mice were administered tetrachloroethylene in doses of 0, 20, 100, 200, 500, 1,000, 1,500, and 2,000 mg/kg/day in corn oil by gavage for 6 weeks. The amount of total metabolites found in the urine increased logarithmically with dose and approached a plateau with doses of tetrachloroethylene higher than 1,000 mg/kg/day (Buben and O'Flaherty 1985). Following a 6-hour inhalation exposure, the amount of tetrachloroethylene excreted as metabolites decreased with increasing exposure concentration in both Fischer-344 rats and $B6C3F_1$ mice (Reitz et al. 1996). In rats exposed to 11.9, 318, or 1,146 ppm tetrachloroethylene, 33%, 14.6%, and 11.3% was excreted as metabolites, respectively. In mice exposed to 11, 365, or 1,201 ppm tetrachloroethylene, 85%, 44%, and 26% of the dose was excreted as metabolites.

In addition to TCA, other metabolites have been identified following treatment of rats and mice with tetrachloroethylene (Figure 2-4). Urinary oxalic acid accounted for 18.7% and 6% of the dose following inhalation exposure of Sprague-Dawley rats to tetrachloroethylene at 10 and 600 ppm, respectively (Pegg et al. 1979). An *N*-acetylcysteine glutathione conjugate has also been found in the urine of Wistar rats and NMRI and $B6C3F_1$ mice and in the bile of Fischer-344 rats exposed to tetrachloroethylene by inhalation (Dekant et al. 1986; Green et al. 1990). Levels were higher in rat urine than in mouse urine, and higher after gavage dosing than after inhalation exposure. The glutathione pathway was found to be minor at low doses but began to increase following saturation of the cytochrome P-450 pathway (Green et al. 1990). The formation of the *N*-acetylcysteine glutathione conjugate requires glutathione conjugation, which occurs in the liver, and the action of P-lyase which is found in the kidneys. Green et al. (1990) compared the activities of these enzymes in humans, $B6C3F_1$ mice, and Fischer-344 rats (Table 2-5). Glutathione conjugation to tetrachloroethylene could not be detected using liver cytosol from humans, while the rate of glutathione conjugation was higher in rat relative to mouse liver cytosol. β-Lyase activity in kidney cytosol was also higher in rats relative to mice and humans. Small amounts of the glutathione conjugate *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine were found in the urine of four workers occupationally exposed to tetrachloroethylene at 50 ppm for 4 or 8 hours/day, 5 days/week (Bimer et al. 1996). The concentrations of *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine were 2.2-14.6 pmol/mg creatinine

FIGURE 2-4. Proposed Pathways for the Metabolism of Tetrachloroethylene to Metabolites in Addition to Trichloroacetic Acid*



*Derived from Dekant et al. 1986; EPA 1985d; Green et al. 1990; Pegg et al. 1979

[a]*S*-(1,2,2-trichlorovinyl)glutathione
[b]*S*-(1,2,2-trichlorovinyl)cysteine
[c]*N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine

glu = γ-glutamic acid; gly = glycine

TABLE 2-5. Metabolism of Tetrachloroethylene in Mice, Rats, and Humans

Parameters		Human	Mouse	Rat
Total tetrachloroethylene metabolism[a]				
V_{max}/body weight (nmol/(min/kg))		5.30–61 [13 (2.0)]	210–1860 [710 (2.95)]	27.2–400 [144 (2.95)]
K_m (nmol/mL blood)		1.2–193 [13 (5.1)]	1.6–32 [9.4 (2.95)]	1.8–108 [21 (4.57)]
$V_{max}/(K_m$ body weight)[b] (mL blood/(min/kg))		0.05–9.3 [0.74 (4.3)]	12–248 [75 (2.57)]	3.7–15 [6.9 (1.69)]
In vitro liver cytosolic GSH conjugation of tetrachloroethylene[c]				
Rate (pmol/min/mg protein)		not detected	6.4	18.2
In vitro liver cytosolic metabolism of tetrachloroethylene[d]				
Rate (pmol/min/mg protein)		2.08 ± 2.57	19.26 ± 1.33	3.87 ± 2.12
In vitro kidney cytosolic metabolism of *S*-(1,2,2-trichlorovinyl)-L-cysteine (β-lyase activity)[c]				
K_m(mM)	male	2.53 ± 0.09	5.69 ± 2.22	0.68 ± 0.06
	female	2.67 ± 2.11	4.43 ± 1.42	1.26 ± 0.21
V_{max}(nmol/min/mg protein)				
	male	0.49 ± 0.07	1.15 ± 0.31	4.00 ± 0.11
	female	0.64 ± 0.54	1.66 ± 0.27	3.64 ± 0.41
V_{max}/K_m	male	0.21	0.20	5.88
	female	0.28	0.37	2.88

[a]Summarized by Hattis et al. (1990); values are range [geometric mean (geometric standard deviation)].
[b]Indicator of intrinsic low-dose metabolic clearance rate
[c]From Green et al. 1990; values are means or means ± standard deviations.
[d]From Reitz et al. 1996

GSH = glutathione

compared to concentrations of 13-65 nmol/mg creatinine for trichloroacetic acid and trichloroethanol combined. The amount of tetrachloroethylene exhaled was not determined so it is not possible to estimate what percentage of the total dose of tetrachloroethylene was metabolized to *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine.

Dichloroacetylated mitochondrial and cytosolic proteins (N^{ϵ}-[dichloroacetyll-L-lysine) detected in the kidneys of tetrachloroethylene-treated Wistar rats suggests that the glutathione, β-lyase pathway may have a role in the renal toxicity of tetrachloroethylene (Birner et al. 1994). How the differences in tetrachloroethylene metabolism between humans, rats, and mice affect toxicity is discussed in Section 2.4.2.

2.3.4 Elimination and Excretion

Exhalation of unmetabolized parent compound is the primary route of excretion of an absorbed dose of tetrachloroethylene in humans, regardless of the route of exposure.

2.3.4.1 Inhalation Exposure

In six male volunteers exposed by inhalation for 4 hours to either 72 or 144 ppm tetrachloroethylene, most (80-100%) of the total compound absorbed was exhaled unchanged after 162 hours (Monster et al. 1979). From concentration-time course curves of tetrachloroethylene in the exhaled air and blood, the half-lives of tetrachloroethylene in three major body compartments were calculated to be 12-16 hours for the vessel-rich group, 30-40 hours for the muscle group, and 55 hours for the adipose group, respectively. Tetrachloroethylene was postulated to have a long half-life in adipose tissue because of its high adipose/blood partition coefficient and because of the relatively low rate of blood perfusion to this tissue (Monster 1986). The concentration of tetrachloroethylene in alveolar air was determined for volunteers (three males, three females) exposed to 0.02-0.40 mmol/m^3 (0.5-9.8 ppm) of the chemical for durations of l-60 seconds (Opdam and Smolders 1986). Measurements made in the post-exposure period showed tetrachloroethylene concentrations increased with residence time of the chemical in the lung for residence times ranging from 5 to 10 seconds. This could be explained by excretion of tetrachloroethylene by mixed venous blood. The study authors stated that the concentration of tetrachloroethylene in arterial blood could be reasonably estimated by the

concentration of the chemical in alveolar air during normal breathing (residence time of about 5 seconds).

In humans, the urinary excretion of metabolites of tetrachloroethylene represents a small percentage of the absorbed dose of tetrachloroethylene following inhalation exposure. Urinary excretion of TCA represented less than 1% of the total estimated absorbed dose of tetrachloroethylene in volunteers exposed by inhalation to 72 or 144 ppm for 4 hours (Monster et al. 1979). Using a linear regression model, it was estimated that 2% of the tetrachloroethylene absorbed through the lungs following an 8-hour exposure to 50 ppm tetrachloroethylene would be metabolized and excreted in the urine. It has been reported that the urinary excretion of TCA in volunteers increased linearly with tetrachloroethylene concentrations in the air and plateaued at 50 ppm (Ikeda et al. 1972). This finding indicates that the metabolism of tetrachloroethylene is saturable and that the concentration of urinary metabolites would not reflect the amount of exposure at a concentration above the saturation of metabolism. Another study showed that 67 hours after a 3-hour exposure to tetrachloroethylene vapors, the excretion of TCA in the urine of four male volunteers was 1.8% of the estimated tetrachloroethylene retained (Ogata et al. 1971). Dry cleaning employees showed an increased trend of excretion of thioethers throughout the week, but the significance of this finding is unclear since the levels of thioethers were well within the range found in unexposed individuals (Lafuente and Mallo1 1986). A linear relationship was found for the urinary concentration and the exposure concentration for workers exposed to tetrachloroethylene in various industries (Ghittori et al. 1987; Imbriani et al. 1988). The biological half-life of urinary metabolites of tetrachloroethylene was found to be about 6 days in occupationally exposed individuals (Ikeda and Imamura 1973).

The relative importance of the routes of excretion of tetrachloroethylene and metabolites following inhalation exposure in animals depends on the concentration in air and the species. Following a 6-hour inhalation exposure to 10 ppm radiolabelled tetrachloroethylene in Sprague-Dawley rats, the parent compound (68% of the absorbed dose) and radiolabelled carbon dioxide (3.6% of the absorbed dose) were exhaled over a 72-hour period (Pegg et al. 1979); 24% of the absorbed dose was excreted as nonvolatile metabolites in urine and feces, and 3-4% remained in the carcass 72 hours after exposure. When the exposure concentration was increased to 600 ppm, the percentage of the absorbed dose exhaled as unmetabolized parent compound over a 72-hour period increased to 88%. At this higher exposure level (600 ppm), 9% of the absorbed dose was excreted in the urine and feces and 2% remained in the carcass (Pegg et al. 1979). In contrast to rats, mice excreted most of an absorbed dose

of inhaled tetrachloroethylene as metabolites in the urine. In $B6C3F_1$ mice exposed to the relatively low concentration of 10 ppm of radiolabelled tetrachloroethylene for 6 hours, 12% of the absorbed dose was excreted as unmetabolized compound in the expired air in a 72-hour follow-up period (Schumann et al. 1980). Most of the absorbed radioactivity was excreted in the urine as metabolites. The major route of elimination was urinary excretion. Mice were not exposed to higher concentrations in this study. In a study by Yllner (1961), female mice (unspecified strain) exposed for 2 hours to ^{14}C-tetrachloroethylene vapors at 1,300 mg/kg absorbed 70% of the dose. In 4 days, 90% of the absorbed radioactivity was excreted, 70% in expired air, 20% in the urine, and less than 0.5% in the feces. TCA and oxalic acid comprised 52% and 11% of the label in the urine, respectively. Traces of dichloroacetic acid were also present in the urine. The apparent disagreement between the results of Yllner (1961) and those of Schumann et al. (1980) regarding the percentage of unchanged tetrachloroethylene in the expired air demonstrates that as the body burden of tetrachloroethylene increases, the percentage of unchanged parent compound excreted increases. This observation suggests that the metabolism of tetrachloroethylene and the urinary excretion of metabolites are limited and dose dependent.

2.3.4.2 Oral Exposure

The only study of the excretion of tetrachloroethylene and metabolites following oral exposure in humans is a case report of a 6-year-old boy who accidentally ingested 8-10 mL of pure tetrachloroethylene (Koppel et al. 1985). The bulk of the ingested tetrachloroethylene was exhaled unchanged; however, this was not under normal conditions since the patient was hyperventilated to facilitate pulmonary elimination of the compound. Tetrachloroethylene, TCA, and trichloroethanol were detected and quantified in the urine. Total urinary tetrachloroethylene decreased from 30 μg on day 1 of treatment to 3 μg on day 3. Total urinary trichloro-compounds increased from 8 mg on day 1 to 68 mg on day 3.

In animals, exhalation of unchanged tetrachloroethylene was the main route of excretion-of the orally administered chemical. Sprague-Dawley rats given a single oral dose of tetrachloroethylene (1 mg/kg) excreted 72% of the absorbed dose in the breath as the unmetabolized component and 16% as metabolites in the urine over a 72-hour period (Pegg et al. 1979). When the administered dose was increased to 500 mg/kg, the percentage of the dose exhaled as unmetabolized parent compound over a 72-hour period increased to 90%, whereas the percentage of the dose excreted as metabolites in the

urine dropped to 5%. Similar results were reported in Sprague-Dawley rats following ingestion of tetrachloroethylene-saturated drinking water solutions *ad libitum* for 12 hours (Frantz and Watanabe 1983). Administration of tetrachloroethylene in the drinking water provided a dose (about 8 mg/kg) that was somewhat lower than the doses of tetrachloroethylene given in gavage studies. Excretion of the absorbed dose was similar, however, for both methods of oral administration. Of the absorbed dose, 88% was exhaled as unmetabolized parent compound, and 7.2% of the absorbed radioactivity was excreted in the urine over a 72-hour period. Exhalation of unmetabolized tetrachloroethylene was also the predominant mode of excretion of an orally administered tetrachloroethylene dose in B6C3F_1 mice (Schumann et al. 1980). Mice given a single oral dose of tetrachloroethylene (500 mg/kg) exhaled 83% of the absorbed dose as the unmetabolized compound and 10% as metabolites in the urine over 72 hours. Exposure at 500 mg/kg resulted in saturation of oxidative metabolism in the mouse. There was a shift in the route of elimination from metabolism and urinary excretion to excretion in expired air.

A comparison of the disposition of tetrachloroethylene in Sprague-Dawley rats and Beagle dogs following oral exposure, indicates that the rate and magnitude of exhalation and metabolism are markedly higher in the rat than the dog (Dallas et al. 1994a). Although exhalation of tetrachloroethylene was not measured directly, the smaller blood:air partition coefficient in rats (19.6) compared to dogs (40.5) indicates that tetrachloroethylene more readily diffuses from the pulmonary blood into the alveolar air of the rat. Whole body clearance of tetrachloroethylene in rats and dogs treated with a single oral dose was 30.1 mL/minute/kg at 3 mg/kg and 32.5 mL/minute/kg at 10 mg/kg for rats, and 14.6 mL/minute/kg at 3 mg/kg and 25 mL/minute/kg at 10 mg/kg for dogs (Dallas et al. 1995).

2.3.4.3 Dermal Exposure

Volunteers who immersed their thumbs for 30 minutes in liquid tetrachloroethylene exhaled the compound unchanged for time periods exceeding 5 hours (Stewart and Dodd 1964). The maximum mean alveolar air concentration of tetrachloroethylene in these subjects was 0.3 ppm, and the study authors were able to construct concentration-time curves for the mean alveolar tetrachloroethylene concentrations.

Following immersion (up to their shoulders) of anesthetized hairless guinea pigs in water containing 10-64 ppb tetrachloroethylene, about 14% of the estimated dose was excreted in the urine during the 4 weeks after exposure (Bogen et al. 1992). During the 6 days after exposure, 95% of the metabolized dose was excreted in the urine, relative to 95% of the metabolized dose excreted in the urine in 1 day following a subcutaneous injection.

2.3.5 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). 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 parametrization, (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.

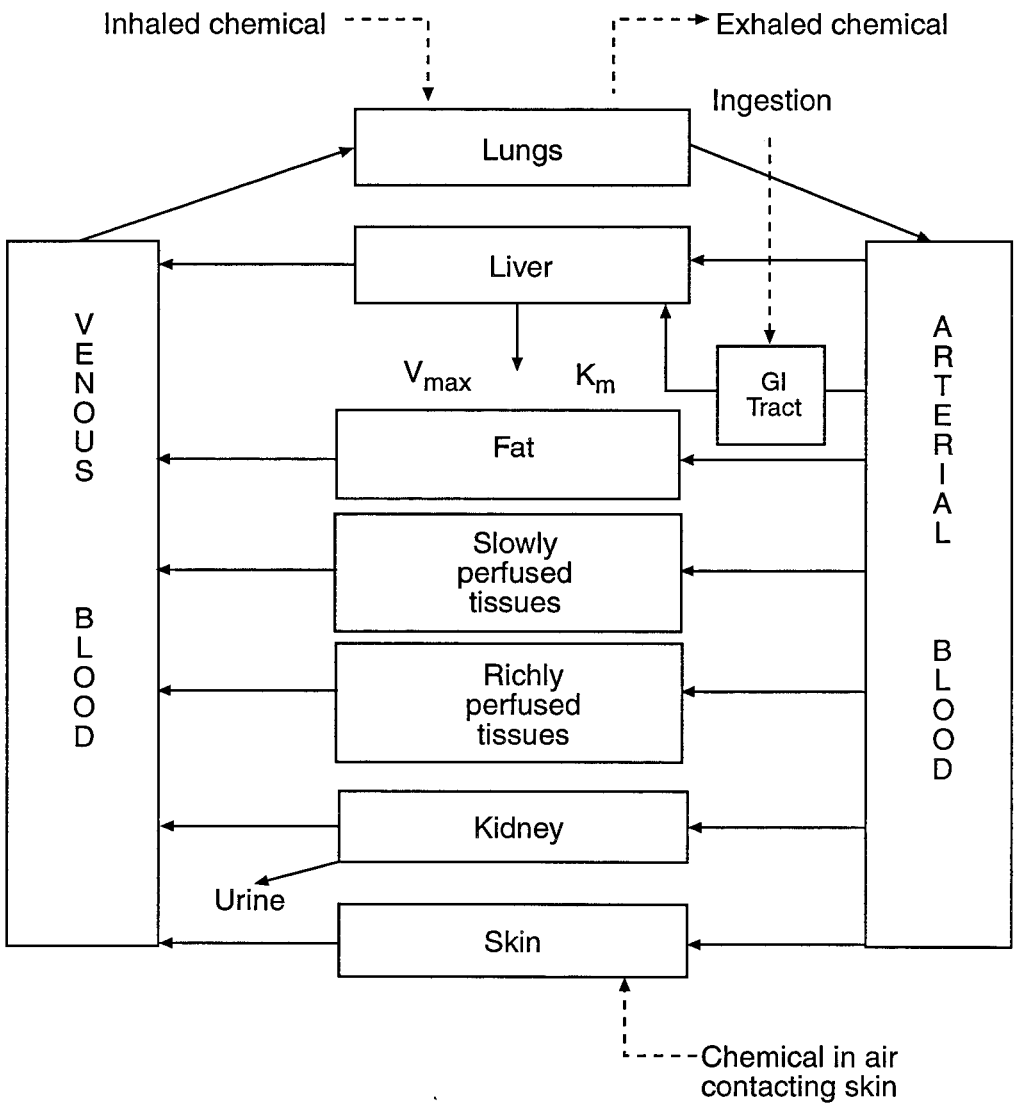
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many 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 2-5 shows a conceptualized representation of a PBPK model.

If PBPK models for tetrachloroethylene 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.

As described in Section 2.3.3, the metabolism of tetrachloroethylene to TCA is saturable, and mice have a greater capacity to metabolize tetrachloroethylene to TCA than either rats or humans. In addition, the production of TCA is associated with liver tumors in mice but not in rats (NTP 1986). Therefore, numerous investigators have used PBPK modeling coupled with low-dose extrapolation to estimate risk to humans based on rodent data. Hattis et al. (1990) reviewed seven of these models to determine which parameters contribute most to the uncertainty of the predictions. The models reviewed all have structures similar to the one shown in Figure 2-5. All of the models assume that the blood flowing through the lungs comes into complete equilibrium with alveolar air, with no absorption assumed for dead space air that enters the respiratory system without reaching the alveoli. Blood flowing through each compartment was also assumed to come into full equilibrium with the tissue, and

Figure 2-5 Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical



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.

all metabolism was assumed to occur in the liver. The range of metabolic parameters used in these models is shown in Table 2-5, while the range of physiological parameters is shown in Table 2-6. In the human models, Hattis et al. (1990) assumed low-dose exposure (1 ppm for 1 hour followed by a week of no exposure) in each model. For the animal models, Hattis et al. (1990) used the low-dose inhalation exposure from the NTP (1986) bioassay: 100 ppm 6 hours/day, 5 days/week for mice and 200 ppm 6 hours/day, 5 days/week for rats. The prediction of human low-dose metabolism was found to be highly dependent on the data sets used to calibrate the metabolic parameters. The ratios of low-dose human to rodent bioassay metabolism spanned a 28-fold range (0.0026-0.072) for the six available human/rat comparisons and a 13-fold range (0.0066-0.084) for the seven available human/mouse comparisons. For example, the Monster et al. (1979) study predicts that humans exposed to 1 ppm tetrachloroethylene for 1 hour will metabolize 0.51 μmol, while rats exposed to 200 ppm for 6 hours, for 5 days, will metabolize 192 μrnol. The ratio of these two values (0.51/192) is 0.0026.

Bois et al. (1990) used Monte Carlo simulations of a coupled PBPK, multistage model to predict a median cancer risk estimate for humans. With their model, they predicted that a concentration of 0.00015 ppm was associated with a theoretical upper-bound risk of 1.6 new cases of cancer per million exposed individuals. The 5, 25, 75, and 95 percentile risk estimates are 0, 0.04, 2.8, and 6.8 per million, respectively. The kinetic parameters defining the metabolic rate were the most influential parameters in the model. Without PBPK modeling, the theoretical upper-bound human cancer risk for exposure to 1 μg tetrachloroethylene/m^3 was estimated to be $5.1x10^{-7}$ (Travis et al. 1989). With PBPK modeling using a model similar to those described by Hattis et al. (1990), the theoretical upper-bound cancer risk was estimated to be $3.1x10^{-7}$ (Travis et al. 1989).

Hattis et al. (1993) compared expectations from 10 human PBPK models for tetrachloroethylene with actual dose-response data following inhalation exposure. All the models were similar to the model shown in Figure 2-5. The models all showed a time pattern of departure of predictions of air and blood levels relative to experimental data. For data in which there was an appreciable amount of time since the end of chronic exposure, the models tended to underpredict blood tetrachloroethylene concentrations, often by over twofold. For measurements taken shortly after the end of chronic exposure, models both under- and overpredicted blood tetrachloroethylene levels. When measurements were taken immediately after the end of a single short-term exposure, there was a tendency for the models to overpredict tetrachloroethylene blood concentrations. Hattis et al. (1993) suggested that

TABLE 2-6. Range of Physiological Parameters Used in PBPK Modeling for Tetrachloroethylene*

Parameters	Mouse range Geometric mean (Geometric SD)	Rat range Geometric mean (Geometric SD)	Human range Geometric mean (Geometric SD)
Alveolar ventilization/kg body weight (L air/min/kg)	0.45–1.12 0.83 (1.441)	0.24–0.53 0.38 (1.487)	0.049–0.131 0.095 (1.408)
Liver blood flow/kg body weight (L blood/(min/kg))	0.107–0.28 0.194 (1.382)	0.081–0.111 0.092 (1.147)	0.0183–0.023 0.021 (1.077)
Blood/air partition coefficient	16.9–24.4 18.1 (1.149)	18.8–18.9 18.9 (1.003)	10.3–14 11.3 (1.146)
Whole body tissue/air partition coefficient	85–303 186 (1.713)	149–228 187 (1.003)	126–421 314 (2.5)
Blood clearance rate via exhalation/kg body weight	25–63 45 (1.405)	12–26.2 19.1 (1.463)	4.4–9.85 7.7 (1.284)

*Modified from Hattis et al. (1990)

SD = Standard deviation

more sophisticated models that incorporated heterogeneity in the fat compartment or intertissue diffusion between the fat and muscle and the vessel-rich tissues would correct the departures from actual data. Models using a resting alveolar ventilation rate of about 5.4 L/minute seemed to be most compatible with the most reliable set of tetrachloroethylene uptake data.

Metabolic parameters and blood air partition coefficients were also found to have the greatest impact on the prediction of the amount of tetrachloroethylene metabolized in PBPK models developed by Reitz et al. (1996). The models, developed for rats, mice, and humans, used V_{max} values of 0.325, 0.355, and 41.5 mg/hours for the three species, respectively, and K_m values of 5.62, 3.69, and 4.66 mg/L, respectively. Validation of the models showed a close correspondence to the rat data, but difficulties in fitting mouse data were attributed to difficulties in estimating the K_m. The model for humans was able to predict the distribution of tetrachloroethylene in blood and expired air, but metabolism data adequate to fully validate the model were not identified.

PBPK models following oral exposure to tetrachloroethylene in rats and dogs (Dallas et al. 1994a) have also been developed. The models were validated using oral and intraarterial dosing experiments (Dallas et al. 1995). Over a 10-fold range of doses, tetrachloroethylene blood concentrations in the rat were well predicted by the model following intraarterial dosing and slightly under predicted following oral exposure. The blood concentrations in dog blood were generally over-predicted, except for fairly precise predictions in dogs given a single oral dose of 3 mg/kg.

The majority of the available PBPK models are concerned with the carcinogenesis of tetrachloroethylene. However, noncancer end points are also of concern based on available literature. For example, logistic regression analysis of noncancer tetrachloroethylene toxicity suggests that for humans exposed by inhalation, the central nervous system may be the most sensitive target of tetrachloroethylene toxicity (Rao et al. 1993). One PBPK model has been developed to predict brain concentrations following exposure to tetrachloroethylene in the shower or while bathing (Rao and Brown 1993). The model has six compartments: liver, fat, rapidly perfused tissues, slowly perfused tissues, brain, and skin. The skin compartment was treated only as a portal of entry, and skin/blood, skin/air, and skin/water partition coefficients of 26.7, 275.2, and 348.4, respectively, were estimated based on data for dihalomethanes. Additional parameters obtained from the literature that were used in the model included a skin permeability value of 0.125 cm/hour, a V_{max} of 6.77, and a K_m of 4.56. Using this model, Rao and Brown (1993) estimated that taking a 15minute shower with water

containing 1 mg tetrachloroethylene/L would result in maximum brain and blood tetrachloroethylene concentrations of 42 and 11 μg/L in an adult, and a 30minute bath would result in maximum brain and blood concentrations of 52 and 13 μg/L and 71 and 20 μg/L in an adult and a 3-year-old child, respectively. Estimated steady-state brain levels following exposure to tetrachloroethylene vapor at 0.6 ppm were 0.148 and 0.153 mg/L for an adult and child, respectively. Based on the modeling data, Rao and Brown (1993) concluded that showering or bathing with water containing ≤2 mg/L would not be expected to produce neurological effects in humans, but that concentrations of >3 mg/L may result in an unacceptable health risk. Further description of the parameters used to develop the exposure model is presented in Chapter 5. Models predicting exposure from a dry cleaning worker exhaling tetrachloroethylene (Thompson and Evans 1993) and infant exposure through breast milk (Byczkowski and Fisher 1994, 1995; Byczkowski et al. 1994; Schreiber 1993) are also presented in Chapter 5.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

The absorption, distribution, storage, and excretion of tetrachloroethylene are largely determined by its lipophilic nature. The blood/air partition coefficient estimated for humans is 10-20, the fat/air partition coefficient is 1,450-1,638, and the fat/blood partition coefficient is 125-159 (Byczkowski and Fisher 1994; Gearhart et al. 1993; Ward et al. 1988). Therefore, tetrachloroethylene is readily taken up by blood and is then distributed to fatty tissues where it is retained with a half-life of about 55 hours. The affinity of tetrachloroethylene for fat also results in its translocation into milk (Byczkowski and Fisher 1994).

2.4.2 Mechanisms of Toxicity

Experimental studies in rodents have shown that tetrachloroethylene alters the fatty acid pattern of brain phospholipids and amino acids (Briving et al. 1986; Kyrklund et al. 1984, 1990), which could be partially responsible for tetrachloroethylene-induced neurotoxic effects. Alternatively, the effects of tetrachloroethylene on the central nervous system may result from the incorporation of this lipophilic compound into brain membranes, which may alter neural conduction velocity. A study by Wang et al. (1993), which examined neuronal and glial cell markers in different regions of the brain in rats exposed to tetrachloroethylene, suggests that the frontal cerebral cortex is more sensitive to

tetrachloroethylene than other regions of the brain, that cytoskeletal elements are more sensitive than cytosolic proteins. How tetrachloroethylene produces changes in the central nervous system still needs to be elucidated.

In contrast to nervous system effects, which are thought to be a result of tetrachloroethylene, effects on the liver including cancer in mice are thought to be a result of the metabolite, TCA. Rodents, especially mice, produce more TCA than humans (Hattis et al. 1990). In addition, mice and rats also respond to TCA and many other chemicals by induction of hepatocellular peroxisomes, while humans are relatively insensitive to peroxisome proliferators, or do not respond at the doses that cause a marked response in rats and mice (Bentley et al. 1993). How peroxisome proliferation leads to liver cancer is still being elucidated. The proliferation process appears to require a specific receptor, that when activated, induces peroxisomal enzymes that produce hydrogen peroxide as a by-product without inducing catalase. The increased production of hydrogen peroxide may increase DNA damage. In addition, peroxisome proliferators may promote endogenous lesions by sustained DNA synthesis and hyperplasia which may be sufficient for tumor formation (Bentley et al. 1993). Liver cancer is not observed following tetrachloroethylene exposure of rats because the threshold concentration of TCA required to induce peroxisome proliferation is not reached as a result of saturation of the metabolic pathway for the production of TCA (Green 1990). Because humans produce little TCA following tetrachloroethylene exposure (ACGIH 1995; Hattis et al. 1990), and because the peroxisome proliferation response in humans is minimal (Bentley et al. 1993), liver hypertrophy and tumor development as is observed in mice (NCI 1977; NTP 1986) may not occur by the same mechanisms in humans.

An *in vitro* study (Kukongviriyapan et al. 1990) suggests that tetrachloroethylene can directly affect hepatocytes. Vapor exposure of rat hepatocytes to tetrachloroethylene (2-4 μL) significantly decreased the hepatocyte uptake of taurocholate, ouabain, and 2-aminoisobutyric acid, all substances that require adenosine 5'-triphosphate (ATP) for uptake. The uptake of cadmium and 3-*O*-methyl-D-glucose, substances that do not require ATP, was not affected. Cellular ATP was decreased by tetrachloroethylene but only at cytotoxic levels. Tetrachloroethylene also decreased membrane ATPase activity leading the investigators (Kukongviriyapan et al. 1990) to hypothesize that the effect of tetrachloroethylene on transport may result from both a decrease in ATP levels and an inhibition of cell membrane ATPases.

2. HEALTH EFFECTS

The metabolism of tetrachloroethylene is mediated by a cytochrome P-450 catalyzed oxidation reaction involving the formation of an epoxide intermediate. Evidence of the role of hepatic microsomal cytochrome P-450 during the *in vitro* metabolism of tetrachloroethylene was provided in the study by Costa and Ivanetich (1980). This evidence included production of a type I difference spectrum (indicating tetrachloroethylene binding to cytochrome P-450), production of known metabolites of tetrachloroethylene following its incubation with hepatic microsomes and the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), and inhibition of spectral binding and of metabolite formation by cytochrome P-450 inhibitors. Many investigators (Buben and O'Flaherty 1985; Daniel 1963; Henschler 1977; Leibman and Ortz 1977; Yllner 1961) have postulated that an epoxide is initially formed following interaction of tetrachloroethylene with the cytochrome P-450 system, but as with other substrates for this system, current technology does not permit the isolation of an epoxide intermediate. It is hypothesized that the major pathway from the epoxide intermediate involves nucleophilic attack by water or enzymatic reduction by epoxide hydrase to yield a tetrachlorinated diol (Pegg et al. 1979). As indicated in Section 2.3.3, the metabolism of tetrachloroethylene to TCA by the P-450 pathway is saturable. In addition, as indicated in Table 2-5, mice have a greater capacity to metabolize tetrachloroethylene than rats or humans.

A low incidence of kidney cancer has been observed in male rats following inhalation exposure to tetrachloroethylene (NTP 1986). Kidney cancer may in part be a result of the formation of the genotoxic metabolites from *S*-(1,2,2-trichlorovinyl)glutathione by β-lyase. As indicated in Section 2.3.3, this pathway, which requires glutathione conjugation of tetrachloroethylene in the liver, is most likely to occur when the P-450 pathway becomes saturated. Because glutathione conjugation was not detected in the cytosol of human livers, and because P-lyase activity is low in the cytosol of human kidneys (Green et al. 1990), the formation of reactive metabolites by β-lyase in humans may not play a role in the renal toxicity of tetrachloroethylene in humans.

Tetrachloroethylene has also been shown to selectively affect the tubular S2 segment in the kidney of male rats through the accumulation of α-2μ-globulin (Bergamaschi et al. 1992). This mechanism of renal effects observed in male rats may not be relevant to human risk assessment because humans do not produce α-2μ-globulin or proteins in the same family (lipocalin) in large quantities as observed in male rats (Swenberg et al. 1989).

2.4.3 Animal-to-Human Extrapolations

The difference in the toxic action of tetrachloroethylene in rats and mice correlates well with differences in the metabolism of the compound. Mice, which are most sensitive to the liver effects of tetrachloroethylene, produce the most TCA. The liver effects of TCA in mice are also thought to be a result of peroxisome proliferation, a response to chemical exposure that is minimal in humans (Bentley et al. 1993). Therefore, for liver effects, the mouse may not be the most appropriate model for humans.

Rats, which are most sensitive to the kidney effects of tetrachloroethylene, have the greatest potential for producing reactive intermediates from the glutathione conjugate of tetrachloroethylene through the activity of kidney β-lyase (Green et al. 1990). Male rats also develop α-2μ-globulin nephropathy following exposure to tetrachloroethylene. Therefore, for kidney effects, the male rat seems to be a poor model for humans, especially at doses above saturation of the P-450 pathway, where the glutathione conjugation pathway may become important.

Nervous system effects have been well documented in humans. Although tetrachloroethylene is thought to be responsible for the nervous system effects, the possible role of metabolites has not been well studied. If tetrachloroethylene is the active nervous system toxicant, metabolism to TCA may serve to reduce nervous system toxicity. Therefore, rats, which metabolize less tetrachloroethylene to TCA than mice (Hattis et al. 1990), may serve as a better model of nervous system effects in humans.

2.5 RELEVANCE TO PUBLIC HEALTH

Inhalation and oral routes are the major routes of human exposure to tetrachloroethylene. In the following discussions, inhalation exposures are presented in ppm, and oral exposures are presented in mg/kg/day. Inhalation exposure may occur near hazardous waste sites as well as in urban and industrial areas. Occupational exposure to tetrachloroethylene (dry cleaners, chemical workers) is generally by inhalation. Because most of the absorbed tetrachloroethylene is slowly exhaled, this compound is not confined to the occupational setting. Workers exposed to tetrachloroethylene bring the compound home to their families. For example, the tetrachloroethylene concentration in the apartments of dry cleaners was 0.04 ppm relative to 0.0003 ppm in the control apartments (Aggazzotti et al. 1994a). Oral exposure to tetrachloroethylene is primarily through drinking contaminated

groundwater. Because tetrachloroethylene readily volatilizes from water, contaminated water is also a source of inhalation exposure to tetrachloroethylene. Compared to inhalation exposure, little tetrachloroethylene vapor is absorbed across the skin (Riihimaki and Pfaffli 1978). However, when tetrachloroethylene is trapped against the skin beneath an impermeable barrier, small amounts of the solvent are absorbed (Stewart and Dodd 1964).

Central nervous system effects are the most predominant and sensitive effects of tetrachloroethylene in humans. Acute exposure (<2 hours) to high concentrations of tetrachloroethylene at l,000-1,500 ppm has caused mood changes, slight ataxia, and dizziness (Carpenter 1937). Exposure to 100 ppm for 7 hours produced symptoms of headache, dizziness, difficulty in speaking, and sleepiness (Stewart et al. 1970). Subjective evaluation of electroencephalographic scores suggested cortical depression in subjects exposed to 100 ppm, 7.5 hours/day for 5 days (Hake and Stewart 1977). Altmann et al. (1990, 1992) found a significant increase in latency of pattern reversal visual-evoked potentials in male volunteers exposed to tetrachloroethylene at 50 ppm 4 hours/day for 4 days, compared to subjects exposed at 10 ppm for the same duration. No effects on brainstem auditory-evoked potentials were noted. Tests of visual contrast measured in a few individuals showed a tendency for loss of contrast in the low and intermediate spatial frequencies at 50 ppm (Altmann et al. 1990). Significant performance deficits for vigilance and eye-hand coordination were also observed at 50 ppm (Altmann et al. 1992). Following occupational exposure, Cai et al. (1991) reported an increase in subjective symptoms including dizziness and forgetfulness in workers exposed to tetrachloroethylene at a geometric mean concentration of 20 ppm relative to unexposed controls. Loss of color vision has also been reported in dry cleaning workers exposed to tetrachloroethylene at an average concentration of 7.3 ppm (Cavalleri et al. 1994); however, no effect on color vision was observed in workers exposed at average concentrations of 15.3 and 10.7 ppm for men and women, respectively (Nakatsuka et al. 1992). The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) of 25 ppm (ACGIH 1995) is very near the threshold for neurological effects in humans.

Subtle renal effects such as increased urinary lysozyme, fibronectin, albumin, brush border antigens, transferrin, laminin fragments, and tissue-nonspecific alkaline phosphatase have been noted in humans occupationally exposed to tetrachloroethylene (Franchini et al. 1983; Lauwerys et al. 1983; Mutti et al. 1992; Price et al. 1995; Vyskocil et al. 1990). The observed changes could be a physiological adaptation to exposure or may represent an early state of progressive renal disease. Kidney effects, including cancer, following tetrachloroethylene exposure have also been noted in animals, predominantly male

rats (Goldsworthy et al. 1988; Green et al. 1990; NCI 1977). The mechanism for the development of kidney effects in rats may differ from that in humans. After saturation of the P-450 metabolic pathway, which produces TCA, male rats produce more glutathione (GSH) conjugates of tetrachloroethylene than humans (Green et al. 1990). The GSH conjugates are then metabolized to reactive metabolites by β-lyase found in the kidneys. In addition, an accumulation of α-2μ-glolbulin, which is a male rat-specific phenomenon, is observed in male rats exposed to tetrachloroethylene (Bergamaschi et al. 1992).

Liver effects including enlarged liver, fatty changes, and elevated SGOT have been reported in humans exposed to high levels of tetrachloroethylene (Coler and Rossmiller 1953; Hake and Stewart 1977; Levine et al. 1981). These limited case studies do not provide exposure concentrations. Tetrachloroethylene is clearly a hepatic toxicant in rodents, with mice exhibiting a greater response than rats. The hepatic toxicity of tetrachloroethylene correlates well with the production of TCA (Travis et al. 1989), and mice metabolize more tetrachloroethylene to TCA than rats and humans (Hattis et al. 1990). Mice are also more sensitive to the hepatic effects of tetrachloroethylene because they respond to TCA with hepatic peroxisome proliferation, while humans are relatively insensitive to peroxisome proliferators, or do not respond at the doses that cause a marked response in mice (Bentley et al. 1993). Therefore, hepatotoxic effects from tetrachloroethylene in humans may result from a mechanism that differs from the mechanism that produces hepatotoxic effects in mice.

Limited studies of women occupationally exposed to tetrachlorethylene suggest an association with menstrual disorders (Zielhuis et al. 1989) and spontaneous abortions (Ahlborg 1990; Kyyrönon et al. 1989). Other studies have not found a significant association between tetrachloroethylene exposure and birth outcome (Bosco et al. 1986; McDonald et al. 1986; Olsen et al. 1990). An increase in the percentage of round and narrow sperm has been noted in dry cleaners relative to the unexposed controls, but the overall percentage of abnormal sperm was similar between the two groups (Eskenazi et al. 1991a). There is some indication from questionnaires that it may take slightly longer for wives of dry cleaners to become pregnant, and they are more likely to seek help for an infertility problem (Eskenazi et al. 1991a). In a multigeneration study, reduced litter size and reduced survival of offspring were the only reproductive effects noted in rats exposed to tetrachloroethylene at 1,000 ppm, a concentration that also resulted in sedation and kidney effects (Tinston 1995). No reproductive effects were identified at 300 ppm. Increased resorptions have also been noted in rats treated by

gavage with tetrachloroethylene at 900 mg/kg/day on gestation days 6-13, a dose that also resulted in maternal toxicity (Narotsky and Kavlock 1995).

Without providing the data, Narotsky and Kavlock (1995) indicated that an increase in micro/anophthalmia was observed in the offspring of rats treated by gavage with tetrachloroethylene at 900 mg/kg/day on gestation days 6-19. At the 900-mg/kg/day dose, maternal ataxia and body weight gain approximately 25% less than controls were also observed. Hyperactivity in adult mice treated while the nervous system was developing was the most sensitive end point among oral studies of tetrachloroethylene (Fredriksson et al. 1993), suggesting that the developing nervous system may be especially sensitive to tetrachloroethylene. Infants can be exposed to tetrachloroethylene that has been transferred into breast milk, and by inhalation to tetrachloroethylene that has been exhaled or released from dry cleaned clothes. Therefore, because of both potential exposure and a sensitive and possibly permanent effect, infants should be considered a susceptible population for exposure to tetrachloroethylene.

Minimal Risk Levels for Tetrachloroethylene

Inhalation MRLs

- An MRL of 0.2 ppm has been derived for acute inhalation exposure (14 days or less) to tetrachloroethylene. This MRL is derived from the study by Altmann et al. (1992) in which human volunteers were exposed to tetrachloroethylene at 10 or 50 ppm, 4 hours/day for 4 days. At 50 ppm, pattern reversal visual-evoked potential latencies increased ($p<0.05$), and significant performance deficits for vigilance ($p=0.04$) and eye-hand coordination ($p=0.05$) were observed. No effects on brainstem auditory-evoked potential were noted at either concentration. Because faint odor was reported by 33% of the subjects at 10 ppm and 29% of the subjects at 50 ppm on the first day of testing, and by 15% of the subjects at 10 ppm and 36% of the subjects at 50 ppm on the last day of testing, the investigators concluded that only a few subjects could identify their exposure condition. The MRL was derived based on the NOAEL of 10 ppm for neurological effects.

  In a similar study by Altmann et al. (1990), significant ($p<0.05$) increased latencies for pattern reversal visual-evoked potentials were observed in 10 male volunteers exposed to tetrachloro-

ethylene at 50 ppm, compared to 12 men exposed at 10 ppm. Exposures in this study were also 4 hours/day for 4 days. Effects on brainstem auditory-evoked potentials were also not observed in the Altmann et al. (1990) study. Tetrachloroethylene in the blood increased with exposure duration, and linear regression to associate blood tetrachloroethylene with pattern reversal visual-evoked potential latencies was significant ($r = -0.45$, $p<0.03$). Additional tests of neurological function were not conducted in this study.

Hake and Stewart (1977) did not find any changes in flash-evoked potentials and equilibrium tests in four male subjects exposed to increasing concentrations of tetrachloroethylene 7.5 hours/day for 5 days. The subjects were sequentially exposed to 0, 20, 100, and 150 ppm (each concentration 1 week). Subjective evaluation of EEG scores suggested cortical depression in subjects exposed at 100 ppm. Decreases in the Flanagan coordination test were observed at ≥100 ppm. This study confirms that the nervous system is a sensitive target following exposure to tetrachloroethylene. It does not serve as the basis of the acute-duration inhalation MRL because effects were observed at a lower concentration in the Altmann et al. (1992) study. The lack of effect on flash-evoked potentials in the Hake and Stewart (1977) study at concentrations up to 150 ppm compared to changes in pattern reversal visual-evoked potentials observed in the Altmann et al. (1992) at 50 ppm may reflect the greater inter- and intrasubject variability of flash-evoked potentials compared to pattern reversal visual-evoked potentials (Otto et al. 1988).

- An MRL of 0.04 ppm has been derived for chronic (≥1 year) inhalation exposure to tetrachloro-ethylene. This MRL is derived from the study by Ferroni et al. (1992) in which significantly prolonged reaction times were observed in women (n=60) who had been exposed to tetrachloroethylene at an average concentration of 15 ppm for an average period of 10 years. Tests that were significantly different from controls were a test of simple reaction times ($p<0.0001$) and shape comparison tests which were constructed to test vigilance ($p<0.005$) and moderate stress ($p<0.005$). Exposure was estimated by determining tetrachloroethylene concentrations in both blood and air samples.

  The nervous system is a well-established target of tetrachloroethylene exposure in humans, and logistic regression of toxicity data suggests that it may be the most sensitive target (Rao et al. 1993). Cai et al. (1991) reported increased subjective symptoms including dizziness and forgetfulness in workers exposed to tetrachloroethylene at an average of 20 ppm for

l-120 months. Exposure was measured using diffusive sampling with carbon cloth. Additional details were not provided. In a study in which the duration of exposure is unclear (Seeber 1989), perceptual speed and digit reproduction as a memory test were impaired in workers exposed to an average of 12 ppm. No detrimental effects on critical flicker fusion, simple and 9-choice visual reaction time, and a sustained attention test were observed in 22 workers exposed to tetrachloroethylene at an average of 21 ppm for about 6 years (Lauwerys et al. 1983). In this study, the neurological function tests were completed both before and after work; therefore, training effects and effects of tetrachloroethylene exposure on learning may have contributed to the difference between the Ferroni et al. (1992) study and the Lauwerys et al. (1983) study. Although exposure measurements were more comprehensive in the Lauwerys et al. (1983) study (the investigators measured urinary TCA daily for 1 week, air concentrations with personal air samplers and badges, and breath and blood concentrations of tetrachloroethylene), the measurements were completed during 1 week, while in the Ferroni et al. (1992) study, the more limited measurements were completed during the summer and winter and may better represent chronic exposure.

Loss of color vision has also been reported in dry cleaners exposed to tetrachloroethylene at an average of 7.3 ppm for an average of 106 months (Cavalleri et al. 1994). Although this study seems to identify an effect at a lower concentration than the Ferroni et al. (1992), fewer subjects were studied (n=22 exposed subjects), and exposure concentrations were only measured in air on 1 day, while Ferroni et al. (1992) completed air and blood measurements in both the winter and summer. In addition, no effect on blue-yellow color vision was noted in 30 men or in 34 women occupationally exposed to tetrachloroethylene at average concentrations of 15.3 and 10.7 ppm, respectively (Nakatsuka et al. 1992). Therefore, because of inconsistent reports on the effect of tetrachloroethylene on color vision, and because of the better exposure assessment and the larger number of subjects (n=60) in the Ferroni et al. (1992) study compared to the Cavallari et al. (1994) study, the Ferroni et al. (1992) study was chosen as the basis for the MRL.

An additional study did not reveal any effects on neurological function among 14 persons who lived above or next to dry cleaning facilities for l-30 years compared to 23 controls matched for age (± l year, in two cases 3 and 5 years) and gender when the absolute values of the tests were examined (Altmann et al. 1995). Median tetrachloroethylene exposure concentrations were 0.2 ppm in the apartments of the exposed individuals and 0.0003 ppm in the apartments of

control subjects, and blood concentrations were 17.8±46.9 μg/L in exposed individuals and less than the detection limit of 0.5 ug/L in the controls. When multivariate analysis was completed to adjust for age, gender, and education, an increased response time in a continuous performance test ($p<0.05$), increased simple reaction time to a visual stimuli ($p<0.05$), and decreased performance in a test of visual memory ($p<0.05$) were observed. No effect on pattern reversal visual-evoked potentials was observed. The 0.2-ppm concentration is considered a NOAEL because of the lack of effect on the absolute values of the tests. This study does suggest that further studies of larger populations exposed to very low levels of tetrachloroethylene would be useful.

Additional studies of workers exposed to relatively low concentrations of tetrachloroethylene have also reported minor indicators of renal tubular damage. Franchini et al. (1983) reported increased urinary levels of lysozyme and β-glucuronidase in workers occupationally exposed to tetrachloroethylene at a TWA concentration of 10 ppm for an average of 14 years. Mutti et al. (1992) found increased urinary albumin, transferrin, the brush-border membrane antigens B50, BBA, and HF5, and tissue nonspecific alkaline phosphatase in workers exposed to an average tetrachloroethylene concentration of 15 ppm for an average period of 10 years. Urinary fibronectin was significantly decreased relative to the controls. The investigators concluded that the results showed increased shedding of epithelial membrane components from tubular cells. Vyskocil et al. (1990) found an increase in urinary lysozyme in workers exposed to tetrachloroethylene at an average of 23 ppm for 9 years. No effects on urinary β_2-microglobulin, creatinine, lysozyme activity, glucose, low-density lipoprotein, or total proteins were noted.

Although both nervous system and mild kidney effects appear to occur at similar concentrations in persons occupationally exposed to tetrachloroethylene, the nervous system effects were considered a more appropriate basis for the MRL. The nervous system effects noted (decreased reaction times), could lead to accidents, and at higher concentrations for shorter time periods, tetrachloroethylene clearly produces incoordination (Stewart et al. 1970). The significance of the mild kidney changes observed following low-level occupational exposure to tetrachloroethylene is not clear. The kidney changes may be an adaptive effect rather than an adverse effect. In addition, in the study reporting kidney effects at 10 ppm (Franchini et al. 1983), the exposure level was estimated using urinary TCA concentrations, so the actual exposure concentrations are unknown.

2. HEALTH EFFECTS

An intermediate-duration inhalation MRL was not derived. The only available intermediate-duration human studies were two case reports (Abedin et al. 1980; Meckler and Phelps 1966) and a case control study of reproductive outcome in women occupationally exposed (Ahlborg 1990) that did not identify exposure concentrations. Minimal changes in flash-evoked potential were observed in rats exposed to 800 ppm tetrachloroethylene 6 hours/day, 5 days/week, for 13 weeks, with no effects at 200 ppm (Mattsson et al. 1992). The testing was completed 1 week after the end of exposure. A study in mice (Kjellstrand et al. 1984) indicates that liver enlargement occurs following intermediate-duration exposure (30 days, 24 hours/day) at 9 ppm, a less-serious LOAEL for animals. Because mice metabolize more tetrachloroethylene to TCA than humans, and because the peroxisomal proliferative response in mice is much greater than in humans, data in humans were considered more appropriate for the derivation of MRLs.

Oral MRLs

- An MRL of 0.05 mg/kg/day has been derived for acute-duration oral exposure to tetrachloroethylene. This MRL is derived from the study by Fredriksson et al. (1993) in which a significant ($p<0.01$) increase in total spontaneous activity (locomotion and rearing) was observed in 60-day-old mice treated with tetrachloroethylene for 7 days beginning at 10 days of age. Hyperactivity was observed at both 5- and 320-mg/kg/day doses which did not cause observable symptoms of toxicity or differences in body weight gain. Behavior was similar to that of the controls in mice tested at 17 days of age. The change in behavior at 60 days of age was similar in both dose groups. An inhalation study (Nelson et al. 1980) in which hyperactivity was observed in 31- and 32-day-old rats that were exposed during gestation (900 ppm) supports the observation that the developing nervous system is a target of tetrachloroethylene toxicity. The developing nervous system is also at risk because tetrachloroethylene is known to cross the placenta, and it is found in breast milk (Schreiber 1993).

Intermediate- and chronic-duration oral MRLs were not derived. Longer term oral studies in animals have not focused on neurological effects, the principal effect of tetrachloroethylene in humans. Intermediate-duration oral studies have noted liver effects in rats (Hayes et al. 1986) and mice (Buben and O'Flaherty 1985) and kidney effects in male rats (Hayes et al. 1986). There are species differences in the metabolism of tetrachloroethylene and the response to metabolites which contribute to the liver effects. The kidney effects are associated with α-2μ-globulin, a male rat-specific protein.

Therefore, the liver and kidney effects were not considered appropriate for the derivation of an MRL. Chronic-duration oral studies in animals have not identified NOAELs or less serious LOAELs at doses below those causing decreased survival of rats and mice (NCI 1977).

Death. At high concentrations (>l,000 ppm), tetrachloroethylene vapor acts as an anesthetic agent, producing collapse, loss of consciousness, and death in humans. Death may be related to depression of respiratory centers of the central nervous system or cardiac arrhythmia and heart block. Death following acute inhalation of concentrations that produce unconsciousness has been confirmed by animal studies (Carpenter 1937; NTP 1986). Oral exposure of a malnourished man to a dose of 152 mg tetrachloroethylene/g resulted in death (Chaudhuri and Mukerji 1947). Animal studies of oral exposure suggest that anesthesia and death would be likely occurrences in humans if high doses were swallowed (Berman et al. 1995; Hayes et al. 1986; Wenzel and Gibson 1951). There are no reports of fatalities in humans or animals exposed solely by the dermal route.

It appears unlikely that death would occur in humans exposed to the levels of tetrachloroethylene that occur in the environment or in the vicinity of hazardous waste sites.

Systemic Effects

Respiratory Effects Respiratory tract irritation has been reported at concentrations as low as 216 ppm in volunteers exposed for 45 minutes to 2 hours (Rowe et al. 1952). At concentrations of >l,000 ppm, tetrachloroethylene is intensely irritating (Carpenter 1937; Rowe et al. 1952). Changes in pulmonary function tests were not observed in four male volunteers exposed to 0, 20, 100, or 150 ppm tetrachloroethylene for 7.5 hours/day, 5 days/week, for 1 week at each exposure concentration (Stewart et al. 1981). Exposure of mice to 300 ppm of tetrachloroethylene (300 ppm) for 6 hours/day for 5 days has resulted in degeneration of the olfactory and respiratory mucosa (Aoki et al. 1994). Respiratory effects were not reported in animals after oral exposure (NCI 1977). Environmental exposure to tetrachloroethylene in air or water is unlikely to pose a risk to the respiratory system.

Cardiovascular Effects. Despite the relatively large number of people occupationally exposed to tetrachloroethylene, there are few reported cases of tetrachloroethylene-associated cardiotoxicity. Cardiac arrhythmias in a small number of Wobum residents cannot be directly related to chronic tetrachloroethylene exposure (Byers et al. 1988). Experimental exposure studies have not found

changes in electrocardiograms for persons exposed at concentrations up to 100 ppm for 5.5 hours, 5 days/week (Stewart et al. 1977) or up to 150 ppm for 7.5 hours/day, 5 days/week, for 1 week (Stewart et al. 1981). The case report of Abedin et al. (1980) suggests an association of inhaled tetrachloroethylene with cardiac arrhythmia, but the patient described may have been an unusually sensitive individual. These investigators hypothesized that exposure to tetrachloroethylene may sensitize the myocardium to endogenous epinephrine. In an experiment in dogs, however, inhalation exposure to high levels of tetrachloroethylene failed to sensitize the heart to epinephrine (Reinhardt et al. 1973). In contrast, intravenous administration of tetrachloroethylene to rabbits and dogs enhanced myocardial sensitivity to an exogenous epinephrine challenge (Kobayashi et al. 1982). The available studies provide no strong evidence that people exposed to environmental levels of tetrachloroethylene or levels typically found at hazardous waste sites would develop cardiovascular effects.

Gastrointestinal Effects. Nausea and vomiting have been experienced in some individuals given an oral dose of tetrachloroethylene as an anthelminthic (Wright et al. 1937). Forestomach ulcers have been reported following chronic inhalation exposure of rats to high concentrations of tetrachloroethylene (NTP 1986). Gastrointestinal effects resulting from exposure to tetrachloroethylene at a hazardous waste site are unlikely to occur.

Hematological Effects. There are no studies that support hematological effects in humans after acute or chronic exposure to tetrachloroethylene by any route.

Several animal studies indicate that tetrachloroethylene exposure in drinking water can affect the hematopoietic system, particularly the erythrocytes. Tetrachloroethylene in the blood may enter the polar phospholipid layer of the rodent erythrocyte membrane and alter the structure, thus resulting in mechanical fragility and hemolysis (Marth 1987). Thus, there is a potential, though unsubstantiated, risk of subclinical hematological effects resulting from exposure to tetrachloroethylene in drinking water.

Musculoskeletal Effects. There are no studies regarding musculoskeletal effects in humans following exposure to tetrachloroethylene by any route.

An intermediate-duration study did not find any microscopic changes in the limb muscles of rats exposed to tetrachloroethylene (Mattsson et al. 1992). Because of the very limited data, it is not

possible to determine whether musculoskeletal effects would occur in humans following tetrachloroethylene exposure at hazardous waste sites.

Hepatic Effects. Tetrachloroethylene has been shown to cause hepatotoxic effects in humans following inhalation exposure (Brodkin et al. 1995; Hake and Stewart 1977; Meckler and Phelps 1966; Saland 1967) and in animals exposed by the inhalation (Kylin et al. 1963; NTP 1986; Odum et al. 1988; Schumann et al. 1980) and oral routes (Berman et al. 1995; Buben and O'Flaherty 1985; Goldsworthy and Popp 1987). For humans, reports of hepatotoxicity consist almost entirely of case studies of accidental exposures in which reliable quantitative exposure information was not available (Coler and Rossmiller 1953; Hake and Stewart 1977; Meckler and Phelps 1966; Saland 1967). In most cases, hepatic effects in humans have been reported as transient in nature. Human exposure studies (Stewart et al. 1977, 1981) have not found any effects on serum alkaline phosphatase, SGPT, SGOT, or serum bilirubin in volunteers exposed to tetrachloroethylene at concentrations up to 150 ppm for 7.5 hours/day for 1 week. Changes in serum levels of liver enzymes may not be the most sensitive marker of liver damage following exposure to tetrachloroethylene. Diffuse parenchymal changes detected with ultrasound were observed in the livers of dry cleaning workers exposed to an average of 15.8 ppm tetrachloroethylene for at least 6 months (Brodkin et al. 1995). No changes in serum markers of liver damage (SGOT, SGPT, γ-glutamyl transferase, alkaline phosphatase, total and direct bilirubin) were noted in these workers.

In animals, liver effects are characterized by hypertrophy, fatty degeneration, and peroxisome proliferation. Mice are much more sensitive to the hepatic effects of tetrachloroethylene than rats because of their higher rate of oxidative metabolism of tetrachloroethylene to TCA (Odum et al. 1988). TCA is also a peroxisome proliferator in rodents (Goldsworthy and Popp 1987; Odum et al. 1988). Oral exposure to tetrachloroethylene has also been shown to induce CYP2B P-450 enzymes in rats (Hanioka et al. 1995). Although liver damage can occur in humans exposed to tetrachloroethylene, the mechanism of damage may be different from that occurring in rodents. Hepatic effects in humans following exposure to tetrachloroethylene at environmental levels or at a hazardous waste site cannot be ruled out.

Renal Effects. Reversible kidney damage has been reported in humans accidentally exposed to acutely toxic amounts of tetrachloroethylene vapors (Hake and Stewart 1977). There are also data that suggest that occupational exposure to hydrocarbon solvents as a class may contribute to chronic renal

disease (Kluwe et al. 1984). Subtle renal perturbations have been detected in studies of chronically exposed workers in dry cleaning workshops (Franchini et al. 1983; Mutti et al. 1992; Price et al. 1995; Vyskocil et al. 1990). Mutti et al. (1992) suggested that the observed effects indicated increased shedding of epithelial membrane components from tubular cells, which could be a physiological adaption to exposure or could be an early state of clinically silent renal disease.

Studies of tetrachloroethylene in animals support the fact that renal effects are produced. One acute study of tetrachloroethylene administered intraperitoneally to dogs resulted in alteration of phenolsulfonphthalein excretion indicative of tubular dysfunction, in the absence of microscopic lesions (Klaassen and Plaa 1967). Inhalation or oral exposure of rodents to tetrachloroethylene induces renal effects. However, the data showing an increased incidence of protein droplet nephropathy in male rats may have little relevance to human health, as discussed below.

Chemically induced protein droplet nephropathy in sexually mature male rats is characterized by accumulation of α-2μ-globulin in lysosomes, degeneration and necrosis of tubular cells, formation of granular casts, and regeneration of the tubular epithelium (Swenberg et al. 1989). Chemicals that are known to induce protein droplet nephropathy bind to α-2μ-globulin, yielding a complex that is more resistant to proteolytic enzymes in the lysosomes, leading to the accumulation of the complex in the tubule cells. α-2μ-Globulin has not been found in immature male rats, female rats, or humans (Alden 1986). Humans synthesize and excrete trace amounts of proteins similar to α-2μ-globulin. However, human male urine has a very low protein content compared to male rat urine (1% of male rat urine). In addition, human urinary proteins are primarily of high molecular weight compared to those of rats, and human urinary protein has a relatively small proportion of cationic to total proteins. These findings suggest that humans are not at risk for tetrachloroethylene-induced renal damage analogous to the type found in male rats (Olson et al. 1990). Nevertheless, because of tubular effects detected in workers and in animal species other than rats, risks of subclinical renal changes to humans exposed to environmental levels of tetrachloroethylene or levels near hazardous waste sites cannot be discounted.

Endocrine Effects. Ferroni et al. (1992) reported increased prolactin levels in women occupationally exposed to tetrachloroethylene. Because the prolactin levels were still within the normal range, it is not clear if the observed effect had any biological significance. Histopathological changes in the adrenal glands were not observed in female rats treated by gavage with tetrachloroethylene for 14 days at doses that resulted in hepatotoxicity (Berman et al. 1995). Adrenal medullary hyperplasia was

observed in rats chronically exposed to tetrachloroethylene by inhalation (NTP 1986). Studies of endocrine function are too limited to conclude whether or not endocrine effects may occur in humans following exposure to tetrachloroethylene at hazardous waste sites.

Dermal Effects. Skin damage (burns) has been reported in humans exposed to concentrations of tetrachloroethylene liquid or vapors high enough to cause anesthetic effects (Morgan 1969). No damage to skin has been reported in animals exposed chronically (Van Duuren et al. 1979). Data are too limited to predict if dermal effects can occur following environmental exposure of humans.

Ocular Effects. Intense ocular irritation has been reported in humans exposed to concentrations of tetrachloroethylene vapors high enough to cause anesthetic effects (Morgan 1969). Transient eye irritation was also reported in six subjects during the first few minutes of exposure at 75-80 ppm (Stewart et al. 1961b). Data are too limited to predict if ocular effects can occur following environmental exposure of humans.

Body Weight Effects. Decreased body weight gain has been observed in animals following inhalation exposure (NTP 1986; Rowe et al. 1952; Wang et al. 1993) or oral exposure (Hayes et al. 1986; Narotsky and Kavlock 1995; NCI 1977; Schumann et al. 1980) to high levels of tetrachloroethylene. The decreased body weight gain occurred at doses that were associated with other adverse effects, indicating that tetrachloroethylene does not cause a selective effect on body weight. Body weight effects are unlikely in humans exposed to tetrachloroethylene in the environment or at hazardous waste sites.

Immunological and Lymphoreticular Effects. Immunological effects in humans related specifically to tetrachloroethylene exposure have not been reported. Atrophy of the spleen and thymus have been noted in rats treated by gavage with 2,000 mg/kg/day of tetrachloroethylene for 5 days (Hanioka et al. 1995). Histopathological changes in the spleen and thymus were not observed in rats treated by gavage with tetrachloroethylene at 1,500 mg/kg/day for 14 days (Berman et ah 1995). No effects on natural killer cell, natural cytotoxic, and natural P-815 killer cell activities or humoral and T cell mitogenesis were observed in cells harvested from rats and mice treated with three daily intraperitoneal doses of 829 mg tetrachloroethylene/g/day (Schlichting et al. 1992). In a study limited by high mortality in the control group, susceptibility to infection was enhanced in mice exposed to

tetrachloroethylene (Aranyi et al. 1986). The relevance of these findings to public health is, therefore, unclear.

Neurological Effects. The symptomatology of acute inhalation exposure to high levels of tetrachloroethylene is well documented in humans and includes headache, dizziness, and drowsiness. EEG studies done on male and female volunteers resulted in changes in the EEG of three of four male subjects and four of five female subjects during exposure to 100 ppm (Stewart et al. 1981). In the majority of subjects, the EEG changes were characterized by a reduction in overall wave amplitude and frequency, most strikingly evident in the occipital leads. This altered pattern is similar to that seen in a healthy adult during drowsiness, light sleep, and the first stages of anesthesia. Altmann et al. (1990) reported increases in the latency of pattern reversal visual-evoked potentials in volunteers exposed to tetrachloroethylene at 50 ppm for 4 hours/day for 4 days. In a similar study, significant performance deficits for vigilance and eye-hand coordination, as well as increased latencies for pattern reversal visual-evoked potentials were observed in subjects exposed to tetrachloroethylene at 50 ppm for 4 hours/day for 4 days (Altmann et al. 1992). No effects were noted at 10 ppm. An acute inhalation MRL was derived based on the lack of neurological effects at 10 ppm.

In a study completed over an 1l-week period, decrements in coordination were observed in volunteers exposed at 100 ppm but not 20 ppm (Stewart et al. 1977). Longer term occupational exposure to tetrachloroethylene has resulted in an increase in subjective complaints including headache and dizziness (Abedin et al. 1980; Cai et al. 1991; Coler and Rossmiller 1953). The exposure concentrations were not well defined in these studies. Deficits in behavioral tests that measured shortterm memory for visual designs have been reported in dry cleaning workers exposed to an average of 40.8 ppm tetrachloroethylene for at least 1 year (Echevenia et al. 1995). Loss of color vision has been reported in dry cleaning workers exposed to tetrachloroethylene at an average of 7.3 ppm for an average of 106 months (Cavalleri et al. 1994). However, no loss of color vision was noted in workers exposed to tetrachloroethylene at average concentrations of 15.3 and 10.7 ppm for an unspecified duration (Nakatsuka et al. 1992). Reaction times were increased in workers exposed to tetrachloroethylene at an average of 15 ppm for about 10 years (Ferroni et al. 1992). Exposure in the Ferroni et al. (1992) study was assessed with both blood and air measurements completed during more than one season. Because of the better exposure assessment and more study subjects compared to the study by Cavalleri et al. (1994), a chronic inhalation MRL of 0.04 ppm has been derived based on the LOAEL of 15 ppm identified in the Ferroni et al. (1992) study. In all of the occupational studies

assessing neurological effects, it is not clear if the observed effects are a result of peak exposures or the TWA concentrations.

In a study of 14 persons living above or next to dry cleaning facilities, effects on neurological function tests were noted when multivariate analysis was used to analyze the data, but not when the absolute values of the tests were examined (Altmann et al. 1995). Median tetrachloroethylene exposure concentrations were 0.2 ppm in the apartments of the exposed individuals and 0.0003 ppm in the apartments of control subjects. The 0.2-ppm concentration is considered a NOAEL because of the lack of effect on the absolute values of the tests. This study does suggest that further studies of larger populations exposed to very low levels of tetrachloroethylene would be useful.

Electrophysiologic changes measured on the last day of exposure (e.g., reduced amplitude and decreased latency in flash-evoked potentials) were reported in rats exposed to 800 ppm tetrachloroethylene 6 hours/day for 4 days (Albee et al. 1991). Exposure of rats at 800 ppm 6 hours/day, 5 days/week for 13 weeks, only resulted in minimal changes in flash-evoked potential when measured 1 week after the end of exposure (Mattsson et al. 1992). According to the investigators, these studies suggest that the electrophysiologic changes are a result of repeated acute exposure rather than permanent damage to the nervous system. Further investigation is required to determine if the minimal changes observed in the 13-week study are reversible since the neurological testing was done at one time point only (i.e., 1 week after the last exposure).

An inhalation multigeneration study in rats suggests that animals may adapt to some of the neurological effects of tetrachloroethylene. Exposure at 1,000 ppm 6 hours/day, 5 days/week resulted in decreased activity, reduced response to sound, salivation, breathing irregularities, and piloerection (Tinston 1995). The effects were observed in each generation only during the first 2 weeks of a 19-week study, and recovery from these effects was noted about 30 minutes before the end of each exposure period.

Subchronic and chronic inhalation exposure in rats and mice (NTP 1986) did not result in brain lesions. Experimental studies in rodents have shown, however, that tetrachloroethylene alters the fatty acid pattern of brain phospholipids and amino acids (Briving et al. 1986; Kyrklund et al. 1984, 1990). Taurine is known to be a nonspecific membrane stabilizer; therefore, a reduction in the content of this amino acid may lead to alterations in nerve impulse transmission and could be partially responsible for

tetrachloroethylene-induced neurotoxic effects. Alternatively, the effects of tetrachloroethylene on the central nervous system that were observed may have resulted from the incorporation of this lipophilic compound into brain membranes and the resultant alteration of parameters such as neural conduction velocity. Decreased DNA content concomitant with a decrease in astroglial protein was found in the brain of gerbils exposed continuously to tetrachloroethylene concentrations as low as 60 ppm (Rosengren et al. 1986). It was unclear, however, whether the astroglial response represents a direct effect of tetrachloroethylene toxicity or an indirect reaction in response to neuronal cell damage. A study by Wang et al. (1993), which examined neuronal and glial cell markers in different regions of the brain in rats exposed to tetrachloroethylene, suggests that the frontal cerebral cortex is more sensitive to tetrachloroethylene than other regions of the brain, that cytoskeletal elements are more sensitive than cytosolic proteins, and that glial cells are more sensitive than neurons.

The relevance of neurotoxic effects to individuals following exposure to low concentrations of tetrachloroethylene, most likely by inhalation, and the oral route through contaminated water, is unclear.

Reproductive Effects. Epidemiological studies of women occupationally exposed to tetrachloroethylene in the dry cleaning industry suggest that they may have an increased risk of adverse reproductive effects, primarily menstrual disorders and spontaneous abortions (Ahlborg 1990; Bosco et al. 1986; Kyyronen et al. 1989; Windham et al. 1991; Zielhuis et al. 1989). Interpretation of these studies is complicated by limiting factors, such as small sample populations, failure to account for possible confounding factors, lack of exposure data, and inadequate data collection methods. Other studies have not found an association between tetrachloroethylene exposure and spontaneous abortions (McDonald et al. 1986; Olsen et al. 1990). Wives of dry cleaners who had significantly more rounded sperm did not have more spontaneous abortions, although there was some evidence that it may take slightly longer for these women to become pregnant (Eskenazi et al. 1991a, 1991b). Therefore, it is not possible to speculate on whether adverse reproductive effects could occur in environmentally exposed people. Decreased litter sizes and decreased survival during lactation were observed in rats exposed to 1,000 ppm in a multigeneration study (Tinston 1995). Sedation was also noted at this concentration. No significant effects on reproduction were observed at 300 ppm. This study suggests that at concentrations below those that result in frank neurological effects, reproductive effects are unlikely to occur. Increased resorptions have also been noted in rats treated by gavage with

tetrachloroethylene at 900 mg/kg/day on gestation days 6-13, a dose that also resulted in maternal toxicity (Narotsky and Kavlock 1995). Lower doses were not examined in this study.

Developmental Effects. Studies examining the association between drinking water contamination and birth outcome in humans suggest that there may be an association between birth defects, especially oral cleft defects, and tetrachloroethylene contamination (Bove et al. 1995; Lagakos et al. 1986). These studies are confounded by more than one contaminant, and the Lagakos et al. (1986) study combined birth defects in the analysis in a manner that has questionable biological relevance.

Results from inhalation studies in animals also suggest that tetrachloroethylene is fetotoxic but not teratogenic at concentrations that are also maternally toxic (Schwetz et al. 1975). Fetotoxicity in rodents is usually expressed by decreased fetal weight and delayed skeletal ossification. These effects have been associated with exposure to 300 ppm, and NOAELs have not been reported. A gavage study in rats reported that tetrachloroethylene caused an increase in micro/anophthalmia in the offspring of rats treated by gavage with tetrachloroethylene at 900 mg/kg/day on gestation days 6-13 (Narotsky and Kavlock 1995). This dose also resulted in transient maternal ataxia and decreased maternal body weight gain. The lack of teratogenic effects in the inhalation studies compared to the oral study may be the result of different dose rates; gavage treatment may result in higher peak blood concentrations compared to inhalation studies.

Gestational exposure to higher concentrations of tetrachloroethylene (900 ppm) was associated with behavioral and neurochemical alterations in some rat offspring (Nelson et al. 1980). Following oral exposure of mice to 5 mg tetrachloroethylene/kg for 7 days beginning at 10 days of age, hyperactivity was observed at 60 but not by 17 days of age (Fredriksson et al. 1993). These studies suggest that the developing nervous system may be sensitive to tetrachloroethylene. Based on the LOAEL of 5 mg/kg/day identified in the Fredriksson et al. (1993) study, an acute-duration oral MRL of 0.05 mg/kg/day has been derived.

A high concentration of the tetrachloroethylene metabolite TCA has been detected in the amniotic fluid of mice following maternal inhalation exposure to tetrachloroethylene (Ghantous et al. 1986). TCA levels in the amniotic fluid were higher following exposure to tetrachloroethylene compared to exposure to TCA, suggesting that tetrachloroethylene can cross the placenta and be metabolized to TCA by fetal tissues. Because TCA also appeared in the fetal urinary bladder, TCA may recirculate

several times before leaving the fetoplacental compartment. This process may contribute to long-term retention in the murine fetus.

Genotoxic Effects. The lack of strong genotoxic effects seen in assays of human lymphocytes following occupational exposure to tetrachloroethylene is consistent with data on the metabolism of this compound. The metabolism of tetrachloroethylene by the hepatic cytochrome P-450 enzymes does not result in the formation of compounds that are mutagenic or that otherwise interfere with the integrity of the DNA. However, the metabolites that are formed are oxiranes and acyl chlorides; these are highly cytotoxic, which may contribute to the weak hepatocarcinogenic effect of tetrachloroethylene (Buben and O'Flaherty 1985; Daniel 1963; Yllner 1961). Another biotransformation pathway of this compound is glutathione conjugation. This process results in the formation of strong mutagens, e.g., *S*-(1,2,2-trichlorovinyl)glutathione, in the kidney and could explain the carcinogenic effects seen in this organ in rats (Dekant 1986).

A large number of studies of *in vitro* genotoxicity of tetrachloroethylene have been performed using prokaryotic, eukaryotic, and mammalian cells. The results of *in vitro* and *in vivo* studies are summarized in Tables 2-7 and 2-8, respectively. Most of the studies using the Ames test with *Salmonella typhimurium* have indicated that tetrachloroethylene itself is not a mutagen (Bartsch et al. 1979; Haworth et al. 1983; NTP 1986). Several chlorinated aliphatic compounds identified in the spent liquor from the softwood kraft pulping process were found to be mutagenic (Kringstad et al. 1981). Tetrachloroethylene was one of several compounds isolated that was shown to be mutagenic for *S. typhimurium* TA 1535 without the addition of liver microsomes for metabolic activation. In contrast, purified tetrachloroethylene was not mutagenic with or without exogenous metabolic activation. However, preincubation of tetrachloroethylene with purified rat liver GSH *S*-transferases in the presence of GSH and rat kidney fraction resulted in the formation of the conjugate, *S*-(1,2,2-tri-chlorovinyl) glutathione, which was unequivocally mutagenic in the Ames test (Vamvakas et al. 1989). Tetrachloroethylene oxide, an epoxide intermediate of tetrachloroethylene, was found to be mutagenic in bacterial studies (Kline et al. 1982).

Studies of mutagenicity on *Escherichia coli* have been negative (Greim et al 1975; Henschler 1977), as have been tests for mitotic recombination in yeast (Callen et al 1980; Koch et al. 1988). Mixed results were obtained in yeast when no metabolic activation was used in the experiments by Bronzetti et al. (1983). Koch et al. (1988) postulated that the lack of mutagenicity of tetrachloroethylene was because

TABLE 2-7. Genotoxicity of Tetrachloroethylene *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	–	Bartsch et al. 1979; Haworth et al. 1983; NTP 1986
Escherichia coli	Gene mutation	–	–	Greim et al. 1975; Henschler 1977
Lower eukaryotic system:				
Saccharomyces cerevisiae	Gene mutation	–	–	Bronzetti et al. 1983; Callen et al. 1980
S. cerevisiae	Recombination	(+/–)	–	Bronzetti et al. 1983; Callen et al. 1980; Koch et al. 1988
Mammalian cells:				
RaLV/Fisher rat embryo cells	Cell transformation	+	NR	Price et al. 1978
BALB/C3T3 mouse cells		–	NR	Tu et al. 1985
L5178Y/TK$^{+/-}$ mouse lymphoma cells		–	–	NTP 1986
Rat and mouse hepatocyte	DNA damage (unscheduled DNA synthesis)	–	NR	Costa and Ivanetich 1980
Human fibroblast cells	DNA damage (unscheduled DNA synthesis)	(+/–)	(+/–)	NIOSH 1980
Chinese hamster ovary cells	Sister chromatid exchange	–	–	NTP 1986

– = negative result; (+/–) = mixed results; + = positive result; DNA = deoxyribonucleic acid; NR = not reported

TABLE 2-8. Genotoxicity of Tetrachloroethylene *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Human lymphocystes/sister chromatid exchange	Sister chromatid exchange	–	Ikeda et al. 1980
		–	Seiji et al. 1990
Mouse/induction of single strand breaks in DNA	DNA damage	+	Walles 1986
Mouse/tetrachloroethylene binding to or alkylation of liver DNA	DNA binding or alkylation	–	Schumann et al. 1980
Rat/binding of rat kidney DNA	DNA binding or alkylation	+	Mazullo et al. 1987
Mouse/binding of mouse liver DNA	DNA binding or alkylation	+	Mazullo et al. 1987
Rat, mouse/genetic damage in germinal system	Germ cell chromosome damage	–	NIOSH 1980
Rat, mouse/altered sperm morphology	Mutation in germ cells	(+/–)	NIOSH 1980
Mouse/reticulocytes	Micronucleus	–	Murakami and Horikawa 1995
Mouse/reticulocytes	Micronucleus		Murakami and Horikawa 1995
Before partial hepatectomy		–	
After partial hepatectomy		+	
Hot-mediated assays:			
Drosophila melanogaster/sex-linked recessive lethal mutation	Gene mutation	–	NIOSH 1980; Valencia et al. 1985
Rat bone marrow cells/ chromosomal aberrations	Chromosomal aberrations	–	NIOSH 1980
Human lymphocytes/ chromosomal aberrations	Chromosomal aberrations	–	Ikeda et al. 1980
Drosophila melanogaster/sex-linked recessive lethal mutation	Gene mutation	–	NTP 1986

– = negative result; + = positive result; (+/–) = mixed results; DNA = deoxyribonucleic acid

of its highly toxic effects on cells and that lower doses would be required to demonstrate unequivocally the presence or absence of mutagenic effects.

Direct effects on DNA by tetrachloroethylene have been investigated in several cell systems. Human fibroblasts were assayed for unscheduled DNA synthesis following exposure to tetrachloroethylene, but the results were equivocal (NIOSH 1980). This study is difficult to interpret because negative results were obtained using the higher concentrations, whereas the lower doses produced a weak positive response. In addition, the positive control chemicals (*N*-methyl-*N*-nitro-*N*-nitrosoguanidine, benz[a]pyrene) produced only weak positive responses. Induction of single-strand breaks in mouse liver and kidney DNA, but not in lung DNA, following intraperitoneal injection of 4-8 mmol tetrachloroethylene/kg body weight was reported (Walles 1986). Most of the data do not support a directly mutagenic effect of tetrachloroethylene itself (Costa and Ivanetich 1980). The inconsistent results could be due to differences between tested species in metabolism or activation, protocol differences, or purity of the compound tested. Other investigators found no effects on the DNA of rat and mouse hepatocytes (Costa and Ivanetich 1980). However, evidence of DNA binding of tetrachloroethylene in mouse liver and rat kidney was seen in experiments that utilized liver microsomes and the addition of glutathione transferases (Mazzullo et al. 1987), further substantiating the evidence that the glutathione metabolites may be responsible for the mutagenic and carcinogenic properties of tetrachloroethylene. A single intraperitoneal injection of tetrachloroethylene given to mice at doses up to 2,000 mg/kg did not increase micronuclei in reticulocytes or hepatocytes when mice were treated before partial hepatectomy (Murakami and Kazumi 1995). Micronuclei were increased in hepatocytes at 1,000 and 2,000 mg/kg when mice were treated after partial hepatectomy.

There are few data on clastogenic effects of tetrachloroethylene following *in vitro* exposure. When Chinese hamster ovary cells were assayed for sister chromatid exchanges, no increase in frequency was found (NTP 1986). Two assays of cell transformation in mouse cells treated with tetrachloroethylene were negative (NTP 1986; Tu et al. 1985). However, Fischer rat embryo cells were transformed in the absence of metabolic activation.

Most of the studies on tetrachloroethylene have been done using commercial or technical grade chemical, which means that contaminants may be involved when effects are seen. Stabilizers are added to tetrachloroethylene to prevent decomposition. Stabilizers are amines or mixtures of epoxides and esters. Epoxides are themselves highly reactive because of the unstable three-member ring

structure. They easily generate hydroxide radicals, which can have deleterious cellular effects. Problems with unusual dose-response curves, cytotoxic doses of chemical, and small sample sizes are examples of factors that limit the interpretation of these studies. There is growing evidence that the mutagenic properties of tetrachloroethylene depend on the metabolic pathway that involves glutathione conjugation, a pathway more prominent in rats than mice or humans (Green et al. 1990). Therefore, it is not clear whether the low levels of tetrachloroethylene found at most hazardous waste sites would cause observable genotoxic effects in humans.

Cancer. Some epidemiological studies of dry cleaning workers suggest a possible association between chronic tetrachloroethylene exposure and increased cancer risk (Anttila et al. 1995; Blair et al. 1990; Chapman et al. 1981; Duh and Asal 1984; Katz and Jowett 1981; Lynge and Thygesen 1990 Ruder et al. 1994). Both the Anttila et al. (1995) and Ruder et al. (1994) studies reported a small number of cancers in their study populations, and that no significant excess number of cases of malignancy occurred. However, there was an increase in certain types of cancers which did develop. The cancer types most consistently showing an increase were esophageal cancer (Blair et al. 1979, 1990; Ruder et al. 1994), cervical cancer (Anttila et al. 1995; Blair et al. 1979, 1990; Brown and Kaplan 1987), and non-Hodgkin's lymphoma (Anttila et al. 1995). In general, these studies are confounded by concomitant exposure to other solvents, smoking and other life-style variables, and methodological limitations in choosing control populations and maintaining complete follow-up. The Woburn study (Lagakos et al. 1986), which attempted to correlate an increased risk of childhood leukemia with exposure to solvent-contaminated water, has been refuted by many scientists. In a study in New Jersey, tetrachloroethylene contamination of the drinking water was associated with an increased incidence of non-Burkitt's high-grade non-Hodgkin's lymphoma in females (Cohn et al. 1994). The investigators noted that the conclusions of their study are limited by potential misclassification of exposure because of a lack of individual information on duration of residence and water consumption.

Occupational exposure to tetrachloroethylene and other solvents did not generally result in increased risk of hematopoietic neoplasms. Although there was one report of familial chronic lymphocytic leukemia in five of seven members of a family who had worked for years in the dry cleaning industry (Blattner et al. 1976), it appears that an inherited defect was the cause of this family's susceptibility to leukemia. In addition, there was a study on occupational exposure of parents whose children had acute nonlymphocytic leukemia. Paternal (but not maternal) exposure to agents categorized as

"solvents" was reported to pose a significant risk for development of childhood leukemia (Buckley et al. 1989). However, the risk was nonsignificant when controlled for household exposure (including marijuana use) and paternal exposure to petroleum products.

The carcinogenicity of tetrachloroethylene has been documented in animals exposed by inhalation (NTP 1986) or oral (gavage) routes (NCI 1977). By both routes of exposure, mice but not rats developed compound-related hepatocellular neoplasms. One mechanism for tetrachloroethyleneinduced hepatocellular tumors in mice has been hypothesized to be the formation of a genotoxic epoxide intermediate during metabolism of tetrachloroethylene by mixed function oxidases (MFOs) (Buben and O'Flaherty 1985). However, data from numerous studies also indicate that chlorinated hydrocarbon-induced hepatocellular tumor development in rodents is related to peroxisomal proliferation. Tetrachloroethylene induces hepatocellular peroxisomal proliferation in mice but not in rats (Goldsworthy and Popp 1987). This species difference appears to result from differences in metabolic rates between rats and mice, with mice forming higher levels of TCA, a major tetrachloroethylene metabolite (Odum et al. 1988). TCA itself induces peroxisomal proliferation in mouse liver (Goldsworthy and Popp 1987). Both TCA and dichloroacetic acid (DCA), a minor metabolite of tetrachloroethylene, can induce hepatocellular tumors in mice (Herren-Freund et al. 1987; Pereira 1996). The tumors produced by TCA were basophilic, and lacked glutathione *S*-transferase-π, consistent with mouse liver tumors caused by other peroxisome proliferators (Pereira 1996). Humans are exposed to a number of disparate chemicals, including therapeutic hypolipidemic agents, that cause peroxisomal proliferation and liver cancer in rodents. These compounds, including TCA, cause little peroxisome proliferation in humans (Bentley et al. 1993). Nevertheless, the mechanism of carcinogenicity via peroxisomal proliferation is not well understood, and a cause and effect relationship has not been established. Therefore, the relevance of this end point to human risk remains unclear.

Other cancer end points in the inhalation study of tetrachloroethylene in rats, but not in mice, were significantly increased incidences of mononuclear cell leukemia in both sexes and a low-incidence of renal cancer in males (NTP 1986). Male rats exposed to a diverse group of hydrocarbon chemicals develop a unique form of kidney damage characterized by crystalloid phagolysosomal inclusions in the cytoplasm of renal proximal tubular epithelium (P2 segment) (Alden 1986). Biochemically, these inclusions are composed of the low-molecular-weight protein α-2μ-globulin complexed with a hydrocarbon chemical or its metabolite (Swenberg et al. 1989). This type of nephropathy, with

concomitant increases in cell replication in the damaged segment of the kidney, has been induced experimentally in male rats, but not in female rats, by treatment with doses of 1,000 mg/kg/day tetrachloroethylene or greater by gavage (Goldsworthy et al. 1988; Green et al. 1990). However, a-2μ-globulin accumulation was not seen in rats after inhalation exposure to tetrachloroethylene levels (400 ppm) that produced nephrotoxicity in both sexes and renal tumors in males (NTP 1986). This finding tends to argue against a major role for the α-2μ-globulin mechanism in tetrachloroethyleneinduced renal carcinogenesis in male rats. The complete pattern of nephropathy attributed to α-2μ-globulin accumulators has not been fully characterized for tetrachloroethylene. The available data do suggest, however, that since α-2μ-globulin accumulation was seen only after exposure to dosages that were higher than those inducing nephrotoxicity in the cancer bioassay (NTP 1986), a threshold level for the α-2μ-globulin nephrotoxicity of tetrachloroethylene (above the doses known to cause tumors in male rats) may exist.

In addition, there is evidence that tetrachloroethylene can be metabolized by glutathione conjugation in the liver (Dekant et al. 1986, 1987; Green et al. 1990). The conjugate is further metabolized by the mercapturic acid pathway and excreted in urine as the *N*-acetyl cysteine derivative. The precursor of this metabolite, *S*-(1,2,2-trichlorovinyl)glutathione, is a substrate for the renal enzyme, cysteine conjugate β-lyase. The data presented by Green et al. (1990), which show that the urinary level of the *N*-acetylated metabolite only begins to increase after saturation of the cytochrome P-450 pathway, have been used to support the speculation that hepatic glutathione conjugation of tetrachloroethylene is a "high-dose phenomenon" in rats. However, the saturation of the β-lyase pathway in the kidney would seem to be a more plausible explanation; at high doses, more of the cysteine conjugate would be converted and excreted because the competing β-lyase pathway approaches saturation. In addition, *S*-(1,2,2-trichlorovinyl)glutathione induces a powerful mutagenic response in the Ames bacterial mutation assay when activated by rat kidney fractions (Dekant et al. 1986; Vamvakas et al. 1989). The mutagenic response demonstrated for the cysteine conjugate of tetrachloroethylene suggests a possible genotoxic component in nephrocarcinogenicity of tetrachloroethylene in male rats.

Human metabolism of tetrachloroethylene can be saturated by exposure to more than 100 ppm for 8 hours/day (Ohtsuki et al. 1983). Although glutathione conjugation was not detected in *in vitro* studies of human liver tissues (Green et al. 1990), the results are inconclusive. The small number of human liver samples that were assayed, in conjunction with the relatively weak response reported for rat livers, does not resolve the issue of whether humans are at risk from renal damage caused by the

electrophilic intermediate resulting from glutathione conjugation. Of the various mechanisms hypothesized to be involved in tetrachloroethylene-induced renal tumorigenesis in male rats (i.e., protein droplet nephropathy, chronic nephrotoxicity, and hepatic glutathione-*S*-transferase-conjugation resulting in the formation of a mutagenic cysteine conjugate), the formation of mutagenic metabolites in the kidney appears to be a likely mode of action.

Despite some indication of human risk of leukemia from solvent exposure, the relevance to human health of elevated incidences of mononuclear cell leukemia related to tetrachloroethylene exposure in Fischer-344 rats is unclear. This is a spontaneous and very prevalent neoplasm that is fairly specific for Fischer-344 rats, and the control incidences for this study were higher than historical values. However, NTP's Board of Scientific Counselors considered the incidence of rat leukemias to be a true finding because there was a decreased time to onset of the disease and the disease was more severe in treated as compared to control animals.

The weight-of-evidence for the carcinogenicity classification of tetrachloroethylene represents a departure from the strict categorization scheme outlined in EPA's Cancer Risk Assessment Guidelines (EPA 1986b). Since EPA's carcinogenicity classification of tetrachloroethylene has major ramifications and can influence the public's perceptions of risk, some historical perspective is provided on the major issues arising from the assessment. In 1986, EPA recommended a Group B2 (probable human carcinogen) weight-of-evidence classification for tetrachloroethylene based on sufficient evidence from animal studies and inadequate human evidence (EPA 1991a). EPA's Science Advisory Board (SAB) reviewed tetrachloroethylene-related issues in late 1987; the summarized findings, presented in a letter to the EPA Administrator (March 9, 1988) were that the overall weight-of evidence positions tetrachloroethylene "on a continuum between categories B2 and C" (possible human carcinogen). In 1991, after reevaluation of animal data and additional mutagenicity data, the SAB Executive Committee made the following statement:

> It is the Committee's view that the major issues arising from the assessment of tetrachloro-ethylene have not changed over the past four years, and that SAB's previous response remains appropriate. The available scientific evidence confirms that tetrachloroethylene should be considered as an animal carcinogen, based on three endpoints in two species: liver tumors in male and female mice, kidney tumors in male rats, and, possibly, mononuclear cell leukemia in male and female rats. Complications within each study and in their biological interpretations

have made it difficult to categorize this compound. We do not consider the evidence strong enough to classify this compound as a probable human carcinogen (i.e., B2); on the other hand, the evidence for carcinogenicity is stronger than for most other compounds classified as possible human carcinogens (i.e., C). Therefore, in the spirit of the flexibility encouraged by the Guidelines, our best judgement places this compound on a continuum between these two categories (EPA 1991b).

The carcinogenicity assessment of tetrachloroethylene is still pending (IRIS 1996).

Based on increased risks of esophageal cancer, cervical cancer, and non-Hodgkin's lymphoma in several epidemiologic studies, and increased liver tumors in mice, increased mononuclear cell leukemia in rats, and renal tumors in male rats, IARC (1995) has classified tetrachloroethylene as probably carcinogenic to humans (Group 2A). According to the Department of Health and Human Services' (DHHS) Annual Report on Carcinogens, there is sufficient evidence for the carcinogenicity of tetrachloroethylene in animals, but the data in humans are inconclusive, leading to the conclusion that tetrachloroethylene may reasonably be anticipated to be a carcinogen (DHHS 1994).

2.6 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 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 tetrachloroethylene are discussed in Section 2.6.1.

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 tetrachloroethylene are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Tetrachloroethylene

Biological monitoring for exposure to tetrachloroethylene is possible by measuring levels of the parent compound in the blood, urine, or exhaled air or TCA in the blood or urine. Biological monitoring for tetrachloroethylene exposure has been performed to measure both exposure occurring in the workplace and the environmental exposure of individuals at places other than the work site. In these instances, it has been demonstrated that measurement of tetrachloroethylene in exhaled air is a fairly-simple, effective, and noninvasive method for assessing both occupational and nonoccupational exposure (Stewart and Dodd 1964; Stewart et al. 1961b, 1970, 1981). Tetrachloroethylene is excreted in the breath for long periods after exposure and is measurable on Monday morning following exposure the previous week (Monster et al. 1983). In an experimental exposure study, Stewart et al. (1981) found that breath concentrations reached an equilibrium with exposure concentrations on the third day of

each week. Based on breath analysis decay curves, Stewart et al. (1981) concluded that 16.5 hours after a male worker has been exposed to tetrachlorethylene in air at 100 ppm for 7.5 hours, his breath level should not exceed 10 ppm, while breath concentrations of a female worker should not exceed 6 ppm. Following 3 hours of exposure at 100 ppm, breath levels at 21 hours postexposure should not exceed 5 and 1 ppm for males and females, respectively.

In the experimental exposure studies of Stewart et al. (1961b, 1970, 1981), analysis of the expired breath of exposed subjects for tetrachloroethylene proved to be superior to both blood and urine analyses for determining the magnitude of the previous vapor exposure. A series of Breath Decay Curves was constructed following vapor exposures to 20, 50, 100, 150, and 200 ppm for 1, 3, and 7.5 hours, repeated for 5 days each, which permitted the estimation of the magnitude of the previous exposure. Utilizing the 30-second breath holding technique to collect breath samples, these Breath Decay Curves provide an efficient method for determining whether overexposure has occurred (Stewart et al. 1961a, 1981).

The concentration of tetrachloroethylene in exhaled air was used to measure environmental exposure in a group of 54 healthy volunteers from an urban population (Krotoszynski et al. 1979). In this group of subjects, it was determined that 30.2% had traces of tetrachloroethylene in their breath, with a mean concentration of 2.6 ng/m^3. The measurement of tetrachloroethylene in exhaled air showed that 93% of a sample of about 300 nonoccupationally exposed residents of Bayonne and Elizabeth, New Jersey, had measurable concentrations of tetrachloroethylene in their breath (Wallace 1986). The mean concentration of tetrachloroethylene in the breath in this study was 13.3 μg/m^3, and this mean concentration was increased to 22 μg/m^3 for persons who had visited a dry cleaning establishment. Measurements of tetrachloroethylene in exhaled air were used to determine exposure in children attending a school near a factory and in occupants of a senior citizens home located near a former chemical waste dump. A control group of children had a mean tetrachloroethylene level in their exhaled air of 2.8 μg/m^3, whereas exposed children had a mean tetrachloroethylene level of 24 μg/m^3. In the senior citizens group, people living on the first floor of the home had a mean tetrachloro-Ethylene level of 7.8 μg/m^3, whereas people living on the second floor and above had a mean tetra-chloroethylene level of 1.8 μg/m^3. It was concluded that biological monitoring of tetrachloroethylene in exhaled air was an effective method of assessing total ambient tetrachloroethylene exposure in both the young and aged (Monster and Smolders 1984).

Biological monitoring for recent, as opposed to more remote, exposure to tetrachloroethylene has also been performed by measuring concentrations of tetrachloroethylene and its principal metabolite, TCA, in blood and urine. However, TCA is not specific for tetrachloroethylene because it is also produced from the metabolism of trichloroethylene and l,l,l-trichloroethane (Monster 1988). In a study of occupationally exposed individuals, measurements of tetrachloroethylene and TCA in the blood 15-30 minutes after the end of the workday at the end of the week were judged to be the best parameters for estimating exposure to the chemical. The best noninvasive method for determining tetrachloroethylene exposure was to measure the concentration of the parent compound in exhaled air. After exposure to a TWA concentration of 50 ppm of tetrachloroethylene, the estimated concentrations of tetrachloroethylene and TCA in blood were 2.2 and 5.4 mg/L, respectively; the concentration of tetrachloroethylene in exhaled air was estimated to be 22.5 ppm (Monster et al. 1983). In another study of workers exposed to tetrachloroethylene, urinary metabolites were related to vapor concentrations up to 50 ppm, but little additional increase occurred at higher concentrations (Ikeda et al. 1972). The ACGIH biological exposure index (BEI) associated with a TWA concentration of 25 ppm tetrachloroethylene is 0.5 mg tetrachloroethylene/L in blood and 3.5 mg TCAL in urine (ACGIH 1995). The estimated BE1 in Korean workers exposed to 50 ppm tetrachloroethylene was 1.6 mg tetrachloroethylene/ in blood and 2.9 mg TCAL in urine (Jang et al. 1993), suggesting that there are differences in tetrachloroethylene metabolism among different ethnic populations.

Increased tetrachloroethylene blood levels have been detected after exposure to drinking water polluted by tetrachloroethylene released from a leaking storage tank (Kido et al. 1989). The investigators detected tetrachloroethylene in blood of exposed families when tetrachloroethylene was in drinking water at levels above 120 μg/L.

2.6.2 Biomarkers Used to Characterize Effects Caused by Tetrachloroethylene

Hepatocellular damage and icterus have been related to exposure to tetrachloroethylene. Biomarkers of hepatic cell death, which are not specific for tetrachloroethylene, are increases in serum levels of intracellular liver enzymes including SGOT, SGPT, and lactic dehydrogenase. Biomarkers of icterus include increased serum levels of bilirubin and alkaline phosphatase and increased urobilinogen in urine (Bagnell and Ellenberger 1977; Coler and Rossmiller 1953; Hake and Stewart 1977; Meckler and Phelps 1966; Stewart 1969). Electrophoresis of serum GGT enzymes from tetrachloroethyleneexposed workers with no other evidence of liver effects (SGOT, SGPT, serum alkaline phosphatase,

lactate dehydrogenase, and 5'-nucleotidase) has shown increases in GGT-2 and the appearance of GGT-4, which was not present in the serum of the unexposed controls (Gennari et al. 1992). The investigators indicate that further research is required to determine if changes in GGT enzymes are useful for detecting early liver changes induced by tetrachloroethylene. As increases in GGT also occur with fatty livers, pancreatitis, and following exposure to other xenobiotics (Suber 1989), this liver effect is not specific for tetrachloroethylene. Parenchymal changes detected by ultrasound may also be a useful noninvasive marker of liver effects (Brodkin et al. 1995), although it also is not specific for tetrachloroethylene.

Biomarkers of renal damage are not specific for solvents. For clinical renal damage, these include increased blood urea nitrogen and serum creatinine and abnormal urinalysis findings. Increased urinary levels of lysozyme and the lysosomal enzyme *N*-acetyl-beta-D-glucuronidase, albuminuria, and other urinary markers suggesting increased shedding of epithelial membrane components from tubular cells may indicate subclinical renal damage in workers exposed to a potentially nephrotoxic chemical (Franchini et al. 1983; Meyer et al. 1984; Mutti et al. 1992; Viau et al. 1987).

Neurotoxic effects manifested in the central nervous system have been associated with acute and chronic exposure of humans to tetrachloroethylene. These effects may be monitored by symptomatology, neurological examination, and neuropsychological testing (Gregersen et al. 1984). Neurological effects are not specific for tetrachloroethylene. Therefore, other causes of neurological disease must be ruled out before effects are attributed to tetrachloroethylene exposure.

2.7 INTERACTIONS WITH OTHER CHEMICALS

The hepatic monooxygenase system is primarily responsible for oxidation of tetrachloroethylene. Thus, compounds that stimulate or induce tetrachloroethylene metabolism could influence the toxicity associated with exposure to this chemical. Results of experiments that have investigated possible enhancement of tetrachloroethylene-induced toxicity by increasing tetrachloroethylene metabolism have been equivocal. Pretreatment of rats with ethanol (Cornish and Adefuin 1966; Klaassen and Plaa 1966) and phenobarbital (Cornish et al. 1973; Moslen et al. 1977) failed to enhance tetrachloroethylene hepatic toxicity. Pretreatment with polychlorinated biphenyls (PCBs), on the other hand, increased urinary excretion of tetrachloroethylene metabolites in rats and enhanced tetrachloroethylene-induced hepatotoxicity (Moslen et al. 1977).

2. HEALTH EFFECTS

A study was conducted to evaluate the potential interaction between tetrachloroethylene and ethanol, or tetrachloroethylene and diazepam (Stewart et al. 1977). Twelve healthy volunteers of each sex were exposed to 0, 25, or 100 ppm tetrachloroethylene vapor alone or in combination with either ethanol (0.0, 0.75, or 1.5 mL vodka/kg body weight) or diazepam (0, 6, or 10 mg/day). The subjects exhibited a decrement in performance of at least one of the behavioral or neurological tests while on either drug alone at the highest dose level, but no interaction with tetrachloroethylene resulting in additional test performance decrement could be demonstrated for either combination of solvent vapor and drug.

Giovannini et al. (1992) examined the interaction of ethanol and tetrachlorethylene on the hepatic toxicity in rats. Rats were exposed to 15% ethanol in the drinking water and/or to tetrachloroethylene aerosol for 10 minutes each day for 4 weeks. The tetrachloroethylene concentration used was not provided, but can be assumed to be very high because the rats were unconscious by the end of the lo-minute exposure period. Liver effects, necrotic foci, steatosis, and lymphocyte infiltration were worse after ethanol exposure compared to tetrachloroethylene exposure alone. When the rats were treated with both compounds, tetrachloroethylene tended to reduce the hepatic effects of ethanol. Giovannini et al. (1992) suggest that the reduction of ethanol hepatic effects by tetrachloroethylene is a result of a metabolic interaction between ethanol and tetrachloroethylene.

In a study of dry cleaning workers in China, urinary metabolite levels (total trichloro compounds) were reduced when workers were exposed to mixtures of tetrachloroethylene and trichloroethylene as opposed to trichloroethylene alone (Seiji et al. 1989). The effect on the trichloroethylene metabolite, trichloroethanol was greatest, with little effect on TCA, a metabolite of both trichloroethylene and tetrachloroethylene. The study authors indicated that because of the smaller amount of tetrachloroethylene metabolized, it was not possible to determine if trichloroethylene suppressed the metabolism of tetrachloroethylene. Concurrent administration of tetrachloroethylene and trichloroethylene to mice did not result in additive or synergistic effects in induction of hepatic peroxisomal proliferation as measured by cyanide-insensitive palmitoyl CoA oxidation activity (Goldsworthy and Popp 1987). This may be related to preferential metabolism of trichloroethylene at the dose levels used.

Combined oral treatment of rats with tetrachloroethylene (3,000 mg/kg/day) and vitamin E (400 mg/kg/day) prevented the centrilobular necrosis in the liver and hypercellular glomeruli and congestion of convoluted tubules of the kidneys that was observed when rats were treated with tetra-

chloroethylene alone (Ebrahim et al. 1995). Vitamin E also prevented the tetrachloroethylene-induced increase in protein and protein-bound carbohydrates observed in the liver and kidneys of rats treated only with tetrachloroethylene. This study suggests that free radical metabolites may play a role in the liver and kidney toxicity observed in rats treated with tetrachloroethylene.

Tetrachloroethylene may sensitize the myocardium to effects of other chemicals. For example, high doses of intravenously administered tetrachloroethylene have been found to sensitize the myocardium to the presence of exogenous epinephrine (Kobayashi et al. 1982). However, Reinhardt et al. (1973) did not observe sensitization to epinephrine in beagle dogs exposed to vapors of tetrachloroethylene. Tetrachloroethylene may also have a direct effect on the heart. In synergy with alcohol and hypoxia, tetrachloroethylene prolonged atrioventricular conduction in the perfused rat heart. Because of the perfused heart model, this effect was not catecholamine mediated (Kawakami et al. 1988).

Using the *Tradescantia*-micronucleus assay, Ma et al. (1992) examined the genotoxicity of tetrachloroethylene with lead tetraacetate, arsenic trioxide, and dieldrin. Although tetrachloroethylene, dieldrin, and arsenic trioxide were not genotoxic alone, mixtures of tetrachloroethylene with dieldrin or arsenic trioxide were genotoxic. An interaction between tetrachloroethylene and lead tetraacetate was not observed. When mixtures of three chemicals (combination of any 3: tetrachloroethylene, dieldrin, arsenic trioxide, and lead tetraacetate) were tested, interactions were also not observed.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to tetrachloroethylene than will most persons exposed to the same level of tetrachloroethylene 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 may result in reduced detoxification or excretion of tetrachloroethylene, or compromised function of organs affected by tetrachloroethylene. Populations who are at greater risk due to their unusually high exposure to tetrachloroethylene are discussed in Section 5.6, Populations With Potentially High Exposures.

Patients who had detectable blood levels of volatile organic chemicals (often more than one chemical) and who had a variety of systemic symptoms were classified as “chemically sensitive” by Rea et al. (1987). Tetrachloroethylene was the most common chemical detected in the blood of the

"chemically sensitive" individuals who were studied (found in 72 of 134 patients). No controls were used in this study, so it is not clear if tetrachloroethylene is more frequently detected in chemically sensitive individuals and/or if concentrations of tetrachloroethylene in the blood are greater in sensitive individuals than in the general population. Some adults also appear to have increased sensitivity to certain systemic effects of tetrachloroethylene, e.g., cardiac sensitization (Abedin et al. 1980). Since high doses of tetrachloroethylene are known to cause liver and kidney effects, persons with clinical or subclinical renal or hepatic disease may be predisposed to the effects of tetrachloroethylene. Persons with preexisting nervous system diseases may also be more sensitive to the neurotoxic effects of tetrachloroethylene.

The developing fetus, children, and especially the developing nervous system may be particularly susceptible to the toxic effects of tetrachloroethylene (Frederiksson et al. 1993). Studies in mice suggest that tetrachloroethylene can cross the placenta and that TCA concentrates in the fetus (Ghantous et al. 1986). Unmetabolized tetrachloroethylene has been excreted in breast milk and was detected in an exposed infant with liver damage (Bagnell and Ellenberger 1977). In addition, possible chemical effects were detected in children in Woburn, Massachusetts. These children may have been exposed to solvent-contaminated drinking water as infants or *in utero,* and they had elevated incidences of acute lymphocytic leukemia or impaired immunity (Byers et al. 1988; Lagakos et al. 1986).

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to tetrachloroethylene. 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 tetrachloroethylene. 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 tetrachloroethylene: Ellenhorn and Barceloux 1988; Stetz and Ulin 1992.

2.9.1 Reducing Peak Absorption Following Exposure

Following suspected overexposure to tetrachloroethylene, the person should be promptly placed under the care of a knowledgeable physician. In the case of vapor exposure, the person should be removed from the vapor-contaminated environment and given the standard emergency, and supportive treatment. There is no specific antidote. Anesthetic overexposure may require respiratory assistance and the treatment of cardiac arrythmias. General recommendations for reducing absorption following acute oral exposure have included the administration of water or milk, emesis with ipecac syrup (unless the patient is or could rapidly become obtunded, comatose, or convulsive), gastric lavage, and/or administration of a charcoal slurry with or without a cathartic (Ellenhorn and Barceloux 1988; HSDB 1996; Stutz and Ulin 1992). Induction of emesis is not recommended because of the danger of aspiration resulting in a chemical pneumonitis. In the case of eye exposure, irrigation with copious amounts of water or saline has been recommended (Bronstein and Currance 1988; Haddad and Winchester 1990; HSDB 1996; Stutz and Ulin 1992). For dermal exposure, the removal of contaminated clothing and a thorough washing of any exposed areas with soap and water have been recommended (HSDB 1996; Stutz and Ulin 1992).

2.9.2 Reducing Body Burden

The body does not retain significant amounts of tetrachloroethylene; most of an absorbed dose is excreted within several days of either inhalation or oral exposure (see Section 2.3.4). However, methods aimed at enhancing elimination during this period of retention may be effective in mitigating the serious effects that can occur following absorption of tetrachloroethylene. It is emphasized that no clinical treatments, other than supportive measures, are currently available to enhance elimination.

One possible method for enhancing elimination is increasing the ventilation rate. In a single case report, controlled hyperventilation over a 5-day period enhanced pulmonary elimination in a 6-year-old boy who had ingested between 12 and 16 grams of tetrachloroethylene (Koppel et al. 1985).

Metabolism of tetrachloroethylene is saturable following either inhalation (Ohtsuki et al. 1983; Seiji et al. 1989) or oral (Pegg et al. 1979; Schumann et al. 1980) exposure, and therefore, it is likely that stimulation of the metabolism of tetrachloroethylene will also lead to enhanced elimination. Methods for enhancing elimination through stimulation of metabolism could focus on either P-450-mediated

oxidation or glutathione conjugation. While elimination enhancement through stimulation of either of these pathways may reduce some forms of toxic effects, these same pathways may form reactive metabolites from tetrachloroethylene or from other substances (such as carbon tetrachloride) (Anders et al. 1988; Cornish and Adefuin 1966; Cornish et al. 1973; Dekant et al. 1986; Green et al. 1990; Klaassen and Plaa 1966; Moslen et al. 1977). Therefore, the risks and benefits of stimulating these pathways are unclear.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

Clinical effects caused by acute tetrachloroethylene exposure include central nervous system depression, liver or kidney injury, and in severe cases even death from anesthetic effects (see Section 2.5). Other effects can include malaise, dizziness, fatigue, headache, and lightheadedness, all of which may disappear soon after the exposure is stopped (HSDB 1996). The mechanism of action for the central nervous system effects has not been clearly established but may be related to solvent effects on lipid and fatty acid compositions of membranes (Kyrklund et al. 1984, 1988, 1990).

The mechanism of action for kidney toxicity and nephrocarcinogenicity may involve the formation of reactive intermediates from glutathione conjugates (Dekant et al. 1986, 1987; Green et al. 1990; Henschler 1977). Although evidence from an *in vitro* study with human liver tissue suggests that glutathione conjugation is not an important route of biotransformation in humans (Green et al. 1990), the results are not conclusive. Methods for reducing the destructive damage caused by glutathione conjugates metabolites, or for blocking their formation through inhibition of β-lyase may prove effective in reducing kidney toxicity but are not currently available for clinical use.

One mechanism of action for liver toxicity suggested in the literature is the induction of peroxisome proliferation (and resulting increases in hydrogen peroxide and oxidative damage) by TCA, a metabolite of tetrachloroethylene (Odum et al. 1988). Shifting metabolism away from formation of TCA could theoretically reduce toxicity that might be caused by this mechanism. However, the net effect on all forms of toxicity of tetrachloroethylene by such an alteration in metabolism would need to be evaluated.

2.10 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 tetrachloroethylene 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 tetrachloroethylene.

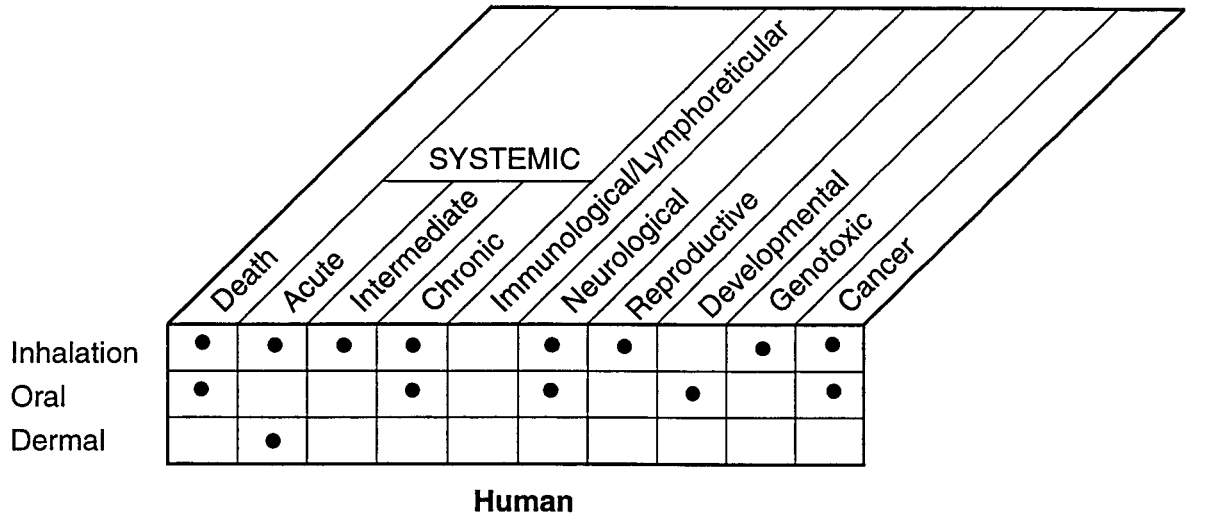
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

2.10.1 Existing Information on Health Effects of Tetrachloroethylene

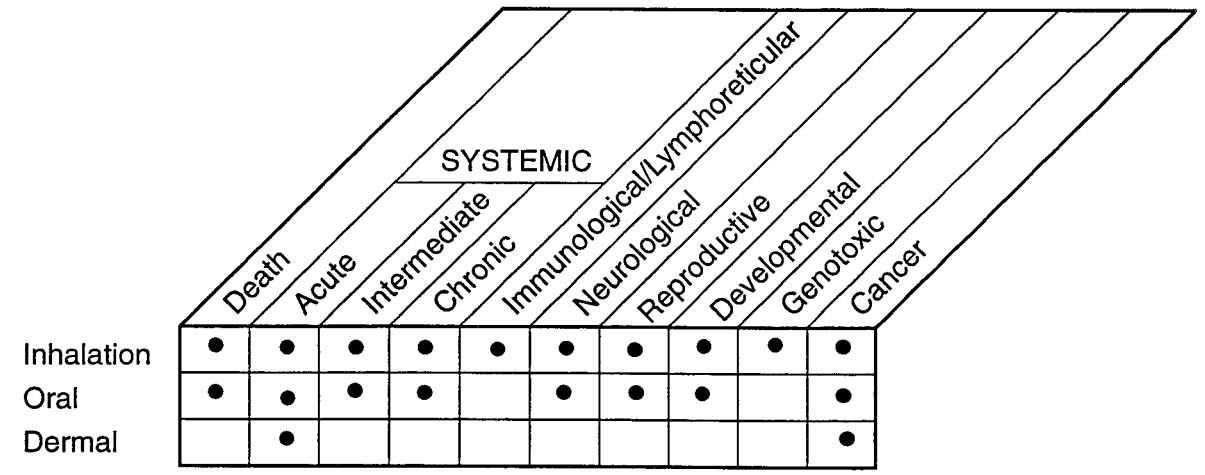
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to tetrachloroethylene are summarized in Figure 2-6. The purpose of this figure is to illustrate the existing information concerning the health effects of tetrachloroethylene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Most of the literature regarding health effects in humans comes from studies of workers exposed to tetrachloroethylene during occupational uses. Case reports describe some of the acute, intermediate, and chronic health effects associated with ingestion or inhalation of the chemical. The predominant mode of exposure in these studies is by inhalation. The primary untoward health effects observed in the humans reported in these occupational and case studies are the result of central nervous system

FIGURE 2-6. Existing Information on Health Effects of Tetrachloroethylene



Human



Animal

● Existing Studies

depression or skin injury. Transient kidney and liver injury are observed when acute and prolonged exposure to higher vapor concentrations occur. Acute exposure to high vapor concentrations has also resulted in death, from either profound respiratory center depression or cardiac arrhythmia. These studies are limited by the lack of reliable data on individual exposure levels. According to one case report, direct dermal exposure to tetrachloroethylene reportedly resulted in erythema and blistering of the skin. Experimental exposure studies at concentrations achieved in occupational settings have confirmed neurological effects.

A large number of studies examining the health effects of inhalation of tetrachloroethylene by animals were reviewed. There were also a number of studies regarding health effects of ingested tetrachloro-ethylene. Primary target organs and systems in animals include the nervous system, kidney, and liver. The mouse is especially susceptible to liver damage leading to increased risk of liver cancer. The rat appears to have an increased sensitivity to kidney damage leading to cancers of the kidney. The limited dermal exposure studies of tetrachloroethylene in animals indicate that the compound can be absorbed following direct application, but the studies have not clearly identified any effects.

2.10.2 Identification of Data Needs

Acute-Duration Exposure. There are reports on acute tetrachloroethylene exposure of humans following inhalation and oral routes, and in animals following inhalation and oral exposure. The primary targets following acute inhalation and oral exposure are the central nervous system (Altmann et al. 1990, 1992; Carpenter 1937; Hake and Stewart 1977; Haerer and Udelman 1964; Kendrick 1929; Moser et al. 1995; NTP 1986; Ogata et al. 1971; Rowe et al. 1952; Savolainen et al. 1977; Stewart 1969; Stewart et al. 1961a, 1961b, 1970, 1981), kidneys (Goldsworthy and Popp 1987), and the liver (Berman et al. 1995; Hake and Stewart 1977; Goldsworthy and Popp 1987; Hanioka et al. 1995; Kylin et al. 1963; NTP 1986; Odum et al. 1988; Saland 1967; Schumann et al. 1980; Stewart 1969). The majority of the human studies are cases involving accidental (Gamier et al. 1996; Koppel et al. 1985; Saland 1967) or occupational exposure (Levine et al. 1981; Lukaszewski 1979; Morgan 1969; Pate1 et al. 1973), or the use of tetrachloroethylene as an anthelminthic (Kendrick 1929; Wright et al. 1937). However, studies are available that reported the thresholds for central nervous system effects in humans resulting from acute-duration inhalation exposures to tetrachloroethylene (Altmann et al. 1990, 1992; Carpenter 1937; Hake and Stewart 1977; Rowe et al. 1952). An acute inhalation MRL of 0.2 ppm has been determined based on the NOAEL for human central nervous system effects

(Altmann et al. 1992). Human oral exposure data, limited to an accidental exposure (Koppel et al. 1985) and descriptions of the use of tetrachloroethylene as an anthelminthic (Chaudhuri and Mukerji 1947; Kendrick 1929; Koppel et al. 1985; Sandground 1941; Wright et al. 1937), do not clearly define threshold dosages. Direct dermal contact with tetrachloroethylene results in chemical burns (Hake and Stewart 1977; Ling and Lindsay 1971; Morgan 1969). Additional effects in humans following dermal exposure only have not been conclusively identified.

There are acute inhalation studies that provide data on lethality (Friberg et al. 1953; NTP 1986) and systemic effects in mice including neurotoxic (NTP 1986), hepatic (Kylin et al. 1963; NTP 1986; Odum et al. 1988), respiratory (Aoki et al. 1994), and immunotoxic effects (Aranyi et al. 1986), and neurotoxic effects in rats (Goldberg et al. 1964; NTP 1986; Rowe et al. 1952; Savolainen et al. 1977). There are also oral lethality studies in rats (Berman et al. 1995; Hayes et al. 1986) and mice (Wenzel and Gibson 1951). Effects noted in acute oral studies of tetrachloroethylene in animals include increased liver weight (Berman et al. 1995; Goldsworthy and Popp 1987; Hanioka et al. 1995), nephropathy (Goldsworthy et al. 1988), decreased body weight gain in rats (Schumann et al. 1980), neurological effects in rats (Moser et al. 1995), and liver hypertrophy (Schumann et al. 1980) in mice. Oral exposure of young mice to tetrachloroethylene resulted in hyperactivity when the mice were tested as adults (Fredriksson et al. 1993). Interpretation of some of these data is difficult because of limitations in the design and conduct of the studies (e.g., decreased survival, poor study methodology). An acute oral MRL of 0.05 mg/kg/day has been derived based on the LOAEL for developmental neurotoxicity (Fredriksson et al. 1993). Acute dermal exposure data in animals were not identified. Additional data on dermal exposure of animals would be useful to provide threshold levels. Because the acute oral MRL is based on a single study showing effects on the developing nervous system (Fredriksson et al. 1993), additional animal studies designed to examine this end point would increase confidence in the database. The targets that seem to be of greatest concern following tetrachloroethylene exposure are the central nervous system, including effects on the developing nervous system, the liver, and the kidneys. Populations living near hazardous waste sites may potentially be exposed for brief periods to tetrachloroethylene via inhalation, oral, or dermal routes.

Intermediate-Duration Exposure. Human data regarding intermediate-duration exposure are limited to inhalation studies that reported adverse neurological effects (Abedin et al. 1980; Meckler and Phelps 1966). However, exposure concentrations are not well defined in these studies. No human data were located regarding oral or dermal exposure to tetrachloroethylene. The target organs

identified in animal studies of intermediate-duration oral or inhalation exposure to tetrachloroethylene include the central nervous system (Carpenter 1937; Karlsson et al. 1987; Kyrklund et al. 1988; Rosengren et al. 1986), liver (Buben and O'Flaherty 1985; Carpenter 1937; Hayes et al. 1986; Kjellstrand et al. 1984; Kylin et al. 1965; Kyrklund et al. 1988; NTP 1986; Odum et al. 1988; Rowe et al. 1985; Story et al. 1986), and kidney (Carpenter 1937; Green et al. 1990; Hayes et al. 1986; NTP 1986; Rowe et al. 1985). These studies were conducted in a variety of animal species including mice, rats, guinea pigs, and gerbils. Intermediate oral studies in animals have reported mortality in rats (NCI 1977), and kidney (Green et al. 1990; Hayes et al. 1986) and liver (Buben and O'Flaherty 1985; Hayes et al. 1986; Story et al. 1986) effects in rats and mice. No intermediate-duration dermal studies in animals were located. An intermediate-duration inhalation MRL was not derived. Exposure concentrations were not well defined in human intermediate-duration studies following inhalation exposure.
The lowest animal LOAEL was for liver effects in mice (Kjellstrand et al. 1984). Because mice metabolize more tetrachloroethylene to TCA than humans, and because the peroxisomal proliferative response in mice is much greater than in humans, data in humans were considered more appropriate for the derivation of inhalation MRLs. Oral studies have not focused on neurological effects, the principal effect of tetrachloroethylene in humans, and the most sensitive end point in an acute oral study (Fredriksson et al. 1993). Therefore, an intermediate-duration oral MRL was not derived. Additional animal studies concerning the threshold of nervous system effects following inhalation, oral, and dermal exposure to tetrachloroethylene would be especially useful for determining levels of significant exposure to tetrachloroethylene that are associated with adverse health effects.

Chronic-Duration Exposure and Cancer. Kidney toxicity (Franchini et al. 1983; Mutti et al. 1992; Price et al. 1995) and symptoms of chronic encephalopathy (Gregersen 1988) were reported in studies of humans occupationally exposed to tetrachloroethylene. Other occupational exposure studies have not identified kidney (Lauwerys et al. 1983; Solet and Robins 1991) or irreversible central nervous system effects (Cai et al. 1991; Coler and Rossmiller 1953; Lauwerys et al. 1983). Deficits in behavioral tests that measured short-term memory for visual designs (Echeverria et al. 1995) have also been noted in humans occupationally exposed to tetrachloroethylene. There are conflicting reports on the effect of tetrachloroethylene on color vision in persons occupationally exposed to tetrachloroethylene. Cavalleri et al. (1994) reported an effect on color vision at an average concentration of 7.3 ppm, while Nakatsuka et al. (1992) reported no effect on color vision at average concentrations of 15.3 and 10.7 ppm for men and women, respectively. Further studies to clarify whether occupational exposure to tetrachloroethylene affects color vision would be useful. Ferroni et al. (1992) reported

increased reaction times in women exposed to tetrachloroethylene in dry cleaning shops at an average concentration of 15 ppm for about 10 years. Based on this LOAEL, a chronic-duration inhalation MRL of 0.04 ppm was derived.

A study of neurological function in persons living above or next to dry cleaning facilities has been completed (Altmann et al. 1995). Although no differences in absolute values of neurological function tests were noted, effects on neurological function tests were observed when multivariate analysis was used to analyze the data. This study suggests that further studies of larger populations exposed to very low levels of tetrachloroethylene would be useful.

Adverse health effects observed in chronic inhalation animal studies include reduced survival in rats and mice (NTP 1986), biochemical alterations in the brains of gerbils (Briving et al. 1986; Kyrklund et al. 1984) and kidney effects (nephropathy) in rats and mice (NTP 1986). Chronic oral animal studies have demonstrated reduced survival and kidney effects in rats and mice (NCI 1977). Doses causing target organ effects in animals following oral exposure are very similar to those causing lethality (NCI 1977). Therefore, no chronic-duration oral MRL was derived. No chronic dermal studies were located. Additional chronic studies in animals that provide information on threshold levels and dose-response relationships for toxic effects following oral or dermal exposure would be useful since populations living near hazardous waste sites are likely to be exposed at low levels over a long period of time.

Epidemiology studies suggest a possible association between chronic inhalation exposure to tetrachloroethylene and cancer (Anttila et al. 1995; Blair et al. 1979, 1990; Brown and Kaplan 1987; Duh and Asal 1984; Katz and Jowett 1981; Lynge and Thygesen 1990; Ruder et al. 1994; Spirtas et al. 1991). The cancer types most consistently showing an increase were esophageal cancer (Blair et al. 1979, 1990; Ruder et al. 1994), cervical cancer (Anttila et al. 1995; Blair et al. 1979, 1990; Brown and Kaplan 1987), and non-Hodgkin's lymphoma (Anttila et al. 1995). In general, these studies are confounded by concomitant exposure to other solvents and lack of consideration of the smoking habits and socioeconomic status of the subjects. The only data on carcinogenicity in humans following chronic oral exposure to tetrachloroethylene are from communities exposed to drinking water contaminated with tetrachloroethylene (Cohn et al. 1994; Lagakos et al. 1986). There are a number of confounding factors (i.e., uncertain exposure duration, exposure to multiple organic compounds) that

render the studies problematic, and the findings do not substantiate an association between tetrachloroethylene and cancer in humans. No chronic dermal exposure data are available for humans.

Inhalation and oral bioassays using rats and mice have been conducted (NCI 1977; NTP 1986). These data provide sufficient evidence to conclude that tetrachloroethylene is carcinogenic in animals. However, the oral study (NCI 1977) was limited by control groups smaller than treatment groups, decreased survival, and dose adjustments during the study. A dermal study conducted in mice reported no incidence of cancer in the test animals (Van Duuren et al. 1979). No additional cancer bioassays in animals appear to be necessary at this time. However, additional studies that clarify the relationship between peroxisome proliferation and hepatic cancers in mice as well as the relevance of hepatic glutathione conjugation of tetrachloroethylene to humans would be useful.

Genotoxicity. *In vivo* genotoxicology studies, including two studies examining human lymphocytes from persons occupationally exposed to tetrachloroethylene (Ikeda et al. 1980; Seiji et al. 1990), were negative for sister chromatid exchange. Similarly, the majority of *in vitro* genotoxicity tests using prokaryotic cells (Bartsch et al. 1979; Haworth et al. 1983; NTF' 1986; Williams and Shimada 1983), eukaryotic cells (Bronzetti et al. 1983; Callen et al. 1980; Koch et al. 1988), and mammalian cells (Costa and Ivanetich 1980; Mazzullo et al. 1987; NIOSH 1980; NTP 1986; Tu et al. 1985; Walles 1986; Williams and Shimada 1983) showed negative or marginal results for gene mutation, recombination, DNA damages and sister chromatid exchanges. Although the results in both *in vivo* and *in vitro* assays generally indicate that tetrachloroethylene is not genotoxic, marginal and equivocal results in some assays indicate that genotoxic effects cannot be ruled out. Data are available indicating that the precursor of the *N*-acetyl cysteine derivative of tetrachloroethylene, *S*-(1,2,2-trichlorovinyl)-glutathione, induces a powerful mutagenic effect in *S. typhimurium* strains in the presence of rat kidney fractions (Vamvakas et al. 1989). It is conceivable, therefore, that the mutagenic potential of the parent compound could be uncovered if the steps involved in the activation of tetrachloroethylene via glutathione conjugation could be replicated in *in vitro* microbial systems. Additional genotoxicity assays would be useful for either substantiating the data that indicate that this chemical may be carcinogenic in humans or for providing information about the carcinogenic mechanism of tetrachloroethylene. Additional data on genotoxic end points from animals exposed *in vivo* would be useful because the available data are inconclusive.

2. HEALTH EFFECTS

Reproductive Toxicity. Reproductive data are available on women occupationally exposed to tetrachloroethylene in dry cleaning operations. Three studies suggest an increase in spontaneous abortion (Ahlborg 1990; Bosco et al. 1986; Kyyronen et al. 1989; Windham et al. 1991), but other studies reported no increase (McDonald et al. 1986; Olsen et al. 1990). However, these studies are limited by the difficulty in identifying appropriate controls and by the problems in controlling for concomitant exposures to other chemicals. Limited evidence also suggests that time-to-pregnancy may be increased among women occupationally exposed to tetrachloroethylene (Sallmen et al. 1995). Wives of dry cleaners who had significantly more rounded sperm did not have more spontaneous abortions, although there was some evidence that it may take slightly longer for these women to become pregnant (Eskenazi et al. 1991a, 1991b). These studies suggest that tetrachloroethylene may affect the ability of men to reproduce. No studies were located regarding reproductive effects in humans after oral or dermal exposure to tetrachloroethylene.

Decreased litter sizes and decreased survival during lactation were observed in rats exposed to 1,000 ppm in a multigeneration study (Tinston 1995). Sedation was also noted at this concentration. No significant effects on reproduction were observed at 300 ppm in air. This study suggests that at concentrations below those that result in frank neurological effects, reproductive effects are unlikely to occur. A significant increase in resorptions was also observed in rats treated by gavage with tetrachloroethylene during organogenesis at 900 mg/kg/day, a dose that resulted in maternal ataxia and decreased body weight gain (Narotsky and Kavlock 1995). Histopathological effects in the testes and ovaries were not observed in rats or mice exposed by gavage to tetrachloroethylene at doses that resulted in increased mortality (NCI 1977). No studies were located regarding reproductive effects in animals following dermal exposure. It would be useful to conduct multigeneration or continuous breeding studies for oral and dermal exposures of animals in order to clarify the potential for tetrachloroethylene to cause reproductive effects in humans via these exposure routes.

Developmental Toxicity. Studies examining the association between drinking water contamination and birth outcome (Bove et al. 1995; Lagakos et al. 1986) have suggested that tetrachloroethylene exposure may be associated with increased eye/ear anomalies and central nervous/chromosomal/oral cleft anomalies. These studies are not conclusive because the water was contaminated with other solvents in addition to tetrachloroethylene. In animal studies, tetrachloroethylene has been shown to cross the placenta and distribute to the fetus and amniotic fluid (Ghantous et al. 1986). Developmental effects following inhalation exposure to tetrachloroethylene were investigated in several animal studies

(Nelson et al. 1980; NIOSH 1980; Schwetz et al. 1975). Developmental studies conducted in rats and mice reported fetotoxic effects but no teratogenic effects at concentrations that were maternally toxic (Schwetz et al. 1975). Decreased fetal weight and delayed skeletal ossification were common observations. In rats, behavioral and neurochemical alterations were observed after maternal exposure to tetrachloroethylene (Nelson et al. 1980). Increased postnatal deaths and increased micro/anophthalmia were observed in the offspring of rats treated by gavage with tetrachloroethylene during organogenesis at 900 mg/kg/day, a dose that resulted in maternal ataxia and decreased body weight gain (Narotsky and Kavlock 1995). Following oral exposure of mice to 5 mg tetrachloroethylene/kg for 7 days beginning at 10 days of age, hyperactivity was observed at 60 but not 17 days of age (Fredriksson et al. 1993). This study suggests possible permanent damage to the nervous system if exposure occurs during development. No NOAEL was identified. Because the Fredriksson et al. (1993) study serves as the basis for the acute oral MRL, additional animal inhalation and oral studies confirming the observation of developmental neurotoxicity would be useful. Studies in more than one species and studies examining whether the effect is a result of tetrachloroethylene or TCA are needed to determine if the results in mice are applicable to predicting effects in humans.

No studies were located regarding developmental effects following dermal exposure to tetrachloroethylene in animals. Additional animal studies should focus on the mechanism by which tetrachloroethylene produces embryotoxic and neurological effects in the offspring. Studies examining the relationship between behavioral effects and morphological changes in the nervous system following tetrachloroethylene exposure would be especially useful. Because tetrachloroethylene crosses into breast milk (Byczkowski and Fisher 1994), and because workers exhale tetrachloroethylene at home, these animal studies should also examine the later stages of nervous system development that occur after birth. Nervous system function should be examined throughout the lifetime of exposed animals to determine if effects are consistently observed as the animals age. Additional studies regarding developmental effects in animals following inhalation, oral, and dermal exposure would provide useful information relevant to humans exposed by these routes in areas near hazardous waste sites.

Immunotoxicity. Immunotoxicity data in either humans or animals are insufficient. Available data indicate possible immunotoxic effects (altered ratios of T lymphocyte subpopulations) in humans chronically exposed to tetrachloroethylene (21 ppb) as well as trichloroethylene (267 ppb) and other solvents from a contaminated water supply (Byers et al. 1988). However, because of other contaminants, it is not possible to infer from these data the exact role of tetrachloroethylene. One

study (Aranyi et al. 1986) in which mice were exposed by inhalation for 3 hours to varying doses of tetrachloroethylene demonstrated increased susceptibility to bacterial infection. Interpretation of this study is complicated by the fact that the controls for one of the treated groups had a higher mortality rate than any other group in the study. In a study in which rats were exposed to tetrachloroethylene vapors, no production of antibodies to tetrachloroethylene was detected (Tsulaya et al. 1977). In a 14-day study, histopathological changes in the spleen and thymus gland were not observed in rats treated by gavage with tetrachloroethylene at a dose that resulted in liver effects (Berman et al. 1995). No effects on natural killer cell, natural cytotoxic, and natural P815 killer cell activities or humor-al and T cell mitogenesis were observed in cells harvested from rats and mice treated with three daily intraperitoneal doses of 829 mg tetrachloroethylene/kg (Schlichting et al. 1992). There are no dermal studies regarding the immunotoxic effects of tetrachloroethylene. Additional data from inhalation, oral, and dermal intermediate-duration animal studies on immune function are needed to confirm or refute the evidence suggested in the human data. There are differences in metabolism across species; data from several species are needed for determining possible immunotoxic effects of tetrachloroethylene among different species.

Neurotoxicity. It has been clearly established that the central nervous system is a target of tetrachloroethylene toxicity in humans and animals following either inhalation or oral exposure. Human data are available for acute inhalation exposure (Altmann et al. 1990, 1992; Carpenter 1937; Hake and Stewart 1977; Morgan 1969; Rowe et al. 1952; Saland 1967; Stewart et al. 1961b, 1970) and acute oral exposure (Haerer and Udelman 1964; Kendrick 1929; Koppel et al. 1985; Sandground 1941; Wright et al. 1937) to tetrachloroethylene. The human studies indicate that the LOAEL for neurological effects (increased latency of pattern reversal visual-evoked potentials and deficits for vigilance and eye-hand coordination) following inhalation exposure is about 50 ppm for 4-hour exposures (Altmann et al. 1990, 1992). Additional nervous system effects including dizziness, headache, sleepiness, and incoordination have been observed following 5.5-7-hour exposures at 100-200 ppm in air (Carpenter 1937; Hake and Stewart 1977; Morgan 1969; Rowe et al. 1952; Saland 1967; Stewart et al. 1961b, 1970). Some human studies (Cavalleri et al. 1994; Echeverria et al. 1995; Gregersen 1988; Lauwerys et al. 1983; Seeber 1989) indicate that chronic occupational exposure to tetrachloroethylene can produce more serious effects including memory deficits (Cai et al. 1991; Echevenia et al. 1995; Gregersen 1988; Seeber 1989), ataxia (Lorenz et al. 1990), disorientation (Coler and Rossmiller 1953), loss of color vision (Cavalleri et al. 1994), and sleep disturbances (Lorenz et al. 1990). A study of neurological function in persons living above or next to dry cleaning facilities has

been completed (Altmann et al. 1995). Although no differences in absolute values of neurological function tests were noted, effects on neurological function tests were observed when multivariate analysis was used to analyze the data. This study suggests that further studies of larger populations exposed to very low levels of tetrachloroethylene would be useful. Effects observed in humans after acute oral exposure appear to parallel those observed after inhalation exposure. No dermal data were located for humans. Adverse neurological effects in animals exposed to tetrachloroethylene by inhalation include biochemical alterations in the brains of rats (Kyrklund et al. 1988; Wang et al. 1993) and gerbils (Briving et al. 1986; Karlsson et al. 1987; Kyrklund et al. 1984; Rosengren et al. 1986), electrophysiological changes in rats (Albee et al. 1991; Mattsson et al. 1992), ataxia in rats (Goldberg et al. 1964; NTP 1986), hypoactivity in rats (NTP 1986; Tinston 1995), and hyperactivity in rats (Savolainen et al. 1977). Ataxia (Narotsky and Kavlock 1995), increased lacrimation, gait changes, and decreased activity (Moser et al. 1995) have been reported in rats following acute oral exposure to tetrachloroethylene. No animal data were located regarding neurological effects following dermal exposure to tetrachloroethylene. Animal studies on the mechanism of tetrachloroethylene neurotoxicity would be useful for mitigating the effects observed. Because studies (Fredriksson et al. 1993; Nelson et al. 1980) suggest that tetrachloroethylene is a developmental neurotoxicant, further animal studies would be useful to determine if the developing nervous system is indeed the most sensitive target of tetrachloroethylene.

Epidemiological and Human Dosimetry Studies. Exposure to tetrachloroethylene may occur in the workplace, near hazardous waste sites, and from certain consumer products, including clothes that have been dry cleaned. Most occupational exposure results from inhalation of tetrachloroethylene. Several epidemiological studies have been conducted that provide evidence of relationships between tetrachloroethylene exposure in dry cleaning workers and cancer (Anttila et al. 1995; Blair et al. 1979, 1990; Brown and Kaplan 1987; Chapman et al. 1981; Duh and Asal 1984; Katz and Jowett 1981; Lynge and Thygesen 1990; Ruder et al. 1994), kidney effects (Bundschuh et al. 1993; Franchini et al. 1983; Mutti et al. 1992; Vyskocil et al. 1990), liver effects (Brodkin et al. 1995; Coler and Rossmiller 1953), and cardiovascular effects (Abedin et al. 1980; Hake and Stewart 1977). Limitations of these studies include exposure to other chemicals, lack of control for socioeconomic status, alcohol consumption, and tobacco consumption. There are also human studies that measured the concentration of tetrachloroethylene in exhaled air to determine exposure concentration (Jang et al. 1993; Monster et al. 1983; Ohtsuki et al. 1983; Solet et al. 1990; Stewart et al. 1977, 1981). Additional epidemiological studies might focus on populations exposed to tetrachloroethylene through contaminated drinking water

in areas surrounding hazardous waste sites in order to determine the effects of chronic, low-level exposures. It would be important for these studies to focus on cancer, reproductive effects, developmental effects, kidney effects, liver effects, and neurological effects, and to document possible confounding factors including other chemical exposure, smoking habits, and gender.

Biomarkers of Exposure and Effect. Exposure to tetrachloroethylene does not produce a unique clinical disease state. However, various central nervous system effects (e.g., dizziness, headache, incoordination, and sleepiness) can result from both inhalation and oral exposure to tetrachloroethylene.

Methods are available that can measure levels of tetrachloroethylene or its metabolites in the blood (Antoine et al. 1986; Michael et al. 1980; Ramsey and Flanagan 1982; Ziglio et al. 1984), urine (Christensen et al. 1988; Michael et al. 1980; Pekari and Aitio 1985a, 1985b), and exhaled air (Wallace et al. 1986a, 1986b). Measurement of tetrachloroethylene in exhaled air is simple, effective, and noninvasive and has been found to be more accurate than measuring metabolites, which are not specific for tetrachloroethylene exposure (Krotoszynski et al. 1979; Monster and Smolders 1984; Wallace 1986). Additional studies that couple measurement of tetrachloroethylene with tests for determining central nervous system effects and other effects (e.g., liver and kidney effects) would be useful to correlate exposure with adverse effects of tetrachloroethylene. This correlation would be useful for monitoring persons possibly exposed to tetrachloroethylene in areas surrounding hazardous waste sites.

Absorption, Distribution, Metabolism, and Excretion. The data indicate that inhalation is the principal occupational route of exposure for humans, and inhalation and oral exposure from contaminated water supplies is a concern for the general public. Absorption rates suggest that tetrachloroethylene is rapidly and readily absorbed following oral (Frantz and Watanabe 1983; Koppel et al. 1985; Pegg et al. 1979; Schumann et al. 1980) or inhalation exposure (Hake and Stewart 1977; Monster et al. 1979). Tetrachloroethylene vapor is not well absorbed across the skin (McDougal et al. 1990; Riihimaki and Pfaffli 1978), but tetrachloroethylene placed directly on the skin can be absorbed (Bogen et al. 1992; Jakobson et al. 1982; Kinkead and Lehy 1987; Stewart and Dodd 1964; Tsurata 1975). Available data indicate that during inhalation exposure, uptake is influenced more by lean body mass than by ventilation rate and that the absorption rate is decreased with increased time (Monster et al. 1979). Oral studies in animals which examine the stability of tetrachloroethylene to

gastrointestinal microbes, and rates of absorption from various sections of the gastrointestinal tract would be useful. Further quantitative data regarding the absorption of tetrachloroethylene following direct skin exposure would be useful because of the potential for dermal exposure at a hazardous waste site.

Several studies are available that describe the distribution of tetrachloroethylene in both humans and animals following inhalation exposure (Chen and Blancato 1987; Ghantous et al. 1986; Guberan and Femandez 1974; Marth 1987; Reitz et al. 1996; Savolainen et al. 1977; Stewart et al. 1970). The distribution of tetrachloroethylene has also been studied in rats and dogs following oral exposure (Dallas et al. 1994a, 1995). Studies using human subjects indicate increases in the body burden with repeated daily exposure (Altmann et al. 1990; Guberan and Femandez 1974; Stewart et al. 1970). No other studies are available that correlate duration of exposure with the distribution kinetics. Animal data support predictions from PBPK models that tetrachloroethylene is primarily distributed to and accumulated in adipose tissue, the brain, and the liver (Green et al. 1990; Marth 1987; Savolainen et al. 1977; Stewart et al. 1970). Animal studies also indicate that tetrachloroethylene crosses the placenta and is distributed to the amniotic fluid and fetus (Ghantous et al. 1986). A study by Byczkowski and Fisher (1994) indicated that tetrachloroethylene does cross into milk in rats exposed to tetrachloroethylene. Models have been developed to estimate the levels of tetrachloroethylene in breast milk of women exposed to tetrachloroethylene (Byczkowski and Fisher 1994, 1995; Schreiber 1993). Additional studies that determine blood-milk transfer coefficients would be useful for risk assessment. Distribution data following oral and dermal exposure of animals would also be useful as the potential exists for both oral and dermal exposure of humans in the vicinity of hazardous waste sites.

Human and animal data are available on metabolism following oral exposures (Bimer et al. 1996; Buben and O'Flaherty 1985; Dallas et al. 1994a; Dekant et al. 1986; Frantz and Watanabe 1983; Green et al. 1990; Pegg et al. 1979) and inhalation exposures (Bimer et al. 1996; Dallas et al. 1994c; Gearhart et al. 1993; Ikeda et al. 1972; Imbriani et al. 1988; Jang et al 1993; Monster 1986; Monster et al. 1983; Odum et al. 1988; Ogata et al. 1971; Ohtsuki et al. 1983; Pegg et al. 1979; Popp et al. 1992; Reitz et al. 1996; Schumann et al. 1980; Seiji et al. 1989; Skender et al. 1991; Yllner 1961), but not following dermal exposures. One human study indicates that the metabolism of tetrachloro-ethylene is saturable following inhalation exposure (Ohtsuki et al. 1983). A similar saturation pattern has been observed in both mice and rats following oral exposure. Differences in the metabolites of

animals and humans have been seen for inhalation exposures (Bois et al. 1990; Hattis et al. 1990; Odum et al. 1988) and oral exposures (Dallas et al. 1994a, 1995; Dekant et al. 1986). Further studies investigating possible differences according to gender, ethnic population group, or nutritional status, and the effects of enzyme induction on the metabolic rate would also be useful. Research to determine if trichloroethanol is a metabolite of tetrachlorethylene, or is produced from trichloroethylene which can contaminate tetrachloroethylene, would also be useful. There are no data available regarding the route of exposure as a factor in the relative rates of metabolism.

There are one oral study (Koppel et al. 1985), one dermal study (Stewart and Dodd 1964), and several inhalation studies (Ikeda et al. 1972; Monster et al. 1979; Ogata et al. 1971; Ohtsuki et al. 1983; Opdam and Smolders 1986) on excretion of tetrachloroethylene by humans. The oral data are presumed to be atypical because the patient was hyperventilated to facilitate pulmonary excretion following an accidental ingestion of the chemical. These human studies indicate that a large percentage of tetrachloroethylene is excreted unchanged in exhaled air (Ohtsuki et al. 1983), with urinary excretion comprising a much smaller percentage (approximately 2%) of the estimated absorbed dose (Ogata et al. 1971). The excretion of the urinary metabolites increased linearly with tetrachloroethylene concentrations but reached a plateau when the metabolic capacity was saturated (Ikeda et al. 1972). Similar saturation excretion patterns were seen in rats (Pegg et al. 1979). As in inhalation exposure, the majority of unmetabolized tetrachloroethylene administered orally to humans and animals was eliminated via the lungs with smaller amounts detected in the urine. The elimination of tetrachloroethylene is well characterized; therefore, further studies are not needed at this time.

Comparative Toxicokinetics. Data are available on the pharmacokinetics of this chemical for different species. Human data (Hake and Stewart 1977; Monster et al. 1979; Opdam and Smolders 1986; Pezzagno et al. 1988; Stewart et al. 1977) and data from rats (Dallas et al. 1994c; Pegg et al. 1979), mice (Schumann et al. 1980), and dogs (Dallas et al. 1994a, 1995) regarding absorption of tetrachloroethylene following inhalation and oral exposure are similar. Distribution following inhalation has not been studied thoroughly in humans, although pharmacokinetic models-have been developed. These models and animal data suggest that tetrachloroethylene accumulates mainly in fat (Green et al. 1990; Guberan and Fernandez 1974; Marth 1987; Monster 1986; Savolainen et al. 1977; Stewart et al. 1970). Both animal and human data suggest that the primary target organs are the central nervous system (Rao et al. 1993; Savolainen et al. 1977; Stewart et al. 1970, 1981), the liver (Marth 1987), and the kidney (Franchini et al. 1983; Green et al. 1990; Mutti et al. 1992).

2. HEALTH EFFECTS

There are differences in the metabolism of tetrachloroethylene in humans and animals. Oxalic acid is an important metabolite in rats (Pegg et al. 1979), but it has not been reported in humans. The metabolism of tetrachloroethylene is known to be saturable in humans (Ohtsuki et al. 1983) and in animals (Pegg et al. 1979; Schumann et al. 1980). No human or animal data were located regarding the metabolism of tetrachloroethylene following dermal exposure. In humans, exhalation of unchanged tetrachloroethylene following inhalation (Ikeda et al. 1972; Ogata et al. 1971; Ohtsuki et al. 1983), oral (Koppel et al. 1985), or dermal exposure (Stewart and Dodd 1964) was the primary route of excretion. Because there are differences in the metabolic pattern between humans and rodents, it may be useful to conduct studies using additional animal models (e.g., primates) so that a metabolic pattern more closely resembling that of humans can be studied. There are also differences in the metabolic patterns of rats and mice (Dekant et al. 1986; Green et al. 1990; Odum et al. 1988). Peroxisome proliferation in the mouse liver has not been shown to have a parallel in the rat kidney, suggesting that the mechanisms of carcinogenicity differ in these two species (Goldsworthy and Popp 1987; Odum et al. 1988). The peroxisome proliferation response in humans is also minimal (Bently et al. 1993), and the liver effects observed in mice may not occur in humans by the same mechanism. Additional pharmacokinetic data in different species, especially regarding the dynamics of the nervous system distribution of tetrachloroethylene, would be useful to improve PBPK analysis.

Methods for Reducing Toxic Effects. The general recommendations for reducing the absorption of tetrachloroethylene following acute inhalation, oral (HSDB 1996; Stutz and Ulin 1992), dermal (HSDB 1996; Stutz and Ulin 1992), or ocular (Bronstein and Currance 1988; Haddad and Winchester 1990; HSDB 1996; Stutz and Ulin 1992) exposure are well established and have a proven efficacy. No additional investigations are considered necessary at this time.

No clinical treatments other than supportive measures are currently available to enhance elimination of tetrachloroethylene following exposure. Studies designed to assess the potential risks or benefits of increasing ventilation to enhance pulmonary elimination or of stimulating enzymatic pathways to increase the metabolism of tetrachloroethylene could prove useful. However, it should be emphasized that once exposure has ended, the body does not retain significant amounts of tetrachloroethylene for long periods.

The development of treatment protocols designed to interfere with the mechanism of tetrachloroethylene-induced toxic effects would require a sizable research effort. Since the body does not retain

significant amounts of tetrachloroethylene for long periods, the relative merits of such an undertaking are not clear. Nevertheless, there is substantive evidence from well-conducted studies suggesting possible methods that could be exploited to block the mode of action that causes neurotoxicity, nephrotoxicity, and hepatotoxicity.

The mechanism of action of tetrachloroethylene for the central nervous system has not been clearly established. However, there are data indicating that the induced neurotoxicity may be related to solvent effects on lipid and fatty acid compositions of membranes (Kyrklund et al. 1984, 1988, 1990). Effects on neurotransmitter systems have also been demonstrated (Korpela and Tahti 1986; Mutti and Franchini 1987). It is reasonable to speculate, therefore, that these effects on neurotransmitters could be mitigated by pharmacologic intervention; however, no such interventions are currently available for clinical use.

The mechanism of action associated with kidney toxicity and nephrocarcinogenicity may involve the formation of reactive intermediates from glutathione conjugates (Dekant et al. 1986, 1987; Green et al. 1990; Henschler 1977). Although evidence from an *in vitro* study of human liver tissue suggests that glutathione conjugation is not important in human biotransformation of tetrachloroethylene (Green et al. 1990), the results are not conclusive. Methods for reducing the destructive damage caused by these intermediates or for blocking their formation through inhibition of β-lyase (Dekant et al. 1986, 1987; Green et al. 1990), may prove effective in reducing kidney toxicity but are not currently available for clinical use.

One mechanism of action of liver toxicity suggested in the literature is the induction of peroxisome proliferation (and resulting increases in hydrogen peroxide and oxidative damage) by TCA, a metabolite of tetrachloroethylene (Odum et al. 1988). Shifting metabolism away from formation of TCA could theoretically reduce toxicity that might be caused via this mechanism. However, the net effect on all forms of toxicity of tetrachloroethylene by such an alteration in metabolism would need to be carefully evaluated.

2.10.3 On-going Studies

ATSDR is conducting a retrospective cohort study of adverse pregnancy outcomes in a military population that resided at Marine Corps Camp LeJeune in North Carolina where there is documented past exposure to tetrachloroethylene, trichloroethylene, and 1,2-dichloroethylene in drinking water supplies.

Glutathione conjugation of tetrachloroethylene is being studied *in vitro* in rat tissues by Dr. Lash and colleagues at Wayne State University in Detroit, Michigan (Lash et al. 1996).