3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 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. Significant study limitations are noted in this chapter if: (1) they help to explain disparate findings between studies; (2) only one or a few studies are available on a particular end point, meaning that the strength of the study is a relatively more important consideration; or (3) the limitations create substantial uncertainty in the conclusions.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (e.g., death, systemic, immunological, neurological, reproductive, developmental, 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. For example, respiratory tract irritation and changes in mood or behavior are considered “less serious” effects. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR

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

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of tetrachloroethylene are indicated in Tables 3-1 and 3-4 and Figures 3-1 and 3-16.

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.

3.2.1 Inhalation Exposure

3.2.1.1 Death

At high vapor concentrations, tetrachloroethylene is both a potent anesthetic agent and increases sensitivity of the heart (myocardium) to catecholamines. Sudden death resulting from acute exposure to high vapor concentrations is presumed to result from either excessive depression of the respiratory center or the onset of a fatal cardiac arrhythmia induced by catecholamine sensitization. Human deaths caused by tetrachloroethylene inhalation have been reported. While published reports have not included estimates or measurements of exposure concentrations in the air, postmortem blood concentrations of tetrachloroethylene in decedents have ranged from 44 to 158 mg/L (Amadasi et al. 2015; Dehon et al. 2000; Garnier et al. 1996; Isenschmid et al. 1998; Lukaszewski 1979).

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 tetrachloro-

ethylene 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/100 mL and 36 mg/100 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 (Garnier et al. 1996). Isenschmid et al. (1998) reported that a 26-year-old male was found dead after intentional inhalation of a pressurized tire repair product containing tetrachloroethylene and chlorodifluoromethane. Chlorodifluoromethane was not detected in biological specimens collected at autopsy; concentrations of tetrachloroethylene, in contrast, were 62 mg/L in blood, 341 mg/kg in the liver, and 47 mg/kg in the lung (Isenschmid et al. 1998). A 45-year-old woman was found unconscious in a laundry area and was transported to the hospital in a coma, where she was observed to exhibit acute respiratory distress syndrome and severe metabolic acidosis (Dehon et al. 2000). She died 7 days after the event from cardiovascular instability and acute renal failure. Autopsy findings included cerebral edema with foci of hemorrhagic infarction, diffuse lesions of edematous and hemorrhagic alveolitis with some foci of aspiration pneumonia in the lungs, diffuse hepatocytic necrosis, and acute renal tubular necrosis. Tetrachloroethylene was detected in the blood at 1.319 mg/L and in urine at 93 μg/g creatinine 2 days after hospital admission. Tissue levels ranged from 0.751 μg/g in muscle to 1.95 μg/g in the liver (Dehon et al. 2000). In these reports, the level of tetrachloroethylene exposure was not reported.

Retrospective cohort mortality studies of workers occupationally exposed to tetrachloroethylene for chronic durations have not suggested increased mortality associated with exposure. Although total mortality was not increased relative to expected deaths ($p>0.05$), Blair et al. (1979) found increased mortality from all circulatory diseases ($p<0.05$), from all neoplasms ($p<0.05$), and from cancers of the lungs ($p<0.05$), cervix ($p<0.05$), and skin ($p<0.05$) among dry cleaners. This study is limited by a lack of control for alcohol and tobacco consumption. Other studies have not shown increased mortality for deaths from all causes in workers (dry cleaners or aircraft maintenance workers) occupationally exposed to tetrachloroethylene, with standard mortality ratios (SMRs) of 0.9 (95% confidence interval [CI] 0.9–1.0) (Blair et al. 1990), 0.86 (95% CI 0.78–0.94) (Brown and Kaplan 1987), and 0.92 (95% CI 0.90–0.95) (Spirtas et al. 1991). These studies did not include exposure measurements, but relied on job descriptions, work history as a surrogate for exposure duration, and/or estimated exposure concentrations. Additional information on cancer mortality reported in epidemiological studies is provided in Section 3.2.1.7 (Inhalation, Cancer).

A 4-hour inhalation LC_{50} of 5,200 ppm for female albino mice has been reported (Friberg et al. 1953); LC_{50} data in other species are not available. Based on comparison of highest nonlethal values and lowest lethal values, mice and rats appear to have similar sensitivities. The highest nonlethal concentrations reported for 4-hour exposure to tetrachloroethylene were 2,000–2,450 ppm in mice (Friberg et al. 1953; NTP 1986; Rowe et al. 1952) and 2,445 ppm in rats (NTP 1986). The lowest lethal concentrations reported for 4-hour exposures were 2,613–3,000 ppm in mice (Friberg et al. 1953; NTP 1986) and 3,786 ppm in rats (NTP 1986). A single 10- or 14-hour exposure of rats to 2,000 ppm did not produce death, while death occurred with exposure to 3,000 ppm for ≥5 hours (Rowe et al. 1952). In a 14-day study of rats and mice, mortality occurred in rats exposed to 1,750 ppm tetrachloroethylene but not in mice (NTP 1986). Compound-related mortality did not occur in either species at exposure concentrations of ≤875 ppm. A 2-week study in F344 rats and Crj:BDF1 mice reported mortality at 3,200 ppm in both species, but not at 1,600 ppm, when administered 6 hours/day, 5 days/week (JISA 1993).

In an intermediate-duration study, increased mortality occurred in rats and mice exposed to 1,600 ppm tetrachloroethylene for 13 weeks, but not in those exposed to concentrations ≤800 ppm (NTP 1986). No deaths were reported in a different 13-week study of rats and mice exposed to concentrations up to 1,400 ppm tetrachloroethylene (JISA 1993). 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 compound-related lesions and neoplasms (NTP 1986). This study is discussed in Sections 3.2.1.2 and 3.2.1.7. Survival was reduced in another chronic bioassay of rats and mice exposed to 600 and 250 ppm tetrachloroethylene, respectively, for 104 weeks (JISA 1993). The study authors did not indicate whether the decreased survival was attributable to neoplasia.

All reliable LOAEL and LC_{50} values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

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

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form	Comments
ACUTE EXPOSURE									
Death									
1	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d				3200	(5 M and 7 F died)	JISA 1993	
2	Rat (Fischer- 344)	2wk 5d/wk 6hr/d				1750	(5/10 rats died)	NTP 1986	
3	Rat (Fischer- 344)	4 hr				3786	(5/10 rats died)	NTP 1986	
4	Rat (albino)	4 hours		2000 F		4000 F	(increased mortality)	Union Carbide 1962	
5	Mouse (NS)	4 hr				5200 F	(LC50)	Friberg et al. 1953	
6	Mouse (Hybrid)	2 wk 5 d/wk 6 hr/d				3200	(9 M and 7 F died)	JISA 1993	
7	Mouse (B6C3F1)	4 hr				2613 F	(2/5 died)	NTP 1986	
Systemic									
8	Human	3 hr	Cardio	87 M				Ogata et al. 1971	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
9	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)		
10	Human	5d 7.5hr/d	Resp	150 M					Stewart et al. 1981	
			Cardio	150 M						
			Hemato	150 M						
			Hepatic	150 M						
			Renal	150 M						
11	Rat (CD)	Gd 6-19 7 d/wk 6 hr/d	Bd Wt	65 F	249 F	(19% decr in maternal body weight gain during Gd 6-9)			Carney et al. 2006	
12	Rat (Fischer- 344)	2wk 5d/wk 6hr/d	Bd Wt	875 M			1750 M	(body weight 28% lower than controls)	NTP 1986	
13	Rat (Fischer- 344)	14d 6hr/d	Hepatic		400	(hypertrophy)			Odum et al. 1988	
			Renal	400						

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
14	Rat (Sprague-Dawley)	4 hrs/day, 8 days	Hepatic	1000 M			Piper and Sparschu 1969	
			Renal		1000 M increased kidney weight, pale kidneys, minimal to moderate hyaline droplet formation			
			Bd Wt	1000 M				
15	Rat (Sprague-Dawley)	7 hrs/day, 8 days	Hepatic	1000 M			Piper and Sparschu 1969	
			Renal		1000 M increased absolute kidney weight, pale kidneys, minimal to moderate hyaline droplet formation			
			Bd Wt	1000 M				
16	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	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
17	Mouse (Hybrid)	2 wk 5 d/wk 6 hr/d	Hepatic	800	1600 (central enlargement of liver)		JISA 1993	
			Renal	400	800 (necrosis and regeneration of proximal tubules)			
18	Mouse (NS)	4 hr	Hepatic		200 F (fatty degeneration)		Kylin et al. 1963	
19	Mouse (B6C3F1)	2wk 5d/wk 6hr/d	Hepatic	425	875 (hepatic vacuolization)		NTP 1986	
			Bd Wt	1750				
20	Mouse (B6C3F1)	14d 6hr/d	Hepatic		400 (peroxisomal proliferation; fatty changes)		Odum et al. 1988	
			Renal	400				
21	Mouse (ddy)	5 days; 6 hrs/day	Resp		300 M (erosion of the nasal mucosa)		Suzaki et al. 1997	
22	Mouse C57BL	Gd 7-15 8 hr/d	Hepatic		664 F (Increased relative liver weight)		Szakmary et al. 1997	
			Bd Wt	664 F				

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
23	Dog (Beagle)	10 min	Resp	5000 M	10000 M	(upper respiratory tract irritation)			Reinhardt et al. 1973	
			Cardio	10000 M						
24	Rabbit (New Zealand)	Gd 7-20 8 hr/d	Bd Wt				1254 F	(58% lower body weight gain)	Szakmary et al. 1997	
Neurological										
25	Human	4d 4hr/d		10 M	50 M	(increased latency of pattern reversal visual-evoked potentials)			Altmann et al. 1990	
26	Human	4d 4hr/d		10 M	50 M	(increased latency of pattern reversal visual-evoked potential, significant performance deficits for vigilance and eye-hand coordination)			Altmann et al. 1992	
27	Human	<3 hr		500	1000	(mood/personality changes)	2000	(anesthesia)	Carpenter 1937	
28	Human	5 d 7.5hr/d		20	100	(cerebral cortical depression)			Hake and Stewart 1977; Stewart et al. 1981	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
29	Human	3 hr		87 M			Ogata et al. 1971	
30	Human	0.05-2 hr		106	216 (dizziness/sleepiness)	280 (incoordination)	Rowe et al. 1952	
31	Human	5d 7hr/d			101 (mood/personality changes)		Stewart et al. 1970	
32	Rat (Long- Evans)	Once 1.5 hr			250 M (reduced amplitude of visual evoked potentials)		Boyes et al. 2009	
33	Rat (Fischer- 344)	4 d 6 hr/d			800 M (altered flash and somatosensory evoked potentials and EEG)		Mattsson et al. 1998	
34	Rat (Fischer- 344)	2wk 5d/wk 6hr/d		875		1750 (hypoactivity; ataxia)	NTP 1986	
35	Rat (Long- Evans)	once 1 hr/d			500 M (impaired sustained attention)		Oshiro et al. 2008	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
36	Rat (Sprague-Dawley)	4d 6hr/d			200 M (increased open-field behavior, i.e., ambulation)		Savolainen et al. 1977	
37	Rat (albino)	4 hours			2000 F (loss of consciousness and anesthesia)		Union Carbide 1962	
38	Mouse (Swiss-Webster)	1 d 4 hr/d			596 M (prolongation of escape-directed behavior)		DeCeaurriz et al. 1983	
39	Mouse (B6C3F1)	2wk 5d/wk 6hr/d		875		1750 (anesthesia)	NTP 1986	
40	Mouse (B6C3F1)	4 hr				2328 (anesthesia)	NTP 1986	
Reproductive								
41	Rat (Sprague-Dawley)	2 wk 2 periods/day 1 hr/period (W)			1700 F (reduced in vitro fertilizability of oocytes from treated rats)		Berger and Horner 2003	
42	Rat (CD)	GD 6-19 7 d/wk 6 hr/d		600 F			Carney et al. 2006	
43	Rat (albino)	up to 10 weeks		500 M			NIOSH 1980	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
44	Rat (albino)	GD 6-18 (7 hrs/day)		500 F			NIOSH 1980	
45	Mouse (CD-1)	up to 10 weeks		100 M	500 M (significant increase in spermhead abnormalities)		NIOSH 1980	
46	Mouse C57BL	Gd 7-15 8 hr/d		664 F			Szakmary et al. 1997	
47	Rabbit (New Zealand)	GD 7-21 (7 hrs/day)		500 F			NIOSH 1980	
48	Rabbit (New Zealand)	Gd 7-20 8 hr/d				1254 F (4/16 litters totally resorbed; increased postimplantation loss)	Szakmary et al. 1997	
Developmental								
49	Rat (CD)	GD 6-19 7 d/wk 6 hr/d		250	600 (decr fetal weight and incomplete ossification of thoracic vertebral centra)		Carney et al. 2006	
50	Rat (Sprague-Dawley)	Gd 14-20 7hr/d		100 F	900 F (transient decreased performance ascent test; decreased brain acetylcholinesterase; increased open-field activity)		Nelson et al. 1980	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
51	Rat (albino)	GD 6-18 (7 hrs/day)		500			NIOSH 1980	
52	Rat (Sprague-Dawley)	Gd6-15 7hr/d				300 F (increased fetal resorptions)	Schwetz et al. 1975	
53	Mouse (Swiss-Webster)	Gd6-15 7hr/d			300 F (decreased fetal weight; delayed ossification)		Schwetz et al. 1975	
54	Mouse C57BL	Gd 7-15 8 hr/d				664 (increased percentage of fetuses with internal malformations)	Szakmary et al. 1997	
55	Rabbit (New Zealand)	GD 7-21 (7 hrs/day)		500			NIOSH 1980	
56	Rabbit (New Zealand)	Gd 7-20 8 hr/d				1254 (4/16 litters totally resorbed; increased postimplantation loss)	Szakmary et al. 1997	
INTERMEDIATE EXPOSURE								
Death								
57	Rat (Fischer- 344)	13wk 5d/wk 6hr/d				1600 (11/20 rats died)	NTP 1986	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
58	Mouse (B6C3F1)	13wk 5d/wk 6hr/d					1600	(6/10 mice died)	NTP 1986	
Systemic										
59	Rat (Sprague-Dawley)	6 hrs/day, 5 days/wk. 4 weeks	Hepatic	100 F	300 F	(increased relative liver weight)			Boverhof et al. 2013	
			Bd Wt	300 F	1000 F	(transient decrease in body weight)				
60	Rat (NS)	7mo 5d/wk 8hr/d	Hepatic	70	230	(decreased glycogen)			Carpenter 1937	
			Renal	230	470	(mild nephropathy)				
61	Rat (Fischer- 344)	28d 6hr/d	Renal	400					Green et al. 1990	
62	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Bd Wt	609 M	1400 M	(decreased body weight gain)			JISA 1993	
63	Rat (Sprague-Dawley)	90 d	Hepatic		320 M	(increased liver weights)			Kyrklund et al. 1990	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
64	Rat (Fischer- 344)	13 wk 5d/wk 6hr/d	Resp	800	1600 (lung congestion)		NTP 1986	
			Hepatic	200	400 liver congestion			
			Bd Wt	800 M		1600 M (body weight 20% lower than controls)		
65	Rat (Fischer- 344)	21d 6hr/d	Hepatic		400 (hypertrophy)		Odum et al. 1988	
			Renal	400				
66	Rat (Fischer- 344)	28d 6hr/d	Hepatic		200 (hypertrophy)		Odum et al. 1988	
			Renal	400				
67	Rat CFY	Gd 1-20 8 hr/d	Bd Wt	221 F		664 F (37% decreased body weight gain)	Szakmary et al. 1997	
68	Rat (Alpk:APfSD)	19wk:11 wk, 5d/wk 6hr/d; daily during mating/lacta	Hepatic	1000			Tinston 1995	
			Renal	300 M	1000 M (minimal chronic progressive glomerulonephropathy; increased pleomorphism within proximal tubular nuclei)			
			Bd Wt	1000				

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
69	Mouse (B6C3F1)	28d 6hr/d	Renal	400			Green et al. 1990	
70	Mouse (Hybrid)	13 wk 5 d/wk 6 hr/d	Hepatic	265	609 (central enlargement of liver)		JISA 1993	
			Renal	265	609 (changes in proximal tubules)			
			Bd Wt	265 M	609 M (decreased body weight gain)			
71	Mouse (NMRI)	30 d 24hr/d	Hepatic		9 (liver enlargement and vacuolization of hepatocytes)		Kjellstrand et al. 1984	
			Bd Wt	150				
72	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 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
73	Mouse (B6C3F1)	13wk 5d/wk 6hr/d	Hepatic	200			400	(centrilobular liver necrosis)	NTP 1986	
			Renal	100	200	(karyomegaly of renal tubular epithelial cells)				
			Bd Wt	1600						
74	Mouse (B6C3F1)	28d 6hr/d	Hepatic		200	(peroxisomal proliferation; fatty changes)			Odum et al. 1988	
			Renal	400						
75	Mouse (B6C3F1)	21d 6hr/d	Hepatic		400	(peroxisomal proliferation; fatty changes)			Odum et al. 1988	
			Renal	400						
Immuno/ Lymphoret										
76	Rat (Sprague-Dawley)	6 hrs/day, 5 days/wk. 4 weeks		1000 F					Boverhof et al. 2013	
Neurological										
77	Rat (Sprague-Dawley)	30 or 90 d			320 M	(changes in the fatty acid composition of the brain)			Kyrklund et al. 1988, 1990	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
78	Rat (Fischer- 344)	13 wks 5 d/wk 6 h/d		200	800 (Increased apmlitude of flash evoked potential peak N3)		Mattsson et al. 1998	
79	Rat (Alpk:APfSD)	19wk:11 wk, 5d/wk 6hr/d; daily during mating/lacta		300	1000 (decreased activity, reduced response to sound, increased salivation, piloerection)		Tinston 1995	
80	Rat (Sprague-Dawley)	4 or 12 wk		300 M	600 M (decreased brain weight; decrease in cytoskeletal proteins)		Wang et al. 1993	
81	Gerbil (Mongolian)	90 d 24hr/d			60 (decreased DNA levels in frontal cortex)		Karlsson et al. 1987	
82	Gerbil (Mongolian)	3 mo 24hr/d			60 (decreased DNA content in the frontal cerebral cortex)		Rosengren et al. 1986	
Reproductive								
83	Rat (albino)	GD 0-18 (7 hrs/day)		500 F			NIOSH 1980	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form	Comments
84	Rat (albino)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 0-18		500 F				NIOSH 1980	
85	Rat (albino)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 6-18		500 F				NIOSH 1980	
86	Rat CFY	Gd 1-20 8 hr/d		221 F		664 F	(increased pre-implantation loss)	Szakmary et al. 1997	
87	Rat (Alpk:APfSD)	19wk:11 wk, 5d/wk 6hr/d; daily during mating/lacta		300		1000	(significant reduction in the number of live born pups; decreased pup survival during lactation)	Tinston 1995	
88	Rabbit (New Zealand)	GD 0-21 (7 hrs/day)		500 F				NIOSH 1980	
89	Rabbit (New Zealand)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 0-21		500 F				NIOSH 1980	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form	Comments
90	Rabbit (New Zealand)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 7-21		500 F				NIOSH 1980	
Developmental									
91	Rat (albino)	GD 0-18 (7 hrs/day)		500				NIOSH 1980	
92	Rat (albino)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 0-18		500				NIOSH 1980	
93	Rat (albino)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 6-18		500				NIOSH 1980	
94	Rat CFY	Gd 1-20 8 hr/d		221		664	(increased percentage fetuses with growth retardation and malformations)	Szakmary et al. 1997	
95	Rabbit (New Zealand)	GD 0-21 (7 hrs/day)		500				NIOSH 1980	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
96	Rabbit (New Zealand)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 0-21		500			NIOSH 1980	
97	Rabbit (New Zealand)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 7-21		500			NIOSH 1980	
CHRONIC EXPOSURE								
Death								
98	Rat (Fischer- 344)	103wk 5d/wk 6hr/d				400 M (reduced survival)	Mennear et al. 1986; NTP 1986	
99	Rat (Sprague-Dawley)	6 hrs/day, 5 days/wk 12 months		300 M		600 M (increased mortality from 5th to 24th month of study attributed to chronic renal disease)	Rampy et al. 1978	
100	Mouse (B6C3F1)	103wk 5d/wk 6hr/d				100 M (reduced survival)	Mennear et al. 1986; NTP 1986	
Systemic								
101	Human	20 yr average	Hepatic		15.8 (diffuse parenchymal changes revealed by ultrasound)		Brodkin et al. 1995	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
102	Human	1-120 mo occup occup	Hemato	20			Cai et al. 1991	
			Hepatic	20				
			Renal	20				
103	Human	14 yr occup	Renal		10 (increased urine b-glucuronidase and lysozyme)		Franchini et al. 1983	
104	Human	6 yr occup	Hepatic	21			Lauwerys et al. 1983	
			Renal	21				
105	Human	10 yr average occup occup	Renal		15 (nephrotoxicity)		Mutti et al. 1992	
106	Human	12 yr average occup	Renal	14			Solet and Robins 1991	
107	Human	9yr occup	Renal		23 F (increased urinary lysozyme activity)		Vyskocil et al. 1990	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
108	Rat (Fischer- 344)	104 wk 5 d/wk 6 hr/d	Hepatic		200 (spongiosis hepatitis in males and increased alanine aminotransferase in females)		JISA 1993	
			Renal	50 M	200 M (increased relative kidney weight; nuclear enlargement of proximal tubules)			
			Bd Wt	50 F	200 F (reduced body weight)			
109	Rat (Fischer- 344)	103wk 5d/wk 6hr/d	Resp		200 thrombosis; squamous metaplasia of nasal cavity		Mennear et al. 1986; NTP 1986	
			Gastro	200 M	400 M forestomach ulcers			
			Renal		200 renal tubular karyomegaly			
			Endocr		200 M (adrenal medullary hyperplasia)			
			Bd Wt	400				

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
110	Rat (Sprague-Dawley)	6 hrs/day, 5 days/wk 12 months	Hemato	600			Rampy et al. 1978	
			Hepatic	600				
			Renal	600				
			Bd Wt	600				
111	Mouse (Hybrid)	104 wk 5 d/wk 6 hr/d	Hepatic	10 M	50 M (angiectasis and increased serum aspartate aminotransferase and alanine aminotransferase)		JISA 1993	
			Renal	50	250 (nuclear enlargement and atypical dilation of proximal tubules)			
112	Mouse (B6C3F1)	103wk 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 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Neurological								
113	Human	1-30 yr		0.2			Altmann et al. 1995	
114	Human			0.2			Altmann et al. 1995	
115	Human	1-120 mo occup occup			20 (increase in subjective symptoms including dizziness)		Cai et al. 1991	
116	Human	106 mo average			7.3[b] F (color vision loss)		Cavalleri et al. 1994	
117	Human	10 yr occup			15 F (increased reaction times)		Ferroni et al. 1992	
118	Human	6 yr occup		21			Lauwerys et al. 1983	
119	Human	occup occup		15.3 M			Nakatsuka et al. 1992	
120	Human			15.3 M			Nakatsuka et al. 1992	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
121	Human	5.8 yr (mean)			0.11 (decreased visual contrast sensitivity)		Schreiber et al. 2002	
122	Human	4.0 yr (mean)			0.32 F (decreased visual contrast sensitivity)		Schreiber et al. 2002	
123	Human	10 yr (mean)			0.05 (decreased visual contrast sensitivity)		Storm et al. 2011	
124	Gerbil (Mongolian)	12 mo 24hr/d			120 M (phospholipid changes in the cerebral cortex and hippocampus)		Kyrklund et al. 1984	
Cancer								
125	Rat (Fischer- 344)	104 wk 5 d/wk 6 hr/d				600 M (CEL: monocytic leukemia of spleen)	JISA 1993	
126	Rat (Fischer- 344)	103wk 5d/wk 6hr/d				200 (CEL: mononuclear cell leukemia)	Mennear et al. 1986; NTP 1986	
127	Mouse (Hybrid)	104 wk 5 d/wk 6 hr/d				250 (CEL: hepatocellular adenomas and carcinomas)	JISA 1993	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
128	Mouse (B6C3F1)	103wk 5d/wk 6hr/d				100 (CEL: hepatocellular carcinoma)	Mennear et al. 1986; NTP 1986	

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

b Used to derive a chronic-duration inhalation minimal risk level (MRL) of 0.006 ppm for tetrachloroethylene; the MRL was derived by converting the LOAEL of 7.3 ppm to an equivalent continuous exposure of 1.7 ppm and dividing by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability) and modifying factor of 3 for database deficiencies. ATSDR has adopted the chronic-duration inhalation MRL as the acute-duration and intermediate-duration inhalation MRLs. See Appendix A for detailed discussion of the inhalation MRLs for tetrachloroethylene.

ad lib = ad libitum; ALT = alanine aminotransferase; B = both sexes; Bd Wt = body weight; BUN = blood urea nitrogen; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); EEG = electroencephalogram; Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LC50 = lethal concentration, 50% kill; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Metab = metabolism; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Occup = occupational; Pmd = pre-mating day; Pnd = post-natal day; Ppd = post-parturition day; Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s); yr = year(s)

3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation

Acute (≤14 days)

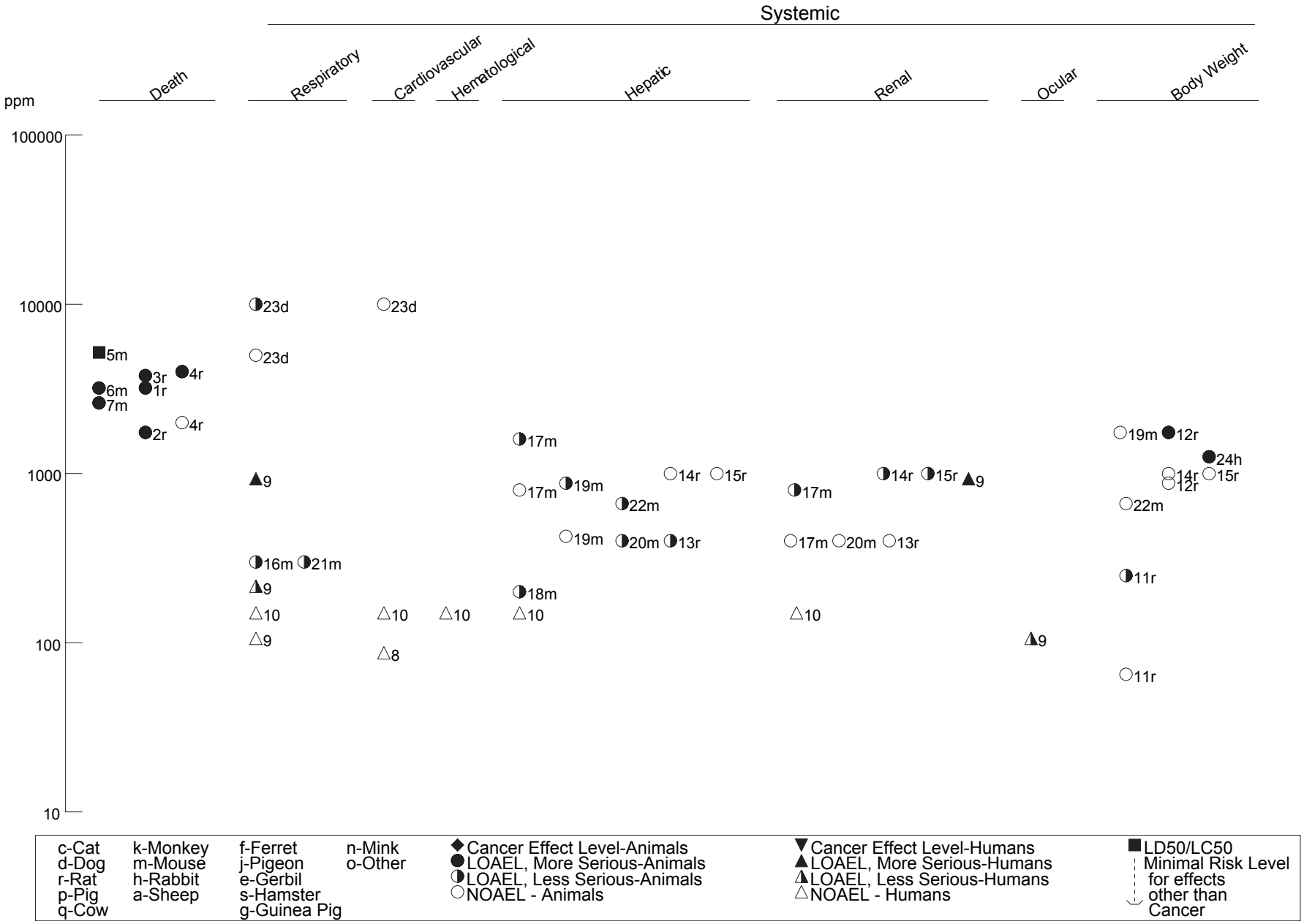
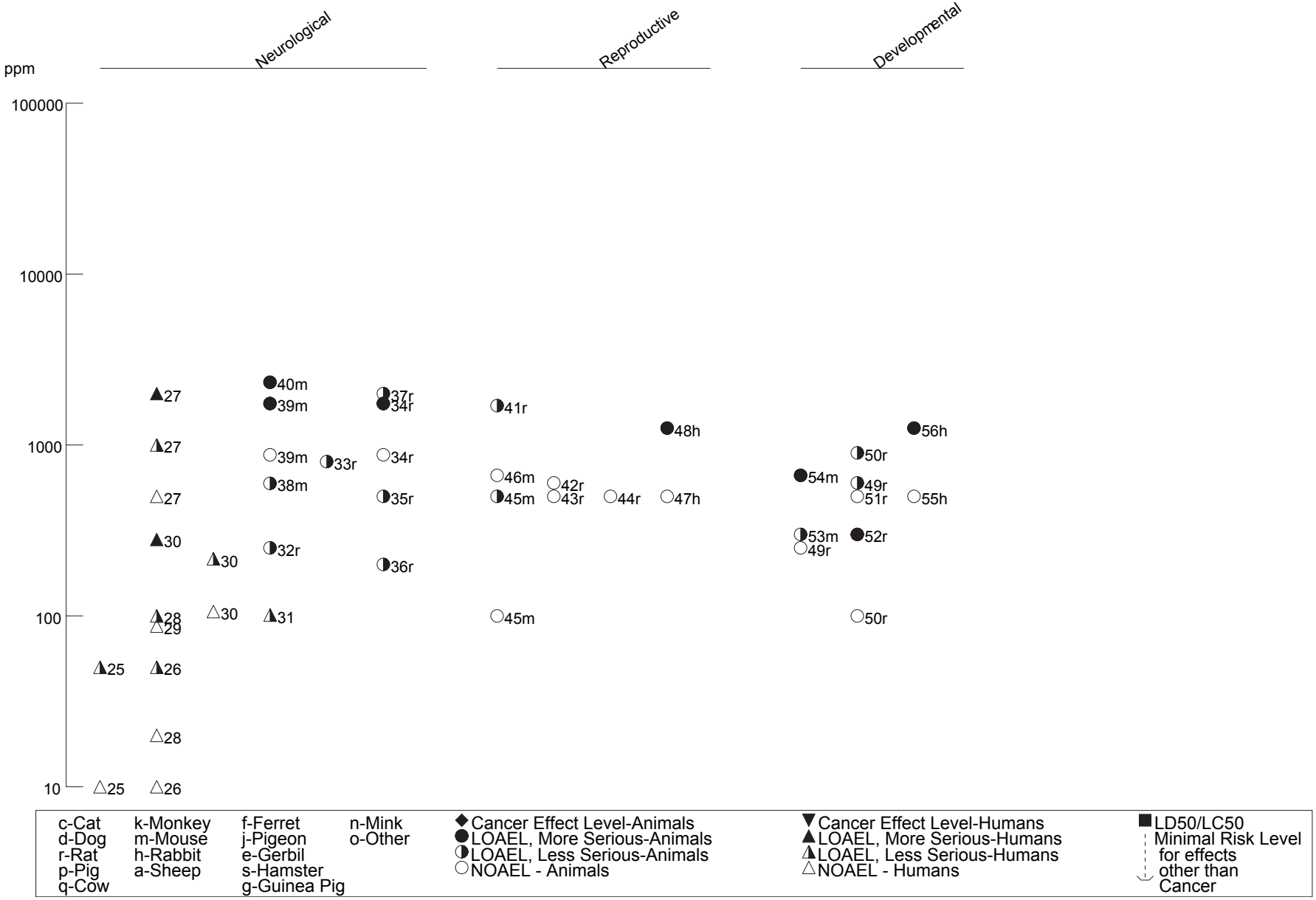


Figure 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation *(Continued)*

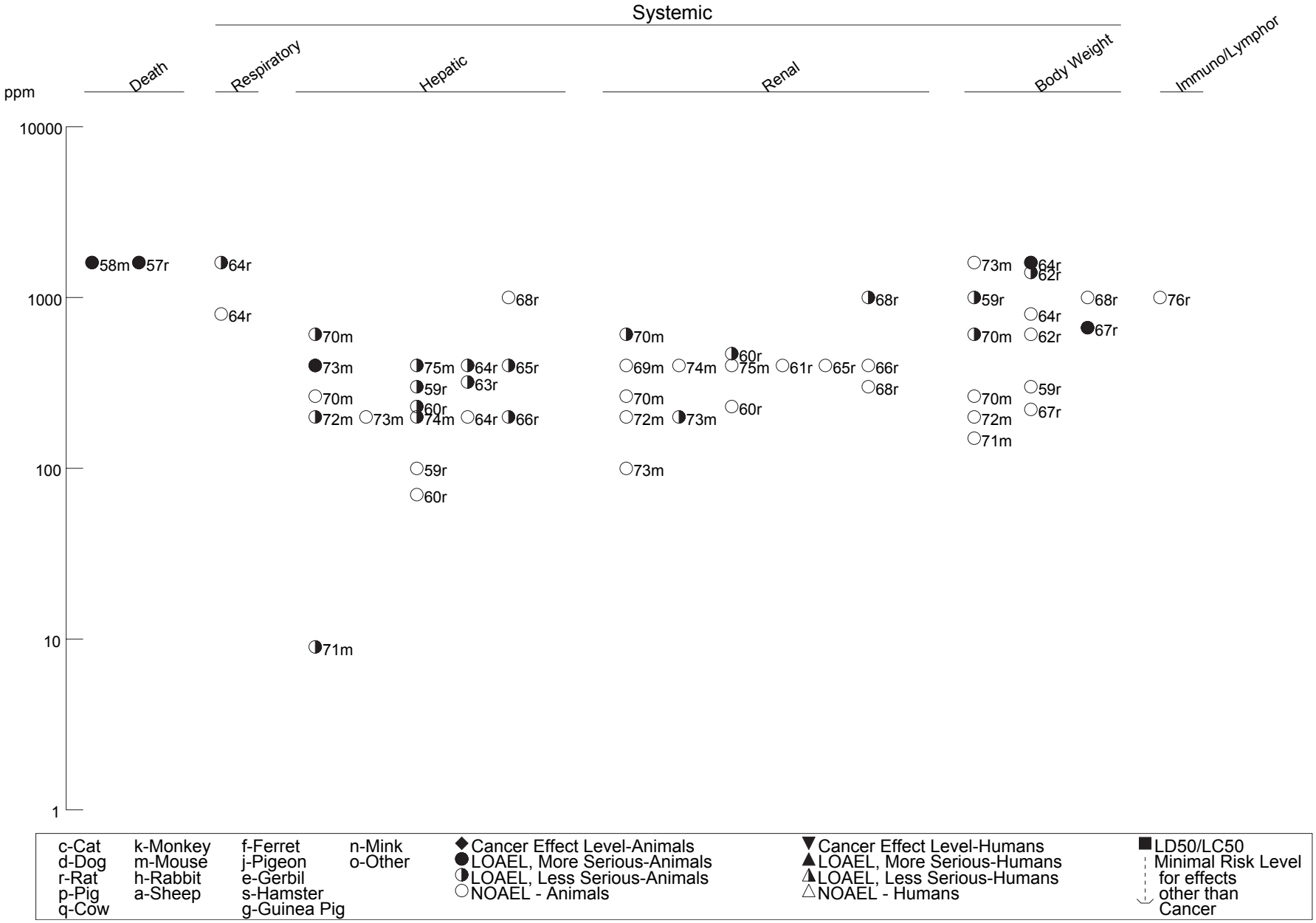
Acute (≤14 days)



3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation *(Continued)*

Intermediate (15-364 days)



c-Cat k-Monkey f-Ferret n-Mink
d-Dog m-Mouse j-Pigeon o-Other
r-Rat h-Rabbit e-Gerbil
p-Pig a-Sheep s-Hamster
q-Cow g-Guinea Pig

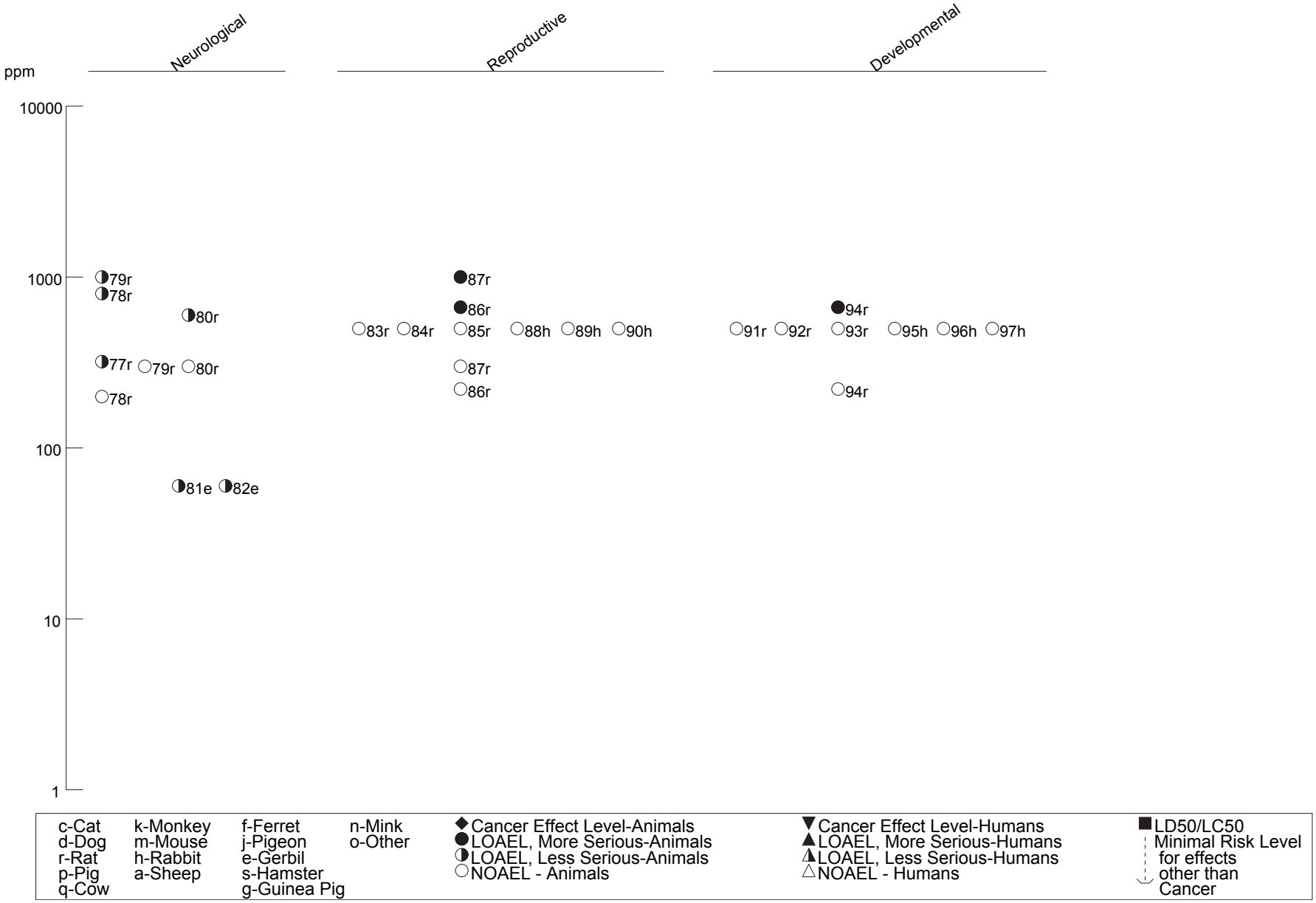
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation *(Continued)*

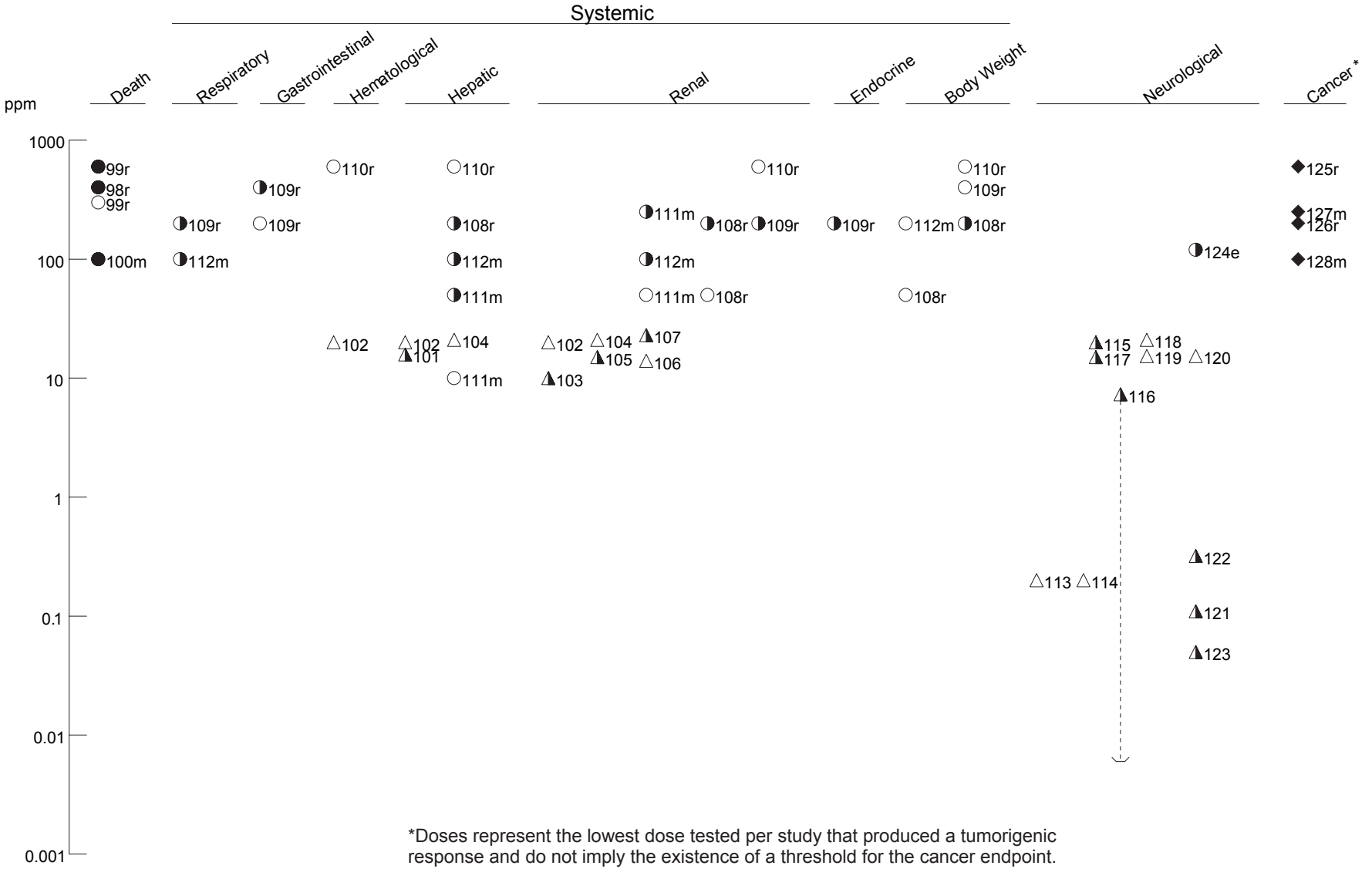
Intermediate (15-364 days)



3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat d-Dog r-Rat p-Pig q-Cow	k-Monkey m-Mouse h-Rabbit a-Sheep	f-Ferret j-Pigeon e-Gerbil s-Hamster g-Guinea Pig	n-Mink o-Other	◆ Cancer Effect Level-Animals ● LOAEL, More Serious-Animals ◑ LOAEL, Less Serious-Animals ○ NOAEL - Animals	▼ Cancer Effect Level-Humans ▲ LOAEL, More Serious-Humans ◭ LOAEL, Less Serious-Humans △ NOAEL - Humans	■ LD50/LC50 Minimal Risk Level for effects other than Cancer

Respiratory Effects. Data on the respiratory effects of tetrachloroethylene exposure in humans are limited to case reports (Carpenter 1937; Patel et al. 1973; Rowe et al. 1952; Tanios et al. 2004) and two experimental studies (Rowe et al. 1952; Stewart et al. 1981). The studies reporting exposure concentrations showed irritation of the respiratory tract at concentrations as low as 216 ppm for 2 hours (Rowe et al. 1952), with intense or unbearable irritation at concentrations ≥1,000 ppm, but no effects on pulmonary function at exposures up to 150 ppm, 7 hours/day for 5 days (Carpenter 1937; Rowe et al. 1952). Other case reports that lacked information on exposure levels and duration (Patel et al. 1973; Tanios et al. 2004) reported respiratory hypersensitivity and pulmonary edema in humans exposed to tetrachloroethylene. In animal studies, nasal lesions were observed in mice exposed to 300 ppm for 5 days (Aoki et al. 1994; Suzaki et al. 1997) and in rats exposed to ≥200 ppm for 2 years (Mennear et al. 1986; NTP 1986). Pulmonary congestion was seen in rats exposed to 1,600 ppm for 13 weeks and in mice exposed intermittently to concentrations ≥100 ppm for 2 years (Mennear et al. 1986; NTP 1986).

Intense irritation of the upper respiratory tract was reported in volunteers exposed to high concentrations (>1,000 ppm) of tetrachloroethylene (Carpenter 1937; Rowe et al. 1952). These older acute inhalation studies in humans were limited by small numbers of experimental volunteer subjects, incomplete characterization of subjects, variable concentrations of tetrachloroethylene, and reliance on self-reported symptoms, which are subjective. 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 1–2 minutes of exposure before leaving the chamber (Rowe et al. 1952).

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 alveolar-capillary 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.

Case reports suggest possible pulmonary effects of exposure to tetrachloroethylene, but do not contain exposure information. A case report of hypersensitivity pneumonitis attributed the condition to tetrachloroethylene exposure; the woman worked as a dry cleaner (Tanios et al. 2004, see also Section 3.2.1.3). Her symptoms included exertion-related dyspnea and a cough; CT scan of her chest showed a ground glass pattern and poorly defined parenchymal nodules. Bronchoalveolar lavage analysis indicated lymphocytosis. The investigators diagnosed the case as hypersensitivity pneumonitis related to tetrachloroethylene exposure. Pulmonary edema occurred in a 21-year-old male laundry worker after exposure to tetrachloroethylene vapors in a distilling operation; he became comatose shortly after exposure and was diagnosed with pulmonary edema after his rescue and admission to the hospital (Patel et al. 1973).

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.

Male mice exposed to 300 ppm tetrachloroethylene for 6 hours/day on 5 days exhibited nasal discharge containing exfoliated epithelial cells and neutrophils, as well as lesions consisting of mucosal erosions in the olfactory region and inflammatory cell infiltration in the olfactory epithelium 2 weeks after exposure (Suzaki et al. 1997). Few changes were noted in the respiratory epithelium. In mice examined 1, 2, and 3 months after exposure, histopathological examination revealed evidence of olfactory mucosa repair; however, some of the normal olfactory epithelium (pseudostratified nonciliated columnar) was replaced by ciliated epithelium, and atrophy of the olfactory nerves and Bowman’s glands was noted (Suzaki et al. 1997).

Congestion of the lungs was reported in rats exposed intermittently to tetrachloroethylene at 1,600 ppm, but not at 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. Few studies have examined cardiovascular effects of tetrachloroethylene in humans or animals. Three acute-duration experimental studies reported no effects on heart rate, blood pressure, and/or electrocardiograms in volunteers exposed to concentrations up to 150 ppm for up to

5 days (Ogata et al. 1971; Stewart et al. 1977, 1981). A case report of cardiac arrhythmia in a male dry cleaning worker did not report exposure concentrations, but did report a plasma concentration of 3.8 ppm tetrachloroethylene (Abedin et al. 1980). Only one animal study examined cardiovascular effects of tetrachloroethylene (Reinhardt et al. 1973); beagle dogs exposed to tetrachloroethylene concentrations up to 10,000 ppm did not display epinephrine-induced arrhythmias (from cardiac sensitization).

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, 3, or 7.5 hours/day, 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 that 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/day, 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 2012), this subject was exposed to relatively high concentrations. The patient was reported to be asymptomatic 1 month after finding different employment (Abedin et al. 1980).

Epinephrine-induced cardiac arrhythmia (from cardiac sensitization) was not induced in beagle dogs (5 and 12 dogs at the low and high exposure levels, respectively) exposed for 10 minutes 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. Available data provide suggestive, but not conclusive, information on potential hematologic effects of inhalation exposure to tetrachloroethylene; an experimental study observed no change from baseline hematology parameters after exposure to concentrations up to 150 ppm (Stewart et al. 1977, 1981), while a study of Egyptian dry cleaners exposed to <140 ppm tetrachloroethylene suggested decrements in hemoglobin and red blood cell count compared with an unexposed referent group (Emara et al. 2010). Limited animal data do not provide support for the findings in humans. Boverhof et al. (2013) observed no changes in hematology parameters in rats exposed to concentrations up to 1,000 ppm for 4 weeks, while a chronic cancer bioassay (JISA 1993) observed only increased mean corpuscular hemoglobin concentration (MCHC) in rats and gender-specific effects in mice.

Controlled human exposure studies of effects on complete blood count have not shown any change from preexposure values after exposures of adult male and female volunteers (6–10 per sex) to 0, 20, 100, or 150 ppm tetrachloroethylene vapor for 1, 3, or 7.5 hours/day, 5 days/week for 1 week at each vapor concentration (Stewart et al. 1981) or to 0, 25, or 100 ppm tetrachloroethylene vapor for 5.5 hours/day, 5 days/week, over an 11-week period (Stewart et al. 1977).

In contrast to the volunteer data, one epidemiological study (Emara et al. 2010) observed changes in selected hematology parameters among men employed as dry cleaners in Egypt; an earlier study (Cai et al. 1991) did not provide support for these findings. Emara et al. (2010) reported significantly ($p<0.05$) decreased hemoglobin, red blood cell counts, and mean cell hemoglobin concentration in male dry cleaner employees when compared with age- and lifestyle-matched unexposed referent subjects (n=40/group; 20 smokers, 20 nonsmokers). Mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were not affected by exposure. Average tetrachloroethylene exposure levels of <140 ppm were estimated from measurements made at various sites in each shop and mean tetrachloroethylene blood levels of 1,681 and 1,696 μg/L were observed among nonsmoking and smoking workers (compared with 0.11 μg/L in each of the control groups), respectively (Emara et al. 2010). No changes in hemoglobin concentration, red or white blood cell count, or hematocrit were observed in Chinese dry cleaning workers (29 men and 27 women) exposed to tetrachloroethylene at a geometric mean TWA concentration of 20 ppm, when compared with unexposed controls (30 men and 35 women) (Cai et al. 1991).

In animals, intermediate-duration studies of exposures up to 1,000 ppm have not suggested effects of tetrachloroethylene on hematology. Hematology end points (including hemoglobin, hematocrit, red cell and reticulocyte counts, total and differential white cell counts, and platelet counts) were not affected in female Sprague-Dawley rats at the end of 4 weeks of exposure to tetrachloroethylene vapors 6 hours/day, 5 days/week at concentrations of 0, 100, 300, or 1,000 ppm (Boverhof et al. 2013). A dose-dependent decrease in erythrocyte δ-aminolevulinate dehydratase activity, which is necessary for heme production, was observed in rats exposed to 200 and 600 ppm, but not 50 ppm, tetrachloroethylene for 4 weeks (Soni et al. 1990). It is not clear if exposure was intermittent or continuous. 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 Seidel et al. (1992) study. Rats exposed to 230 or 470 ppm tetrachloroethylene for up to 160 days exhibited splenic congestion and increased hemosiderin deposits (Carpenter 1937); however, the study is limited by the use of sick animals (parasites, pneumonia), nonstandard study protocols, rats of undefined strain, and inadequate controls.

In a chronic cancer bioassay (JISA 1993), hematology changes observed at sacrifice of Crj:BDF1 mice after 104 weeks of exposure to 250 ppm tetrachloroethylene (the highest concentration tested) included increased red blood cells and hematocrit, increased hemoglobin (females only) and reduced MCV, MCH, and MCHC (males). In the corresponding rat study (JISA 1993), the only hematology change noted was an increase in mean corpuscular hemoglobin in female rats exposed to 600 ppm (the highest concentration tested).

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 tetrachloroethylene at 50, 200, or 800 ppm 6 hours/day, 5 days/week for 13 weeks (Mattsson et al. 1992, 1998).

Hepatic Effects

Hepatic Effects in Humans. The liver may be a target organ in humans exposed to tetrachloroethylene. Case reports (Coler and Rossmiller 1953; Hake and Stewart 1977; Meckler and Phelps 1966; Saland 1967; Stewart et al. 1961a) have documented liver injury consisting of hepatomegaly, icterus, and clinical

chemistry changes in exposed humans, but no information on exposure concentrations was available. Controlled, acute-duration human exposure studies (Stewart et al. 1977, 1981) using concentrations up to 150 ppm tetrachloroethylene have not shown effects on serum levels of hepatic enzymes. However, studies of occupationally-exposed individuals have provided suggestive evidence for subclinical liver effects (changes in gamma-glutamyltransferase [GGT] isozyme fractions and diffuse parenchymal changes seen on ultrasound) in humans exposed chronically to lower levels (10–20 ppm TWA) of tetrachloroethylene (Brodkin et al. 1995; Gennari et al. 1992). Other serum markers for liver function were not altered at these exposure levels (Brodkin et al. 1995; Cai et al. 1991; Lauwerys et al. 1983).

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 in exposed individuals 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 acute exposure to concentrations that resulted 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, 3, or 7.5 hours/day, 5 days/week for 1 week at each exposure concentration (Stewart et al. 1981). No ethanol consumption was permitted during the exposure sequence. A complete panel of clinical chemistries including serum alkaline phosphatase, serum glutamic pyruvic transaminase (SGPT), SGOT, and serum bilirubin was obtained each week. These results were compared to the preexposure values; no deviation from baseline was observed (Stewart et al. 1981). Similarly, when six males and six females were randomly exposed to 0, 25, or 100 ppm tetrachloroethylene vapor for 5.5 hours/day, 5 days/week, over an 11-week period, no deviations from baseline values were observed in weekly blood samples analyzed for serum alkaline phosphatase, SGPT, SGOT, and serum bilirubin (Stewart et al. 1977).

In two studies assessing hepatic enzyme levels in serum of dry cleaners exposed to TWA concentrations of ~20 ppm tetrachloroethylene, no evidence of increased enzyme levels, including SGOT, SGPT, and alkaline phosphatase, was noted (Cai et al. 1991; Lauwerys et al. 1983). However, subtle differences in the isoenzyme fractionation of serum 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 [LDH], 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 effects following exposure to tetrachloroethylene, as an ultrasound study suggested morphological changes in the absence of elevated serum enzymes. In dry cleaning workers exposed to an average of 15.8 ppm tetrachloro-ethylene for 20 years, ultrasound revealed diffuse parenchymal changes in the livers of 18/27 (67%) exposed compared with 10/26 (38%; significantly different at $p<0.05$) unexposed laundry workers (Brodkin et al. 1995). An exposure-related trend was also noted, with parenchymal changes observed in all 5 subjects with exposures >15 ppm, 6 of the 12 subjects with exposures <15 ppm, and 10 of 26 (38%) unexposed laundry workers. No changes in serum markers of liver function (SGOT, SGPT, GGT, alkaline phosphatase, and total and direct bilirubin) were noted in these workers (Brodkin et al. 1995). The mean age and duration of employment of the exposed and control groups differed significantly (average age of exposed subjects was 46 years, compared with 38 years in controls, and exposed subjects had worked an average of 15 years longer than controls), limiting the conclusions that can be drawn from this study.

Hepatic Effects in Animals. Hepatic lesions are clearly shown in experimental animals during inhalation exposure to tetrachloroethylene. Mice are more sensitive to this effect than rats, as demonstrated in studies of acute, intermediate, and chronic duration. The lowest LOAELs for hepatic effects in animals exposed for acute, intermediate, and chronic durations are 200 ppm (mice; Kylin et al. 1963), 9 ppm (mice; Kjellstrand et al. 1984), and 50 ppm (mice; JISA 1993). Chronic exposure of mice to tetrachloroethylene results in hepatocellular adenomas and carcinomas, while these tumor types are not increased by exposure of rats (JISA 1993; NTP 1986). Section 3.2.1.7 provides additional details of the liver cancer data on tetrachloroethylene.

The available acute-duration inhalation studies demonstrate liver effects in mice exposed to concentrations as low as 200 ppm, while rats appear to be resistant to hepatotoxic effects even at concentrations >10-fold higher. Hepatocellular vacuolization occurred after a single 4-hour exposure of mice to ≥200 ppm concentrations of tetrachloroethylene (Kylin et al. 1963). This lesion was also reported in 4/5 male B6C3F1 mice exposed to 875 ppm and in all male and female mice exposed to 1,750 ppm tetrachloroethylene for 14 days; vacuolization was not present at 425 ppm (NTP 1986). In another 14-day study, JISA (1993) observed "fading of the liver" at necropsy of mice exposed to ≥400 ppm, along with "central enlargement" of the liver at the highest concentration (1,600 ppm); no additional details were provided. Liver lesions were not observed in rats exposed for 14 days to concentrations up to 1,750 ppm in the study by NTP (1986) or up to 3,200 ppm in the study by JISA (1993).

The type of liver lesions differs markedly between mice and rats after intermediate- and chronic-duration exposures to tetrachloroethylene. Mice develop vacuolization, peroxisome proliferation, necrosis, and, with prolonged exposure, neoplasia; effects in rats appear to be less severe, consisting of centrilobular hypertrophy and hyperplasia. In a study correlating light microscopic and ultrastructural liver effects with liver levels of cyanide-insensitive palmitoyl CoA oxidase, a marker for peroxisomal β-oxidation, peroxisome proliferation was observed in mice, but not in rats (Odum et al. 1988). Animals were exposed to 200 ppm of tetrachloroethylene for 28 days or to 400 ppm for 14, 21, or 28 days. Centrilobular hepatocellular vacuolization was induced in mice by tetrachloroethylene 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.

When 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; further details were not provided. Relative liver weights were not calculated; however, absolute liver weights were significantly elevated at all exposure concentrations and remained elevated 120 days following exposure to 150 ppm (Kjellstrand et al. 1984). In a 13-week study, male mice exposed to ≥200 ppm tetrachloroethylene exhibited mitotic alterations in the liver, while both sexes had leukocytic infiltrations, centrilobular necrosis, and bile stasis at ≥400 ppm (NTP 1986).

In contrast to the effects seen in mice in the study by Odum et al. (1988), which included vacuolization, lipid accumulation, and peroxisome proliferation, when rats were exposed to 200 ppm tetrachloroethylene for 28 days or 400 ppm for 14, 21, or 28 days, male rats in both dose groups and female rats exposed to 400 ppm developed centrilobular hepatocellular hypertrophy (Odum et al. 1988). Ultrastructural findings consisted of proliferation of smooth endoplasmic reticulum, with no increase in peroxisomes (Odum et al. 1988). Centrilobular hypertrophy was also the only liver lesion in female Sprague-Dawley rats exposed to tetrachloroethylene vapors at 0, 100, 300, or 1,000 ppm, 6 hours/day, 5 days/week for 4 weeks in an immunotoxicity study. Relative liver weight was significantly increased at 300 and 1,000 ppm (8 and 9% higher than controls, respectively) (Boverhof et al. 2013). Very slight hypertrophy of the centrilobular hepatocytes was observed in 4/8 rats exposed to 300 ppm and in 7/8 rats exposed to 1,000 ppm tetrachloroethylene; the control incidence was not reported (Boverhof et al. 2013).

Dose-related liver congestion was observed in rats exposed to tetrachloroethylene for 13 weeks, with 8/20, 10/20, and 15/19 rats affected at 400, 800, and 1,600 ppm tetrachloroethylene, respectively; no liver effects were observed at 200 ppm (NTP 1986). In a reproductive toxicity study, hepatic effects were not observed in parental male or female rats exposed to 1,000 ppm of tetrachloroethylene 6 hours/day, 5 days/week for 11–19 weeks (Tinston 1995).

Chronic inhalation bioassays of mice and rats confirm the sensitivity of mice to hepatic effects of tetrachloroethylene and the qualitative differences in the lesions induced in the two species. Hepatocellular degeneration and necrosis occurred in male mice exposed to 100 and 200 ppm tetrachloroethylene for 103 weeks and in female mice exposed to 200 ppm (NTP 1986). Similar effects were seen in another chronic bioassay of Crj:BDF1 mice; at ≥50 ppm, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were increased and angiectasis was observed in the livers of males, and at 250 ppm, serum AST and ALT were increased and angiectasis was observed in females; absolute and relative liver weight were increased and focal hepatocellular necrosis occurred in males; and central degeneration of the liver was seen in both sexes. Both sexes of mice also had increased incidences of hepatocellular tumors in both studies at exposure concentrations ≥100 ppm (JISA 1993; NTP 1986). Liver effects were not reported in rats exposed chronically to 200 or 400 ppm tetrachloroethylene in the study by NTP (1986), but the effects of mononuclear cell leukemia infiltrates may have obscured subtle compound-induced changes. The other available chronic bioassay (JISA 1993) reported increased serum ALT in female rats and spongiosis hepatis in males exposed to ≥200 ppm. At 600 ppm (the highest concentration tested), serum ALT was increased in males, triglycerides were reduced in females, and the incidence of liver hyperplasia was increased in male rats. Unlike the mice, exposed rats did not exhibit an

increased incidence of liver tumors in either study (JISA 1993; NTP 1986). These studies are discussed further in Section 3.2.1.7.

Renal Effects

Renal Effects in Humans. The kidney may also be affected in humans exposed to tetrachloroethylene, based on information provided in a case report of accidental exposure (Hake and Stewart 1977) and studies of dry cleaning workers exposed chronically to tetrachloroethylene (Bundschuh et al. 1993; Franchini et al. 1983; Mutti et al. 1992; Price et al. 1995; Verplanke et al. 1999; Vyskocil et al. 1990). Several studies of occupational populations suggest an association between tetrachloroethylene exposure to concentrations between 10 and 85 ppm and alterations in urinary and serum markers indicative of glomerular and/or tubular dysfunction (Franchini et al. 1983; Mutti et al. 1992; Vyskocil et al. 1990). These studies were generally of small populations (the largest was 82 subjects) with varying exposure durations, but measured sensitive indicators of renal function. Other studies measuring urinary proteins, *n*-acetyl-glucosaminidase (NAG), blood urea nitrogen (BUN), and serum creatinine have not shown effects at occupational exposure levels (Cai et al. 1991; Solet and Robins 1991). A retrospective cohort study showed an increased risk of hypertensive end-stage renal disease in dry cleaning workers exposed to tetrachloroethylene (Calvert et al. 2011).

Limited information is available on renal effects after acute-duration exposure of humans. Evidence of renal dysfunction, including proteinuria and hematuria, was reported in an individual after accidental exposure to anesthetic concentrations (exposure estimates were not reported, but the subject was unconscious) of tetrachloroethylene vapor (Hake and Stewart 1977). In acute-duration controlled human exposure studies, no changes from baseline levels of urinalysis parameters or BUN were observed after a 1-week exposure to concentrations up to 150 ppm for up to 7.5 hours/day (Stewart et al. 1981).

Assessment of urinary markers of renal damage in dry cleaning workers exposed to tetrachloroethylene in several studies has provided indicators of renal changes after chronic exposure to concentrations of 10–23 ppm (Franchini et al. 1983; Vyskocil et al. 1990). 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 NAG were observed. No effects on BUN or serum creatinine were observed in workers exposed at an average concentration of 20 ppm for 1–120 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, or 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). 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 a more comprehensive examination of kidney function, 9 men and 41 women occupationally exposed to tetrachloroethylene from trace levels to 85 ppm were compared with 50 controls (Mutti et al. 1992). Exposure levels and parameters of kidney function were both measured over a long period of time to account for variability in the working cycle or seasonal fluctuations; however, 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 in the exposed group. The following urinary markers were increased in exposed workers relative to unexposed workers: fibronectin; albumin; transferrin; brush-border antigens BBA, BB50, and HF5; and tissue nonspecific alkaline phosphatase. Serum antiglomerular basement membrane antibodies and serum laminin levels were also 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.

A larger study of workers exposed to lower concentrations showed only subtle effects on urinary markers of renal function. Verplanke et al. (1999) measured urinary markers in dry cleaning employees (82 exposed and 19 unexposed) in the Netherlands, whose TWA exposure, as measured in alveolar air samples, was 8.4 mg/m^3 (1.2 ppm). The exposed and control groups were not different with respect to age, sex, body mass, percent of smokers, alcohol consumption, or duration of employment. No differences in urinary levels of NAG, β-galactosidase, alanine aminopeptidase, or albumin were observed; a significant increase in retinol binding protein (75.4 versus 41.6 μg/g creatinine in unexposed employees) was noted. The study authors reported that retinol binding protein is a more sensitive indicator of renal

tubular dysfunction than NAG. Renal parameters did not correlate with exposure concentration or with a measure of cumulative dose that took into account concentration and exposure duration.

Calvert et al. (2011) observed an elevated risk of hypertensive end-stage renal disease among 1,296 dry cleaning workers in four U.S. cities. The standardized incidence ratios (SIRs) were 1.98 (95% CI 1.11–3.27) for the entire cohort and 2.88 (95% CI 1.15–5.23) in the subgroup exposed only to tetrachloroethylene (n=494). Variable risk of renal disease was reported for workers in other industries (aerospace manufacturing and microelectronics) that are exposed to tetrachloroethylene (Lipworth et al. 2011; Radican et al. 2006; Silver et al. 2014). The SMR for nephritis and nephrosis for aircraft manufacturers employed for at least 1 year was 1.11 (95% CI 0.74–1.60 (Lipworth et al. 2011). Radican et al. (2006) reported a hazard ratio (HR) for end-stage renal disease of 0.97 (95% CI 0.27–3.52) in aircraft workers. A study of workers in a microelectronics and business machine facility did not have an increased hazard (HR at 5 years modified exposure years 0.94; 95% CI 0.47–1.86) (Silver et al. 2014).

Renal Effects in Animals. In animal studies, adverse renal effects have been observed in rodents exposed to tetrachloroethylene. Little information on renal effects after acute-duration exposure is available, but intermediate-duration studies have shown tubular histopathology, increased kidney weights, and glomerulonephropathy in rats, mice, and guinea pigs exposed to concentrations >400 ppm (Carpenter 1937; JISA 1993; Jonker et al. 1996; NTP 1986; Rowe et al. 1952; Tinston 1995). Both male and female mice and rats exhibited renal effects from exposure, but F344 rats appeared to be less susceptible than other strains. Similar nonneoplastic renal effects were observed in male and female rats (including F344 rats) and male and female mice in chronic studies using lower exposure concentrations (JISA 1993; NTP 1986).

An acute-duration study reported 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). JISA (1993) reported few details of its 14-day studies in rats and mice, but indicated that mice exhibited necrosis and regeneration of the proximal tubules in both sexes exposed to ≥800 ppm tetrachloroethylene; no renal effects were reported in rats. In the 14-day study by NTP (1986), no renal histopathology changes were reported in rats or mice at exposure concentrations up to 1,750 ppm.

In intermediate-duration studies, high concentrations of tetrachloroethylene were associated with renal effects in rats, mice, and guinea pigs. Female Wistar rats exposed to 2,500 ppm tetrachloroethylene for 32 consecutive days exhibited increased urine volume; increased protein, GGT, ALP, LDH, and NAG

excretion; increased relative kidney weight; and increased incidences of mild multifocal tubular vacuolation and karyomegaly in the kidneys (Jonker et al. 1996). Minimal chronic progressive glomerulonephropathy and increased pleomorphism within the proximal tubular nuclei were noted in male, but not female, Alpk:ApfSD rats exposed to tetrachloroethylene at 1,000 ppm for up to 19 weeks (6 hours/day, 5 days/week); no effects occurred at 300 ppm (Tinston 1995). Albino rats of unspecified strain exposed to 470 ppm for 150 days or to 7,000 ppm for ≥40 exposures exhibited intratubular casts and swelling and desquamation of tubular epithelium (Carpenter 1937). Available studies in F344 rats show few or no renal effects. Kidney lesions did not occur in F344 rats exposed to 1,600 ppm 6 hours/day, 5 days/week for 13 weeks; kidneys from lower dose groups were not examined microscopically (NTP 1986). Likewise, the JISA (1993) 13-week study reported no renal findings in male or female F344DuCrj rats exposed to concentrations up to 1,400 ppm; however, the study authors reported "sporadic" urinalysis changes in both sexes of rat at exposures ≥609 ppm. It is not clear whether the differences in renal toxicity stem from strain specificity or differences in the exposure regimens.

At concentrations of ≤400 ppm, few renal changes were seen in rats of any strain. Intermittent exposure of Sprague-Dawley rats to 200 ppm tetrachloroethylene for 4 weeks induced renal P-450 enzymes (Soni et al. 1990); other end points of renal function were not assessed. Neither abnormal renal function nor histopathological findings were observed in Wistar-derived rats exposed to tetrachloroethylene vapor concentrations of 0, 100, 200, or 400 ppm for about 6 months (Rowe et al. 1952). Peroxisomal proliferation was not induced in renal tubular epithelium of F344 rats or B6C3F1 mice exposed to 200 or 400 ppm tetrachloroethylene for up to 28 days (Odum et al. 1988). Male rats F344 rats exposed to 400 ppm tetrachloroethylene for 28 days did not develop kidney lesions (Green et al. 1990).

Few data on kidney effects are available in mice exposed for intermediate durations; these studies suggest that renal changes can occur at concentrations of ≥600 ppm for 13 weeks. Renal tubular karyomegaly (nuclear enlargement) occurred in 7/10 male and 7/10 female B6C3F1 mice exposed to 1,600 ppm tetrachloroethylene for 13 weeks (NTP 1986). Renal effects were not seen at 100 ppm; kidneys of the remaining exposure groups (200, 400, and 800 ppm) were not examined microscopically. JISA (1993) reported no urinalysis alterations in Crj:BDF1 mice, but indicated that concentrations of ≥609 ppm resulted in changes in the renal proximal tubules (further details were not provided).

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 (Rowe et al. 1952). Neither abnormal renal function nor histopathological findings were observed in

guinea pigs exposed to tetrachloroethylene vapor concentrations of 0, 100, 200, or 400 ppm for about 6 months (Rowe et al. 1952).

Chronic bioassays indicate similar types of nonneoplastic renal effects in rats and mice at comparable exposure concentrations. In the NTP (1986) chronic inhalation toxicity/oncogenicity study of tetrachloroethylene, F344 rats of each sex were exposed to 0, 200, or 400 ppm tetrachloroethylene, and B6C3F1 mice were exposed to 0, 100, or 200 ppm tetrachloroethylene for 103 weeks. Dose-related increases in the incidence of renal tubular cell karyomegaly occurred in both species and sexes at all exposure concentrations. The highest incidences were seen in male rats (37/49 and 47/50 at 200 and 400 ppm, compared with 1/49 controls) and male mice (17/49 and 46/60 at 100 and 200 ppm, compared with 4/49 controls). This alteration was accompanied by low incidences of renal tubular cell hyperplasia and increased incidences of tubular cell adenoma or adenocarcinoma in male rats, but not in female rats or in male or female mice (NTP 1986). JISA (1993) observed increased absolute and relative kidney weights in male and relative kidney weights in female F344 rats exposed to ≥200 ppm tetrachloroethylene for 104 weeks, nuclear enlargement of proximal tubules of the kidneys at ≥200 ppm in males and at 600 ppm in females, atypical tubular dilation of the proximal tubules and exacerbation of chronic renal disease in males at 600 ppm. In Crj:BDF1 mice exposed for 104 weeks in the bioassay conducted by JISA (1993), nuclear enlargement of proximal tubules of the kidneys was noted in males and females exposed to 250 ppm (the highest concentration tested), and atypical tubular dilation of the proximal tubules occurred at this concentration in females.

Endocrine Effects. Few studies in humans or animals have examined endocrine effects of tetrachloroethylene exposure. Data are limited to a study of prolactin levels in humans exposed occupationally (Ferroni et al. 1992) and histopathology examination of the pituitary glands in rats exposed for 13 weeks (Mattsson et al. 1992, 1998) or adrenal glands in rats and mice exposed for 2 years (JISA 1993; NTP 1986). Cortical and medullary hyperplasia of the adrenal glands is the only adverse effect noted in the available studies.

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 effect observed in this population has biological significance.

Treatment-related 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, 1998) or in rats or mice exposed to concentrations up to 250 ppm for 2 years (JISA 1993; NTP 1986). Medullary hyperplasia of the adrenal glands was observed in male rats at both exposure levels (5/49, 14/49, and 24/49 at 0 [control], 200, and 400 ppm respectively), and increased incidence of cortical hyperplasia of the adrenal glands was observed in female rats at the high exposure (4/50, 6/49, and 11/47 at 0 [control], 200, and 400 ppm respectively), when both groups were exposed to tetrachloroethylene for 103 weeks (NTP 1986). Adrenal glands were not affected in mice in the chronic bioassay by NTP (1986) or in mice or rats in the bioassay reported by JISA (1993).

Ocular Effects. Ocular effects of tetrachloroethylene in humans include irritation and vision decrements. Effects on vision, including impairments in color vision and contrast discrimination, have been reported in people exposed to low levels of tetrachloroethylene (0.02–15 ppm) occupationally or through residing in buildings with co-located dry cleaners (Cavalleri et al. 1994; Gobba et al. 1998; Schreiber et al. 2002; Storm et al. 2011). Because this effect may be a neurological effect rather than a direct action on the eyes, it is discussed in more detail in Section 3.2.1.4.

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 exposures of 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. 1961b). 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. Onofrj et al. (1999) reported acute optic neuritis in a 57-year-old female dry cleaner after 9 hours of ironing; her exposure during this activity was estimated to be as high as 64–252 ppm (see details in Section 3.2.1.4).

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, 1998).

Body Weight Effects. No studies of body weight effects in humans exposed to tetrachloroethylene were identified in the available literature. In studies in laboratory animals, body weights were decreased in rats exposed to ≥1,750 ppm and in mice exposed to 3,200 ppm for 2 weeks (JISA 1993; NTP 1986). Studies of intermediate-duration exposures also showed body weight decrements at high (>1,000 ppm)

concentrations in rats, mice, and guinea pigs (JISA 1993; NTP 1986; Rowe et al. 1952); however, the findings are not consistent across studies of the same species. Reduced body weights were observed in rats and mice exposed to ≥200 ppm in one of two chronic bioassays (JISA 1993) but not in the other (NTP 1986).

Following intermittent exposure to tetrachloroethylene for 2 weeks, body weights of rats, but not mice, were significantly reduced at 1,750 ppm (NTP 1986). JISA (1993) indicated that rats and mice treated for 2 weeks with exposure to tetrachloroethylene concentrations up to 3,200 ppm exhibited decreased body weight gain, but did not indicate the effective concentrations or magnitude of change. Pregnant CD rats exposed to concentrations of 250 or 600 ppm tetrachloroethylene for 6 hours/day on gestation days 6–19 exhibited decreased body weight gain (19% less than controls at both exposures) during gestation days 6–9; body weight gain did not differ from controls for the remainder of the exposure duration (Carney et al. 2006).

Following intermediate-duration exposure to tetrachloroethylene, body weights of rats were significantly reduced at 1,400 ppm (JISA 1993) or 1,600 ppm (NTP 1986); no body weight changes greater than 10% were noted in rats exposed at 800 ppm (Mattsson et al. 1992, 1998) 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); however, decreased body weight gain was reported in male mice exposed to ≥609 ppm and female mice exposed to 1,400 ppm in the 13-week study by JISA (1993). Guinea pigs exposed to tetrachloroethylene at 2,500 ppm for 24 days lost weight, and female guinea pigs exposed to 200 ppm 7 hours/day for 158 exposures in 220 days showed a significantly lower (18% lower than air-exposed controls, $p=0.011$) final body weight (Rowe et al. 1952). Limitations of this study include the use of small numbers of animals and intercurrent infection.

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). However, male rats exposed to 600 ppm, female rats exposed to ≥200 ppm, and male and female mice exposed to 250 ppm tetrachloroethylene for 2 years exhibited body weight decrements (magnitude of changes was not reported) throughout most of the exposure period in the chronic bioassay by JISA (1993).

3.2.1.3 Immunological and Lymphoreticular Effects

The available studies of immunological effects in humans exposed to tetrachloroethylene provide suggestive evidence for alterations in blood biomarkers related to inflammation and hypersensitivity; however, the data are limited and exposure concentrations are uncertain. The only study explicitly examining immune system effects in animals exposed to tetrachloroethylene via inhalation was a 4-week study that observed no immune system effects in rats at concentrations up to 1,000 ppm (Boverhof et al. 2013).

Emara et al. (2010) observed increased serum and cellular IL-4 levels and serum IgE levels, potentially indicative of enhanced hypersensitivity responses, in Egyptian dry cleaners. Hematological parameters (see Section 3.2.1.3), serum immunoglobulin levels, and cytokine levels were measured in groups of male dry cleaner employees and age- and lifestyle-matched unexposed referent subjects (n=40/group; 20 smokers, 20 nonsmokers). Average tetrachloroethylene exposure levels of <140 ppm were estimated from five vapor concentration measurements obtained by sampling various sites in each shop; details of the sampling and analysis methods were not provided. Blood tetrachloroethylene levels in nonsmoking unexposed subjects, smoking unexposed subjects, nonsmoking workers, and smoking workers were measured to be 0.11, 0.11, 1,681, and 1,695 μg/L, respectively. Serum and cellular IL-4 levels and serum IgE levels were significantly increased in both smoking and nonsmoking workers, compared to their respective referent groups. No change was found in serum or cellular IFN-γ levels or serum IgA, IgM, or IgG levels. In a study examining a wide variety of VOCs, Lehmann et al. (2002) reported decreased percentages of IFN-γ-producing T cells in the umbilical cord blood of infants (total n=85) from homes with higher levels of tetrachloroethylene (>7.3 $\mu g/m^3$ or 0.001 ppm, the 75^{th} percentile concentration) compared with infants from homes with lower levels (less than the 75^{th} percentile); the odds ratio (OR; adjusted for family atopy history, gender, and maternal smoking during pregnancy) for reduced percentage of IFN-γ-producing T cells was 2.9 (95% CI 1.0–8.6). In addition, the crude data on percentages of cytokine-producing T cells suggested decreases in TNF-α- and IL-2-producing cells associated with exposure to tetrachloroethylene at concentrations above the 75^{th} percentile. Levels of 28 VOCs in the homes were measured by continuous passive air sampling during 4 weeks after birth. This study is limited by the fact that exposure measurements occurred after the measurement of outcome (cord blood cytokine-producing T-cells), and indoor levels of tetrachloroethylene likely vary over time based on the presence or absence of recently dry-cleaned materials in the home. In addition, the analyses did not account for potential confounding by coexposure to other VOCs. Thus, the association between indoor tetrachloroethylene and cytokine-producing T-cells in neonates is uncertain.

The limited available epidemiological studies investigating allergic sensitization and asthma have not observed a clear role for tetrachloroethylene exposure in the development of these conditions, but a case report of hypersensitivity pneumonitis provides some support. Lehmann et al. (2001) measured indoor concentrations of several VOCs in the bedrooms of 3-year-old children and assessed their association with serum IgE antibodies to food, indoor, and outdoor allergens. The 25th, 50th, and 75th percentile concentrations of tetrachloroethylene were 0.87, 2.54, and 5.09 μg/m^3, respectively. While there were associations between some VOCs and sensitization to food allergens (eggs or milk), there was not an association between indoor tetrachloroethylene levels and food allergies. Further, there was no evidence for increased indoor (e.g., pet) or outdoor (e.g., pollen) allergen sensitization with higher levels of any VOC (Lehmann et al. 2001). Of 26 Hispanic children with asthma in Los Angeles, the daily severity of asthma symptoms was not associated with current ambient air levels of tetrachloroethylene (OR 1.94; 95% CI 0.80–4.70) or the amount of tetrachloroethylene in expired air (OR 1.07; 95% CI 0.51–2.25) (Delfino et al. 2003); limitations of this study include small sample size and lack of full participation at each measurement timepoint. A case report of hypersensitivity pneumonitis attributed the condition to tetrachloroethylene exposure; the woman worked at a dry cleaner (Tanios et al. 2004, see also Section 3.2.1.2). Other potential causes and diagnoses were ruled out by CT of her chest, blood chemistry, and analysis of bronchoalveolar lavage.

Andrys et al. (1997) reported statistically significant alterations in a number of blood immunological parameters when 21 dry cleaning workers were compared with measurements from a referent group of 16 “administrators” or when compared with laboratory reference values (LRVs). However, all of the measurements from the exposed group were within the normal range of the LRVs, and multiple parameters from the control group were outside the normal range of the LRVs, limiting the conclusions that can be drawn from the findings. When a small group of highly exposed subjects (n=6) were analyzed separately and the results were compared with LRVs, significant increases in total leukocyte numbers, lysozymes, circulating immunocomplexes, number of phagocytosing cells in peripheral blood, α2-macroglobulin levels, and C4 complement components were noted, as were decreased prealbumin concentrations. However, the small number of highly exposed subjects limits the interpretation of these findings.

A 4-week rat study of immunotoxicity (Boverhof et al. 2013) observed no evidence for effects on a wide range of immune system end points. No changes in white blood cell counts; the number of cells, protein levels, or amount of LDH in the bronchoalveolar lavage fluid; the phagocytic activity of pulmonary

alveolar macrophages; the splenic antibody forming cell (AFC) response to sheep red blood cells; or the weights or histopathology of immune system organs (spleen or thymus) were observed in female Sprague-Dawley rats exposed to tetrachloroethylene vapors at 0, 100, 300, or 1,000 ppm, 6 hours/day, 5 days/week for 4 weeks (Boverhof et al. 2013).

In a mouse study (see the discussion of respiratory effects in Section 3.2.1.2), 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.

A chronic study of rats exposed to tetrachloroethylene for 104 weeks (JISA 1993) observed no changes in spleen weight or histopathology of thymus or lymph nodes at concentrations up to 600 ppm; increased incidences of mononuclear leukemia of the spleen were noted (see Section 3.2.1.7). The study authors reported that male mice, but not female mice, exposed to 250 ppm tetrachloroethylene for 104 weeks exhibited increased absolute and relative spleen weight (data were not shown; JISA 1993). No histopathology changes of the spleen, thymus, or lymph nodes were reported.

3.2.1.4 Neurological Effects

Neurological Effects in Humans. The nervous system is a major target organ in humans exposed to tetrachloroethylene by inhalation. Acute exposure, depending on concentration, can result in electrophysiological changes, reversible mood and behavioral changes, impairment of coordination, or anesthetic effects. Studies in humans exposed for years in occupational or residential settings have suggested effects on color vision and visual contrast sensitivity, as well as additional neurobehavioral effects. There are no studies of humans exposed to tetrachloroethylene for intermediate durations of time.

Acute-Duration Neurological Effects in Humans. Volunteers exposed to tetrachloroethylene for short periods of time have reported symptoms of lightheadedness, dizziness, and loss of coordination at concentrations between 100 and 300 ppm for <2 hours or 600 ppm for 10 minutes (Carpenter 1937; Rowe et al. 1952; Stewart et al. 1961b). Symptoms of neurological impairment were not reported after exposure to 106 ppm for 1 hour (Rowe et al. 1952). 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). Symptoms of dizziness and drowsiness were reported 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 (Rowe et al. 1952). In an older study, mood changes, slight ataxia, faintness, and dizziness occurred with exposure to concentrations of 1,000–1,500 ppm for <2 hours (Carpenter 1937). With exposure to 2,000 ppm for 5–7 minutes, subjects experienced a sensation of impending collapse (Carpenter 1937). Dizziness has also been reported after a 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; Patel et al. 1973; Stewart 1969; Stewart et al. 1961a).

In contrast to the lack of symptoms reported in humans exposed to 106 ppm for 1 hour (Rowe et al. 1952), 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 to 100 ppm for 7 hours/day on 5 consecutive days, none showed any abnormality except the Romberg test of balance, which was abnormal for three of the five subjects; no control subjects were included in this study (Stewart et al. 1970). Hake and Stewart (1977) reported impaired coordination, as measured by the Flanagan coordination test, at some time points during exposure of four male volunteers to 100 or 150 ppm tetrachloroethylene for 7.5 hours/day for 5 days.

Electrophysiological changes, including EEG alterations and changes in visual-evoked potentials, have been noted in studies of volunteers exposed for up to 5 days to tetrachloroethylene concentrations in the range of 50–100 ppm. EEGs of volunteers exposed to tetrachloroethylene showed evidence of central nervous system depression at concentrations of ≥100 ppm. Subjective evaluation of electroencephalographic scores suggested cortical depression in male volunteers exposed to 100 ppm for 7.5 hours/day for 5 days, but not when the same individuals were exposed to 20 ppm (Hake and Stewart 1977). In a later investigation, a larger group of 19 volunteers (10 males and 9 females) was exposed 5 days/week to tetrachloroethylene vapor concentrations of 0, 20, 100, or 150 ppm for 1, 3, or 7.5 hours/day (subjects were exposed to each concentration for 1 week) (Stewart et al. 1981). Major changes were observed in the EEG of three of four male subjects and four of five female subjects after 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 EEG alterations were similar to those seen in healthy adults during drowsiness, light sleep, and the first stages of anesthesia (Stewart et al. 1981).

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. A second study completed by Altmann et al. (1992) confirmed the effect on pattern reversal visual-evoked potentials at 50 ppm and the lack of effect on brainstem auditory-evoked potentials when 16 male volunteers were exposed 4 hours/day for 4 days and compared with a group exposed to 10 ppm. No effects on flash visual-evoked responses were noted in male volunteers exposed for 5 days, 7.5 hours/day to concentrations up to 150 ppm tetrachloroethylene (Hake and Stewart 1977). The lack of effect on flash visual-evoked potentials in the Hake and Stewart (1977) study may reflect the greater inter- and intrasubject variability of waveforms for flash visual-evoked potentials (Otto et al. 1988).

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. No effects on math skills, time discrimination, or reaction times were noted in male volunteers exposed for 5 days, 7.5 hours/day to concentrations up to 150 ppm tetrachloroethylene (Hake and Stewart 1977).

A case report described the acute onset of optic neuritis in a 57-year-old female dry cleaner (Onofrj et al. 1999). Symptoms of headache, retroorbital pain, and loss of vision other than light perception occurred after the subject had spent 9 hours ironing freshly dry-cleaned clothes and fabrics. Her visual field was markedly restricted, consisting of a “tunnel vision” effect that persisted during the 1 year follow-up time. While ambient measurements of tetrachloroethylene had been within exposure limits (25–50 ppm) when tested biannually, testing conducted to simulate the conditions that she experienced while ironing revealed concentrations as high as 64 and 252 ppm near the newly cleaned fabrics and in the steam from the iron (respectively), suggesting that her exposure may have been much higher than that recorded biannually. Other potential causes of optic neuritis were ruled out, and blood samples collected 2 days after symptom onset showed 1.08 mg/g tetrachloroethylene, leading the authors to suggest exposure as the cause of the optic neuritis (Onofrj et al. 1999). While the subject of this case report was employed in dry cleaning and was thus likely exposed to tetrachloroethylene for a number of years, it appears that the acute, high concentration exposure may have triggered the optic neuritis.

Intermediate-Duration Neurological Effects in Humans. There are no studies of neurological effects in humans exposed for intermediate durations.

Chronic-Duration Neurological Effects in Humans. Studies in dry cleaners suggest that chronic exposure to tetrachloroethylene may result in neurological symptoms and effects on memory, concentration, and reaction time that could persist after cessation of exposure. In a study of 26 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 the overall prevalence of neurological symptoms or in tests of psychomotor performance 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 (7/26 versus 3/33 controls) and difficulty in falling asleep (11/26 versus 6/33 controls). 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. 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 1–120 months relative to unexposed controls. Gregersen (1988) observed persistent symptoms of memory loss and poor concentration among workers who had been free of organic solvent exposure for 6.6 years; however, this study combined workers with exposure to tetrachloroethylene with those exposed to other solvents, so it is not clear whether the persistent changes are attributable to tetrachloroethylene exposure. No increases in signs of neurological effects (pre-narcotic syndrome or drowsiness) were observed in 50 dry cleaning workers compared to 95 controls (matched for age, sex, social status, professional categories, and smoking status) (Lucas et al. 2015). Air concentrations were measured for each worker by a passive diffusion badge. Mean air and blood concentrations of tetrachloroethylene were 7 ppm (range: 0.22–33 ppm) and 125.9 µg/L (11.8–544 µg/L), respectively. The median employment duration was 3 years.

Chronic-duration effects on neurobehavioral function: Three studies examining neurobehavioral function in dry cleaning workers (Echeverria et al. 1995; Seeber 1989) or people residing above or near dry cleaning facilities (Altmann et al. 1995) showed impairments in tasks associated with memory, attention, and reaction time. These studies have suggested a possible effect of chronic tetrachloroethylene exposure on the functioning of the frontal lobes (mediating complex organizational behavior, attention, executive functioning, and reasoning) and the limbic system (mediating mood and memory). Benignus et al. (2009) reported a meta-analysis of these three studies, and observed a higher magnitude of effect (normalized across the three studies and tests applied) with the lower estimated cumulative exposure in the residential study than with the higher occupational exposures. The authors postulated a series of potential explanations for this finding, including the possibility that the findings of low-level residential

effects were related to an effect of acute exposure (e.g., resulting from the exposure in the home during the day(s) prior to testing), which may not have existed in occupational groups tested after several hours or up to 2 days without exposure. Other possible explanations suggested by the authors included: (1) the potential greater susceptibility of residents compared with workers, due to the "healthy-worker" effect or due to differences in age or gender between the two populations; and (2) differences in exposure scenario (i.e., residents are exposed to lower concentrations but more continuously and over longer periods than workers, and workers' time away from work provides greater opportunity for elimination of tetrachloroethylene from the body).

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 presser, and an operator in 19 of the 23 shops studied; exposure groups (low, medium, and high) were then created based on work history. These authors (Echeverria et al. 1995) also described 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.

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 on average 12 and 11 years in the low- and high-exposure groups, respectively (as reported by EPA 2012a). The study showed statistically significant differences, indicative of impairment, between exposed and control groups in test scores for neurological signs, emotional lability, perceptual speed, delayed reactions, digit reproduction, cancellation d2 (fault corrected performance), and digit symbol, after controlling for gender, age, and intelligence. Among these tests, only scores for perceptual speed, delayed reactions, and digit reproduction exhibited monotonic dose-response relationships; for the other tests, the scores were worse in the low exposure group than in the high-exposure group (Seeber 1989). Compared to 30 unexposed women, significantly prolonged reaction times (simple reaction times, $p<0.0001$; 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.

In a study comparing 14 persons living above or next to dry cleaning facilities for 1–30 years with 23 controls with no history of solvent exposure, 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). However, 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 ($p<0.05$) relative to 23 controls. The median concentrations of tetrachloroethylene were 0.2 and 0.003 ppm in the apartments of exposed and control subjects, respectively; blood concentrations measured in the examination room (not in the apartments) were 17.8±46.9 μg/L (mean±standard deviation) in exposed subjects and below the 0.5 μg/L detection limit in controls.

Chronic-duration effects on vision: Chronic tetrachloroethylene exposure may alter specific types of vision functions, including color discrimination and contrast sensitivity; however, the available data include some conflicting findings. The mechanisms for the visual effects of tetrachloroethylene are unknown. Several potential mechanisms may contribute, including effects on calcium channels or neurotransmitter receptors. These are described in Section 3.5.2.

No effect on blue-yellow color vision (assessed using Lanthony's new color and Ishihara's color vision tests) 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; in addition, details of the sampling for tetrachloroethylene concentrations were not provided.

When compared to 35 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, as measured by the Lanthony D-15 desaturated panel (Cavalleri et al. 1994). No significant difference in color vision was found for a group of 13 ironers who experienced exposures to a lower average concentration (4.8 ppm). For the entire group of 35 workers (dry cleaners plus ironers), a multivariate analysis showed a significant association between increasing tetrachloroethylene concentration and

decreased color vision ($p<0.01$). This association was highly influenced by outcomes for three subjects whose exposures exceeded 12.5 ppm. Reexamination of the workers 2 years later showed that those workers whose exposure to tetrachloroethylene had increased (n=19, median exposure increasing from 1.7 to 4.3 ppm based on 4-hour TWA concentration measurements) experienced further decrements in color vision, while those whose exposure had decreased experienced no changes in color vision (n=14, median exposure decreasing from 2.9 to 0.7 ppm); two workers had retired and were not reexamined (Gobba et al. 1998). CCI, again measured using the Lanthony D-15 panel, was increased from 1.16 to 1.26 in the group with increased tetrachloroethylene exposure ($p<0.01$). In both the initial and follow-up studies, the exposure concentrations were measured on a single day; thus, it is not clear how well they represent long-term exposure. Gobba et al. (1998) noted that the Lanthony D-15 panel is a more sensitive test for early color vision loss than the tests used by Nakatsuka et al. (1992), and that the increased sensitivity might be one reason for the conflicting results obtained by Cavalleri et al. (1994) and Gobba et al. (1998) compared with Nakatsuka et al. (1992). Color discrimination (measured by Lanthony D-15 test) was not significantly affected in 4 children or 13 adults exposed to concentrations up to 0.3 ppm tetrachloroethylene for an average of 4–5 years; exposure resulted from living in residential buildings that also housed dry cleaning facilities (Schreiber et al. 2002). The mean CCI score of the exposed persons (1.33±0.09 standard error of mean, SEM) was higher than that of age- and sex-matched controls (1.20±0.07 SEM), but the difference was not statistically significant by two-tailed matched-pair analysis (Schreiber et al. 2002).

Other studies that did not quantify exposure to tetrachloroethylene provide some support for effects on color vision. A study of 14 dry cleaning workers (7 men and 7 women) also observed poorer color discrimination, primarily in the blue-yellow range, when compared with two referent groups (n=27 and 29) consisting of support staff of the investigating university (Sharanjeet-Kaur et al. 2004). Testing using the D-15 and Farnsworth Munsell 100 Hue tests indicated abnormal performance (based on criteria published by Vingrys and King-Smith 1988) among 43 or 93% (respectively) of dry cleaners, compared with 0% of each of the referent groups (statistical analysis was not performed). The authors suggested that the FM 100 Hue test was a more sensitive test for acquired color vision deficits (Sharanjeet-Kaur et al. 2004). The study is limited by the lack of matching in selection of the referent population and lack of control for potential confounders including age and smoking status. Till et al. (2003) compared the color vision and contrast sensitivity in a 30-month-old child whose mother worked as a dry cleaner prior to and during pregnancy with similar test results from three unexposed 2-year-old children. The exposed child exhibited severe red-green color vision deficit, and mild to moderate impairment of blue-yellow color vision (Till et al. 2003). Due to the age and limited language abilities of the children, testing was

accomplished by measurement of transient and sweep visual-evoked potentials. Valic et al. (1997) examined color confusion in 138 individuals who reported exposure to solvents compared with 100 controls. The subjects included 31 individuals who reported exposure to trichloroethylene or tetrachloroethylene for an average of 5 years; urine levels of trichloroacetic acid were measured to validate exposure. Among those exposed to tri- or tetrachloroethylene in combination with ≥250 g of alcohol per week, the CCI (assessed by Lanthony D-15 test) was higher (1.80±0.7 standard deviation) than in those subjects whose alcohol intake was similar but who were not exposed to the chlorinated solvents. Among those without alcohol intake, exposure did not affect CCI. Urinary trichloroacetic acid levels were not correlated with CCI (Valic et al. 1997).

Tetrachloroethylene exposure may also alter visual contrast sensitivity. In one volunteer study that evaluated this end point, tests of visual contrast measured in a few individuals showed a tendency for loss of contrast in the low and intermediate spatial frequencies after exposure to 50 ppm on 4 hours/day for 4 days (Altmann et al. 1990). Two epidemiological studies of exposure to tetrachloroethylene from living or working in buildings that also housed dry cleaners (Schreiber et al. 2002; Storm et al. 2011) suggested that exposure to concentrations of 0.1–0.3 ppm could alter visual contrast sensitivity in adults, and that this end point might be affected at lower concentrations in children. Schreiber et al. (2002) evaluated a group of residents (n=17) and a group of daycare workers (n=9), each of whom was exposed to tetrachloroethylene for an average of 4 or 5.8 years (respectively) originating from a dry cleaner that was colocated with the residence or daycare. Visual acuity, color discrimination, and contrast sensitivity were assessed in these groups and in age- and sex-matched controls without exposure. Ambient and personal air monitoring results suggested mean concentrations of about 0.11 ppm among the residents and about 0.3 ppm among the daycare workers. In both groups, significant ($p<0.001$) decreases in visual contrast sensitivity were observed when compared with the unexposed referent groups. Storm et al. (2011) recruited adults and children living in New York City buildings with or without colocated dry cleaners for a larger study of visual acuity and contrast sensitivity. The exposed subjects were stratified into low and high exposure (<100 or >100 $\mu g/m^3$ tetrachloroethylene) based on 24-hour air samples; exhaled air and blood were also analyzed for tetrachloroethylene. Geometric mean indoor air concentrations of 0.00046, 0.0018, or 0.050 ppm tetrachloroethylene were reported for the referent, low, and high exposure groups of children (n=56, 39, and 11, respectively); for adult participants, the concentrations were 0.00043, 0.0017, or 0.070 ppm (n=49, 43, and 12, respectively). In children, a higher concentration of tetrachloroethylene in indoor air was associated with a higher odds of achieving less than the maximum score (in the poorer performing eye) at a spatial frequency of 12 cycles per degree of visual arc; the effect remained after adjustment for race, ethnicity, and age (adjusted OR 2.64; 95% CI 1.41–5.52). Visual contrast sensitivity

of adults was not associated with measures of tetrachloroethylene exposure. A 30-month-old child whose mother worked as a dry cleaner prior to and during pregnancy exhibited decreased contrast sensitivity in the low and intermediate spatial frequency ranges (measured by transient and sweep visual-evoked potentials), when compared with three unexposed 2-year-old children (Till et al. 2003).

Chronic-duration effects on risk of neurological disease: A study of 99 twin pairs (including 49 identical and 50 fraternal pairs) was conducted to evaluate the association between exposure to solvents and Parkinson's disease risk (Goldman et al. 2012). The twin pairs, from the World War II Veteran Twins Cohort, were discordant for Parkinson's disease (one twin had the disease and one did not). The twins completed detailed questionnaires regarding occupational tasks and hobbies, and their exposure to six solvents was estimated from their answers by experts blinded to disease status. The risk of Parkinson's disease was not elevated among those ever exposed to tetrachloroethylene disease (OR 10.5; 95% CI 0.97–113; p=0.053). However, the power of the study to detect a correlation between tetrachloroethylene exposure and Parkinson's disease was limited by the low number of study participants. Adjustment for exposure to any other solvent and other potential confounders (head injury, smoking, and zygosity) resulted in minimal change in the OR. Additional studies examining the potential relationship between tetrachloroethylene exposure and Parkinson's disease, especially studies with direct and quantitative measures of exposure, are needed before a conclusion can be drawn.

Perrin et al. (2007) observed an increase in the risk for developing schizophrenia among offspring of parents who worked as dry cleaners in Jerusalem. The study group consisted of a population-based cohort of individuals born between 1964 and 1976 (the Jerusalem Perinatal Study). The study collected data on demographics and occupation from birth certificates; these data were then linked to Israel's national Psychiatric Registry to identify schizophrenia patients. Proportional hazards assessment was used to evaluate the risk of schizophrenia among the 88,829 live offspring followed to 1998. Of 144 offspring of parents employed in dry cleaning, four cases of schizophrenia were observed. The relative risk of developing schizophrenia was 3.4 (95% CI 1.3–9.2; p=0.01); this risk was minimally altered when a number of variables, including paternal age, were included in the model (relative risk not reported). No measure of exposure was included in this analysis. Because information relating schizophrenia risk to tetrachloroethylene exposure is limited to one study with a small number of patients and a surrogate measure of exposure, additional studies are needed to clarify the association, if any, with tetrachloroethylene exposure.

In a case-control study of autism spectrum disorders (ASDs), the reported OR was 1.1 (95% CI 0.78–1.59) between developmental exposure to tetrachloroethylene and diagnosis of ASD in children born in 1994 (OR 1.11; 95% CI 0.78–1.59) (Windham et al. 2006). Exposure was estimated using the EPA annual average Hazardous Air Pollutant (HAP) concentration estimates from 1996. Limitations of this study include use of estimated exposures, lack of addresses during the first trimester of pregnancy, and lack of control for other sources of exposure (e.g., occupational) and confounding variables (e.g., smoking). As with the single studies of Parkinson's disease and schizophrenia, more information is needed to assess the relationship between tetrachloroethylene exposure and autism spectrum disorders.

Neurological Effects in Animals. Neurological effects of tetrachloroethylene exposure in laboratory rodents are qualitatively similar to those seen in human studies. Mice and rats have exhibited anesthetic effects after exposure to high concentrations, while lower concentrations have resulted in effects on visual-evoked potentials, EEG patterns, and neurobehavioral tests of attention, as discussed below.

Neurological signs typical of an anesthetic effect of inhaled tetrachloroethylene have been reported in numerous animal studies of acute exposure durations (see Table 3-1). These clinical signs consist of hyperactivity (excitability), ataxia, hypoactivity, and finally loss of consciousness (Friberg et al. 1953; NTP 1986; Rowe et al. 1952). 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). Anesthesia was observed in mice within 2.5 minutes of breathing air containing 6,800 ppm tetrachloroethylene (Friberg et al. 1953). Dogs exposed to 5,000 ppm tetrachloroethylene by face mask for 10 minutes became excited and struggled (Reinhardt et al. 1973); this response may have represented respiratory irritant effects of tetrachloroethylene. Mice inhaling tetrachloroethylene for 4 hours showed signs of anesthesia at a concentration of 2,328 ppm (NTP 1986). Rats became ataxic following exposure to 2,300 ppm for 4 hours (Goldberg et al. 1964). Dyspnea, hypoactivity, hyperactivity, anesthesia, and ataxia were noted in mice and rats exposed to 1,750 ppm on 6 hours/day, 5 days/week for 2 weeks; these effects were not seen at lower concentrations (up to 875 ppm) (NTP 1986).

Acute exposures also demonstrated effects of tetrachloroethylene on visual and/or somatosensory-evoked potentials, as well as EEG changes, in rats. Male Long-Evans rats exposed for 1.5 hours to concentrations of 250, 500, or 1,000 ppm exhibited reduced amplitude of visual-evoked potentials at all exposure concentrations (Boyes et al. 2009). Albee et al. (1991) reported electrophysiological changes including altered shape, reduced amplitude, and decreased latency of flash-evoked potentials; decreased latency of somatosensory-evoked potentials; and EEG changes in male rats exposed to tetrachloro-

ethylene at 800 ppm 4 hours/day for 4 days. Similar findings were observed when male F344 rats were exposed 6 hours/day for 4 days to 800 ppm tetrachloroethylene as a pilot study in preparation for a subchronic study (Mattsson et al. 1998). Alterations in flash-evoked potentials recorded in the visual cortex were observed at 800 ppm, but not at lower exposure concentrations; cerebellar flash-evoked potentials were not affected by treatment. No treatment-related changes in auditory brainstem responses to clicks and tone pips, somatosensory-evoked potentials, or caudal nerve action potentials were observed, and grip strength was not affected by exposure (Mattsson et al. 1998).

Behavioral alteration has been observed in rodents after acute inhalation exposure to tetrachloroethylene. Impairment of sustained attention was observed in male Long-Evans rats exposed for 1 hour to concentrations of ≥500 ppm tetrachloroethylene (Oshiro et al. 2008). The degree of impairment increased with duration of exposure (tests of sustained attention were administered at 12-minute intervals during exposure). Open-field behavior (ambulation) was elevated in groups of 10 male rats exposed to 200 ppm tetrachloroethylene of unspecified purity for 6 hours/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 consisted of 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.

Intermediate-Duration Neurological Effects in Animals. 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, or hind and forelimb grip performance (Mattsson et al. 1992, 1998). 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 environments (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.

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.

Chronic-Duration Neurological Effects in Animals. Histologic lesions in the central and peripheral nervous systems have not been observed in chronic inhalation studies in rats and mice (JISA 1993; NTP 1986).

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

3.2.1.5 Reproductive Effects

Reproductive Effects in Humans. Some adverse reproductive effects in men and women have been reported to be associated with occupational exposure to tetrachloroethylene in dry cleaning operations. These effects include menstrual disorders, spontaneous abortion, sperm abnormalities, and decreased fertility. However, exposure in many of these studies was characterized only by occupation, tetrachloroethylene levels were not measured, and coexposure to other solvents could not be ruled out in many studies; thus, no definitive conclusions regarding the association between tetrachloroethylene inhalation and reproductive end points can be made based on the human data.

In a cross-sectional study, researchers determined that female dry cleaning workers in the Netherlands had menorrhagia (OR 3.0; 90% CI 1.6–5.6), dysmenorrhea (OR 1.9; 90% CI 1.1–3.5), and premenstrual syndrome (OR 3.6; 90% CI 1.5–8.6), compared to female laundry workers (Zielhuis et al. 1989). Limitations of the study are lack of exposure measurements, use of a self-administered questionnaire to evaluate effects, lack of follow-up, failure to account for various confounding factors such as smoking, alcohol consumption, and medicinal drugs, and a relatively small study population.

Olsen et al. (1990) reports that 214 “low” and “high” exposed workers in a Scandinavian case-control study did not have elevated combined statistics for low birth weight, congenital malformations, and stillbirth (1.72; 95% CI 0.40–7.12 versus 0.87; 95% CI 0.20–3.69), respectively. This study was limited by incomplete participation of all dry cleaning facilities, few controls for lifestyle factors, and limited exposure information. When analyses of subpopulations in Finland (Kyyrönen et al. 1989) and Sweden (Ahlborg et al. 1990) were conducted, higher odds of spontaneous abortion were reported in tetrachloroethylene-exposed women from Finland (4.9; 95% CI 1.3–19.5), but not Sweden (0.9; 95% CI 0.4–2.1).

However, a small group of exposed affected workers was included in the Finnish population, and biological monitoring for tetrachloroethylene was conducted after, rather than concurrent with, the first trimester of pregnancy (Kyyrönen et al. 1989). In addition, few pregnancies occurred among exposed women in the Swedish group (Ahlborg 1990).

A case-control study of California women occupationally exposed to tetrachloroethylene in dry cleaning operations reported an unadjusted OR of 4.7 (95% CI 1.1–21.1), suggesting that women exposed to tetrachloroethylene at least doubled their crude risk for spontaneous abortion (Windham 1991). In this study, exposure was assessed through telephone interviews; in addition, coexposure to other solvents, along with limited control for confounding factors, limits the reliability of these findings. In a larger, retrospective study of current and past laundry (n=2,711) and dry cleaner workers (n=399) in the United Kingdom (Doyle et al. 1997), females who were dry cleaner operators during or 3 months prior to pregnancy had a higher incidence of spontaneous abortion than non-operator dry cleaner workers (increased ~50%), laundry workers (increased ~30%), or unexposed women (increased ~45%). Unexposed women were workers not employed in these occupations during or just prior to pregnancy. The increased risk of spontaneous abortion for dry cleaner operators was elevated compared with non-operators (OR 1.63; 95% CI 1.01–2.66; Doyle et al. 1997).

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 a retrospective study, time-to-pregnancy was studied in wives of men biologically monitored for exposure to organic solvents (trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane, styrene, xylene, and toluene) by the Finnish Institute of Occupational Health (Sallmén et al. 1998). Exclusion criteria included contraceptive failure in the study pregnancy, infertility treatments, known reproductive health problems, and diabetes. A multivariate analysis study of 282 couples suggested that paternal exposure to organic solvents may be associated with decreased fecundability, after adjustment for age,

age at menarche, menstrual cycle variability, frequency of intercourse, maternal and paternal smoking, maternal exposure to organic solvents, and calendar year of pregnancy. Specific data on tetrachloroethylene exposure were available for 17 of the exposed men. Multivariate analysis of this subgroup also suggested a decrease in fecundability with paternal exposure specifically to tetrachloroethylene (adjusted fecundability density ratio: "low" exposure, 0.86 [95% CI 0.40–1.84]; and "high" exposure, 0.68 [95% CI 0.30–1.53]). Quantitative exposure concentrations were not reported in this study. Other limitations include methodological problems (retrospective, self-administered questionnaire) and use of surrogate exposure data if exposure was not measured at the time the attempt at pregnancy began (data for individual at different time-point or data for another individual in same job at that time-point). An earlier case-referent study conducted by the Finnish Institute of Occupational Health reported no increase in the risk of spontaneous abortions in wives of men occupationally exposed to tetrachloroethylene (OR 0.5; 95% CI 0.2–1.5) (Taskinen et al. 1989). This study has similar limitations to the more recent study, as well as small subject numbers (4 cases, 17 referents).

Reproductive Effects in Animals. Evidence from a limited number of well-conducted reproductive studies in laboratory animals suggests that tetrachloroethylene is a potential female reproductive toxicant, resulting in decreased number of liveborn pups, increased pre- and postimplantation loss, and increased resorptions. While several additional studies report a lack of reproductive findings, the majority of these have major study limitations (e.g., single-dose exposures, nonstandard protocols, exposure only during gestation). There is also limited evidence that tetrachloroethylene can damage both male and female gametes.

Effects on gametes have been reported in both male and female laboratory animals in acute- and intermediate-duration studies. Decreased oocyte quality was reported in female Sprague-Dawley rats exposed to 1,700 ppm for 2 weeks, as evidenced by significantly decreased *in vitro* fertilizability of oocytes and reduced number of penetrated sperm per oocyte (Berger and Horner 2003). In this study, exposure to tetrachloroethylene did not affect the serum progesterone levels of female rats. Spermhead abnormalities were significantly increased in CD-1 male mice 4 and 10 weeks after a 5-day exposure to 500 ppm tetrachloroethylene (NOAEL: 100 ppm) (NIOSH 1980). Abnormalities were not observed 1 week after exposure, indicating that spermatocytes and spermatogonia, rather than sperm and/or spermatids, are sensitive to tetrachloroethylene exposure in mice. However, male albino [CRL:COBS CD (SD) BR] rats exposed at 100 or 500 ppm did not demonstrate treatment-related increases in spermhead abnormalities (NIOSH 1980).

Szakmáry et al. (1997) reported adverse reproductive effects in rats and rabbits, but not mice, following exposure during gestation. CFY rats were exposed to 0, 1,500, 4,500, or 8,500 mg/m^3 (0, 221, 664, or 1,254 ppm) tetrachloroethylene on gestation days 1–20. Maternal weight gain was reduced in dams exposed to 664 or 1,254 ppm tetrachloroethylene (37–40% lower than controls). Preimplantation losses were increased (more than double the control percentage) at these exposure levels, but there were no treatment-related increases in postimplantation losses or number of resorptions. Rabbits exposed to 4,500 mg/m^3 (1,254 ppm) tetrachloroethylene on gestation days 7–20 also demonstrated a 58% reduction in maternal body weight gain. Litters were aborted in two treated and one control doe; in addition, four treated does exhibited total fetal resorptions. Postimplantation losses were higher in treated does (31% versus 11% in controls). However, mice exposed to 1,500 mg/m^3 (664 ppm) tetrachloroethylene on gestation days 7–15 did not demonstrate any changes in maternal body weight gain or number of post-implantation losses or resorptions. Additionally, gestational studies in rats and rabbits, with and without pre-mating exposure, demonstrated no treatment-related effects on reproductive parameters (e.g., fertility index, number of live litters, pre-/postimplantation loss, number of resorptions) at concentrations ranging from 100 to 1,000 ppm (Carney et al.2006; NIOSH 1980).

In a multigeneration 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 postpartum. The F1 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 F2A litters of the control and 100 ppm exposure groups were exposed daily from day 6 to day 29 postpartum, and dams and F2A litters of the 300 ppm exposure group were exposed daily from day 7 to day 29 postpartum. Dams and F2A litters of the 1,000 ppm group were not exposed during lactation. For all exposure concentrations, dams and F2B litters were not exposed during lactation. The F2C 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 (Tinston 1995). Decreased body weight gain in the parental animals was noted at 1,000 ppm during the pre-mating and lactation periods, but was generally <10%. The proportion of pups born live at 1,000 ppm was significantly lower in the F1A, F2A, and F2B litters (first litter [A] of the F1 generation and first two litters [A and B] of the F2 generation).

The incidence of pup mortality during lactation was also significantly increased at 1,000 ppm in the F1A, F2A, and F2B 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 marked at 1,000 ppm. At the beginning of the pre-mating period for the F1 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 1,000 ppm males was less than controls. Body weights of offspring in the 100 and 300 ppm groups were generally within 10% of control values. In the F2C 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 described treatment-related chronic progressive glomerulonephropathy in the kidneys of adult rats at 1,000 ppm (Tinston 1995). The report indicated 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 were not provided. The 1,000 ppm concentration is considered a serious LOAEL for reproductive effects resulting in a decrease in the number of liveborn pups, and the 300 ppm concentration is considered a NOAEL in rats.

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.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

Limited data are available on developmental effects of tetrachloroethylene in humans exposed via inhalation. Evidence from multiple studies in laboratory animals indicates that gestational exposure to tetrachloroethylene affects growth and development, but it is not overtly teratogenic. In animals, the lowest concentration associated with developmental effects, including growth retardation and skeletal and soft tissue anomalies, was 300 ppm; this concentration also produced maternal toxicity. Two available

neurobehavior studies of rats exposed during gestation gave conflicting findings; it is not clear whether strain differences may have contributed to the different results.

Forand et al. (2012) conducted a birth outcome analysis in the Endicott, New York area where residents may have been exposed to VOCs via soil vapor intrusion (migration of contamination through the soil into structures through cracks in building foundations). Two exposure areas were identified based on indoor air VOC sampling data: one area was categorized as primarily contaminated with trichloroethylene (n=1,090 live births) and the other with tetrachloroethylene (n=350 live births). Maternal residence in the tetrachloroethylene-contaminated revealed variable association of risk for all birth defects (rate ratio [RR]1.24; 95% CI 0.75–2.05), cardiac defects (RR 2.91; 95% CI 0.73–11.65), low-birth weight (RR 0.70; 95% CI 0.39–1.27), and preterm birth (RR 0.74; 95% CI 0.47–1.16), compared with state-wide incidence (excluding New York City). Limitations of the study include the ecological design that precludes assignment of actual exposures to individual subjects, small number of births in the study area, lack of control for potential occupational exposure to tetrachloroethylene (which was associated with elevated risk of adverse birth outcomes), lower socioeconomic status in the study area than the general comparison population, concurrent exposure to other VOCs, and other uncontrolled confounders such as alcohol, diet, and pre-existing maternal illness (Bukowski 2014).

Szakmáry et al. (1997) reported developmental effects in rats, mice, and rabbits exposed to tetrachloroethylene during gestation. Pregnant CFY rats were exposed to 0, 1,500, 4,500, or 8,500 mg/m^3 (0, 221, 664, or 1,254 ppm) tetrachloroethylene on gestation days 1–20. Fetal effects were observed at the two highest concentrations, and included increased percentages of fetuses per litter with weight retardation, "skeletal retardation," and total malformations. Apart from noting an increased number of offspring with supernumerary ribs, the study authors did not detail the fetal findings. Pregnant C57BL mice were exposed to 0 or 1,500 mg/m^3 (664 ppm) tetrachloroethylene on gestation days 7–15. No effects on litter size, numbers of dead or resorbed fetuses, fetal or placental weights, or percentages of fetuses with growth retardation, "skeletal retardation," or skeletal malformations were noted. An increased percentage of fetuses per litter with internal organ malformations (14% versus 0.8% in controls) was observed, but the nature of the malformations was not reported. Pregnant New Zealand rabbits were exposed to 0 or 4,500 mg/m^3 (1,254 ppm) tetrachloroethylene on gestation days 7–20 of gestation. Postimplantation losses were higher in treated does (31% versus 11% in controls) and 4/16 treated does exhibited total fetal resorptions. No effects on fetal weight, skeletal development, or malformation rates were noted. Fetal effects in rats and rabbits occurred at the same concentrations causing significant reductions (37–58%) in maternal body weight gain. Maternal weight gain was not affected in exposed mice.

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). However, neither maternal nor fetal toxicity was reported for rats exposed on gestation days 1–18 or 6–18 or in rabbits exposed on gestation days 1–21 or 7–21 by inhalation to 500 ppm tetrachloroethylene, with or without pre-gestational exposure (Hardin et al. 1981; NIOSH 1980). Limitations of this study include use of only one dose level, use of summary and nonquantitative data, and conduct of portions of the study at two separate laboratory facilities. In a more rigorous study, Carney et al. (2006) observed significantly decreased fetal weights in offspring of CD rats exposed to concentrations of 250 or 600 ppm tetrachloroethylene for 6 hours/day on gestation days 6–19. The decrease in body weight was statistically significant when male and female pups were combined (4% less than controls) and for each sex considered separately at 600 ppm (~10% less than controls). Decreased maternal body weight gain was also observed in the dams (Carney et al. 2006). In addition, a nonsignificant increase in the incidence of incomplete ossification of the thoracic vertebral centra (11/21 litters versus 4/10 control litters) was noted at 600 ppm.

Neurobehavioral and neurochemical alterations were reported in offspring of Sprague-Dawley rats exposed to 900 ppm tetrachloroethylene on gestation days 7–13 or 14–20 (NOAEL 100 ppm) (Nelson et al. 1980). 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). 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 each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.7 Cancer

Cancer Classifications. The potential carcinogenicity of inhaled tetrachloroethylene has been evaluated in numerous epidemiological studies and experimental animal studies. HHS has classified tetrachloroethylene as "reasonably anticipated to cause cancer in humans based on sufficient evidence from studies in experimental animals" (NTP 2016). IARC (2014) has classified tetrachloroethylene as "probably carcinogenic to humans" based on limited evidence in humans and sufficient evidence in animals (Group 2A). EPA (2012a) has characterized tetrachloroethylene as "likely to be carcinogenic in humans by all routes of exposure."

Epidemiological Studies. A large number of cohort and case-control studies have assessed possible associations between exposure to tetrachloroethylene and cancer, with comprehensive reviews conducted by NRC (2010), EPA (2012a), and IARC (2014). The NRC (2010) concluded that there was suggestive evidence for an association between tetrachloroethylene exposure and lymphoma, despite weak and sometimes inconsistent data; limited evidence from epidemiological studies for an association with esophageal cancer; and insufficient evidence for an association with other cancer types including liver, kidney, cervical, lung, and bladder cancer. EPA (2012a) evaluated the studies reviewed by NRC (2010) plus 27 additional studies that were not included in the NRC (2010) review. The EPA (2012a) Toxicological Review concluded that epidemiological data support a pattern of association between tetrachloroethylene exposure and bladder cancer, multiple myeloma, and non-Hodgkin's lymphoma. EPA (2012a) also concluded that epidemiological studies suggest possible associations with other cancers (esophageal, kidney, lung, liver, cervical, and breast cancer), but the data on these cancers were more limited and/or inconsistent. IARC (2014) concluded that "positive associations have been observed for cancer of the bladder" in humans.

Table 3-2 provides an overview of selected epidemiological studies, including information on study types (cohort, case-control), study populations (specific industries or general worker populations), exposure assessments (qualitative versus semi-quantitative, assessment methods), consideration of confounders, and study strengths and limitations. Studies were selected based on the following considerations: studies that EPA (2012a) relied upon to support conclusions regarding associations between tetrachloroethylene exposure and specific cancer types; studies that EPA (2012a) considered to have higher quality exposure

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Meta-analysis			
Vlaanderen et al. 2014; Dry cleaners and launderers; meta-analysis of 3 cohort studies and 11 case-control studies	Job titles; no quantitative exposure	Smoking not considered in all studies	Strengths[b]: dry cleaners were primarily exposed to tetrachloroethylene; lower meta-relative risk for combined launderers and dry cleaners compared to dry cleaners only indicates that launderers may have received little or no exposure to tetrachloroethylene Limitations[b]: job title classification provides little information on exposure estimates
Cohort studies			
Andersen et al. 1999; Dry cleaners and launderers (Denmark, Finland, Norway, Sweden)	Occupational history; no quantitative exposure	Age	Strengths: data from compulsory census; accuracy in cancer incidence data Limitation: lack of lifetime occupational histories; inability to differentiate between launderers and dry cleaners
Anttila et al. 1995; Workers (Finland)	Blood levels of tetrachloroethylene; no quantitative exposure	None reported	Strengths: long follow-up period (26 years); data obtained from Finnish registries Limitations: low power for its analysis of tetrachloroethylene; low tetrachloroethylene blood levels; did not consider confounders; did not infer lifetime exposure based on blood tetrachloroethylene; potential exposure to multiple solvents
Blair et al. 2003; Dry cleaners and launderers (United States)	Union records; no quantitative exposure	None reported	Strengths: tetrachloroethylene exposure estimated by employment duration and intensity Limitations: confounders not reported; inability to determine how many workers were exposed to tetrachloroethylene; lack of detailed job history; possible misclassification because death certificates used to determine cause of death

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Boice et al. 1999; Aircraft workers (United States)	JEM; no quantitative exposure	Birth date; race; sex; duration of exposure; date first employed; employment end date	Strengths: large population; long follow-up period (20–37 years) Limitations: no adjustment for smoking; assumption of living vital status for approximately 7% of the cohort was incorrect; inclusion of subjects with intermittent exposures (likely have low-exposure potential)
Calvert et al. 2011; Dry cleaners and launderers (United States)	Union records; duration of employment and latency periods; no quantitative exposure	None reported	Strengths: large study size; exposure based on duration and intensity Limitations: confounders not considered; work histories not updated after 1982; full latency not available for all participants; smoking and alcohol consumption not considered
Lipworth et al. 2011; Aircraft manufacturers (United States)	JEM; no quantitative exposure	Race; sex; age; calendar year; duration of employment; specific occupation; exposure to other solvents	Strengths[b]: large study size; complete follow-up; comprehensive qualitative exposure assessment Limitations[b]: no quantitative exposure; no information on smoking and alcohol consumption
Lynge and Thygesen 1990; Dry cleaners, launderers, textile dye workers (Denmark)	Occupation based on census codes; no quantitative exposure	Age	Strengths: examined dry cleaners and launderers separately Limitations: prevalence of participants with “low-exposure;” no adjustment for smoking or alcohol consumption; exposure based on census data and not on life-long employment
Pukkala et al. 2009; Dry cleaners and launderers (Denmark, Finland, Iceland, Norway, Sweden)	Occupation based on census records; no quantitative exposure	Age	Strengths: large study population; use of data from census records to identify job titles and from national cancer registries for cancer incidence Limitations: analyses did not include examination of duration of employment; occupational classifications do not allow evaluation according to differing exposure intensities or multiple solvents

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Radican et al. 2008; Aircraft maintenance workers (United States)	JEM; no quantitative exposure	Age; gender; race	Strengths: large study population; long follow-up period (1952–2000) Limitations: small number of tetrachloroethylene-exposed deaths and reduced statistical power; did not control for exposure to other chemicals and solvents; exposure based on job descriptions and other historical information may result in misclassification of exposure
Selden and Ahlborg 2011; Female dry cleaners and launderers (Sweden)	Participant questionnaire; union records; no quantitative exposure	Smoking; alcohol consumption	Strengths: prospective design; exposure information collected before follow-up; long follow-up period (>20 years); smoking and alcohol consumption considered Limitations: no quantitative exposure data; average age of cohort not reported; lack of full occupational history
Silver et al. 2014; Microelectronics and Machine workers (United States)	JEM; no quantitative exposure	Age; sex; chemical exposures; birth cohort; changes in exposure; levels; time since last exposure; hire era; employment duration prior to 1969	Strengths[b]: long follow-up period (>25 years); Limitations[b]: young age of cohort (only17% deceased); lack of exposure data on workers prior to 1974; incomplete exposure data; lack of data on variability of exposure
Pooled case-control studies			
Morton et al. 2014; Dry cleaners; pooled analysis of data from 20 studies	Self-administered questionnaire on occupation; no quantitative exposure	Age; ethnicity; sex; study origin of data	Strengths[b]: pooled data provided large sample cases; examined risk factor heterogeneity for NHL subtypes Limitations[b]: did not review original pathology reports and materials for all cases; to harmonize data, exposure categories were broadened; wide variability of sample size among exposures may have affected ability to detect heterogeneity for certain risk factors; potential for biased risk estimates due to biased study population selection; inaccurate recall of exposures
't Mannetje et al. 2015; Workers; pooled analysis of data from 10 studies	JEM; no quantitative exposure	Age; sex; study center by region; smoking; NHL subtype	Strengths[b]: pooled data provided larger sample cases; used uniform classification of NHL diagnosis across data sets from each study Limitations[b] using only job title for exposure does not include exposure variations

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Case-control studies			
Charbotel et al. 2013; Female workers (France)	TEM; no quantitative exposure	SES; SOC; gynecological history; BMI	Strengths[b]: reduced selection and measurement biases by recruiting controls from the same physicians and geographic location as cases Limitations[b]: low mean age of subjects (36 years); cases and controls differed on HPV infection (cases: 100%; controls: 5.8%)
Christensen et al. 2013; Workers (Canada)	Subject reported job history and expert assessment; no quantitative exposure	Age; income; educational; ethnicity (French-Canadian versus others); questionnaire respondent (self versus proxy); smoking; coffee intake; aromatic amines exposure	Strengths[b]: reliable semiquantitative exposure information, based on expert assessment after detailed interviews regarding occupational history; controlled for potentially important confounders Limitations[b]: no quantitative exposure measurements of personal exposure to each solvent; estimated temporal trends and industry and occupation-specific profiles; potential confounding by unmeasured risk factors or residual confounding by measured risk factors
Dosemeci et al. 1999; Workers (United States)	JEM; no quantitative exposure	Age; smoking; hypertension; diuretic use; use of anti-hypertension medication; BMI	Strengths: none reported Limitations: small number of exposed subjects; potential survival bias; lack of a lifetime occupational history and duration of employment
Gold et al. 2010, 2011; Workers (United States)	JEM; hours of weekly exposure; estimated cumulative exposure	Sex; age; race; education; cancer registry	Strengths: use of detailed occupational information to improve assessment of solvent exposure Limitations: low participation rates; inability to examine race, SES, and solvent exposure; potential for selection bias; small numbers of subjects with exposure to individual chlorinated solvents with limited statistical power
Hadkhale et al. 2017; Workers (Finland, Iceland, Norway, Sweden)	JEM; estimated quantitative exposure	Age; sex; quantified exposures to ionizing radiation, asbestos, benzo[a]pyrene, diesel engine exhaust and sulfur dioxide	Strengths[b]: large study population; controlled for exposure to multiple other agents and variation in exposure levels over time Limitations[b]: no information about smoking
Lynge et al. 2006;	JEM, refined with	Smoking; alcohol use	Strengths: conducted in time-period when

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Dry cleaners and launderers (Denmark, Finland, Norway, Sweden)	questionnaire within dry cleaner settings; includes mean exposure concentrations, but results not based on quantitative exposure		tetrachloroethylene was used as the main solvent; population-based design; controlled for smoking in bladder cancer analysis; examination of dry cleaner versus other dry-cleaning tasks Limitations: lack of personal exposure monitoring data; full employment history not assessed for all participants; large number of "next-of-kin interviews" in cases from Sweden and Norway
Mattei et al. 2014; Workers (France)	JEM; no quantitative exposure	Age at interview; department; smoking history; number of jobs held; occupational exposure to asbestos; SES	Strengths[b]: large number of subjects Limitations[b]: only five subjects exposed to tetrachloroethylene-only; almost all participants exposed to other solvents; small number of exposed women compared to exposed men, leading to wide CIs.
Neta et al. 2012; Workers (United States)	JEM/JTEM; no quantitative exposure	Age at diagnosis; sex; race/ethnicity; hospital site and residential zone; smoking; education; estimated cumulative occupational exposures to lead, magnetic fields, herbicides, and insecticides	Strengths[b]: hospital-based design allowed for rapid ascertainment of newly diagnosed cases; interview of cases and controls under similar conditions; robust exposure assessment, including exposure intensity; assessed cumulative exposure to other agents Limitations[b]: limited power to evaluate exposure-response relationships given the small numbers of subjects; potential exposure misclassification; impaired recall ability of glioma patients regarding past exposures
Pesch et al. 2000a; Workers (Germany)	JEM/JTEM; hospital records; no quantitative exposure	Age; smoking; study center	Strengths: population-based selection of controls; use of a JEM and a JTEM to assess exposure Limitations: lower response rate of controls compared to cases; reliance of self-reported information for exposure assessment

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Pesch et al. 2000b; Germany (Germany)	JEM/JTEM; hospital records; no quantitative exposure	Age; smoking; study center	Strengths: population-based selection of controls; use of a JEM and a JTEM to assess exposure Limitations: grouping of bladder, ureter, and renal pelvis neoplasms; lower response rate of controls compared to cases; reliance of self-reported information for exposure assessment
Purdue et al. 2017; Workers (United States)	JEM/JTEM; exposure duration; estimated probability of exposure	Study center; age at reference; race; sex; education; smoking; BMI; history of hypertension	Strengths[b]: obtained detailed information on workplace tasks; assessed occupational exposure to six different chlorinated solvents Limitations[b]: number of highly-exposed participants for each solvent was small; potential for recall and selection bias; low response rate among controls
Ruder et al. 2013; Workers (United States)	JEM; no quantitative exposure	Sex; age; age group; education	Strengths[b]: large number of histologically confirmed gliomas; use of population-based controls; estimation of workplace exposure by industrial hygienists blinded to the case-control status of participants Limitations[b]: lack of detailed information from participants regarding occupational exposures; assumption that workplace exposure levels were within ranges reported in the literature
Talibov et al. 2017; Workers (Finland, Iceland, Norway, Sweden)	JEM; estimated cumulative exposure	Exposure to toluene, benzene, methylene chloride, other organic solvents, perchloroethylene, trichloroethylene, 1,1,1-trichloroethane, formaldehyde, and ionizing radiation	Strengths[b]: completeness and accuracy of cancer incidence data; accuracy of occupational classification Limitations[b]: potential exposure misclassification; potential variability in exposure intensity; no information on annual job histories

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Vizcaya et al. 2013; Workers (Canada)	JEM; no quantitative exposure	Age; census median income; ethnicity (French versus others); educational attainment; questionnaire respondent (self versus proxy); smoking; exposure to lung carcinogens (asbestos, crystalline silica, chromium VI, arsenic compounds, diesel exhaust emissions, soot, wood dust, and benzo(a)pyrene)	Strengths[b]: relatively high sample size; high participation rates; histological confirmation of diagnoses, intensive expert-based exposure assessment blinded to case/control status; considered confounders Limitations[b]: limited statistical power; high proportion of proxy responses; no measured exposure
Vlaanderen et al. 2013; Workers (Finland, Iceland, Norway, Sweden)	JEM; estimated cumulative exposure	sex	Strengths[b]: examined cumulative exposure tertiles based on JEM Limitations[b]: no adjustment for potential confounders; general population had low exposure prevalence; potential for misclassification error from JEM

[a]Unless otherwise noted, study strengths and limitations were noted by EPA (2012a).
[b]Study strengths and limitations were noted by the study authors.

BMI = body mass index; CI = confidence interval; HVP = human papilloma virus; JEM = job-exposure matrix; JTEM = job/task-exposure matrix; NHL = non-Hodgkin's lymphoma; SES = socio-economic status; SOC = socio-occupational category TEM = task-exposure matrix

assessments; and studies published after EPA (2012a), with higher quality exposure assessments (as defined by EPA 2012a). EPA (2012a) considered higher quality exposure assessments to include the following: biological monitoring data; use of job-exposure matrix (JEM) based on historical data or job title and/or tasks; and use of union records or other data for specific jobs/tasks (Guyton et al. 2014). For additional details and reviews of these and other epidemiological studies assessing the potential carcinogenicity of tetrachloroethylene, the EPA Integrated Risk Information System (IRIS) Toxicological Review for Tetrachloroethylene (EPA 2012a), IARC (2014), and NRC (2010) may be consulted. Additional information is also provided in an assessment on studies of drinking water contaminants, including tetrachloroethylene, at the U.S. Marine Corp Base at Camp Lejeune conducted by ATSDR (2017b).

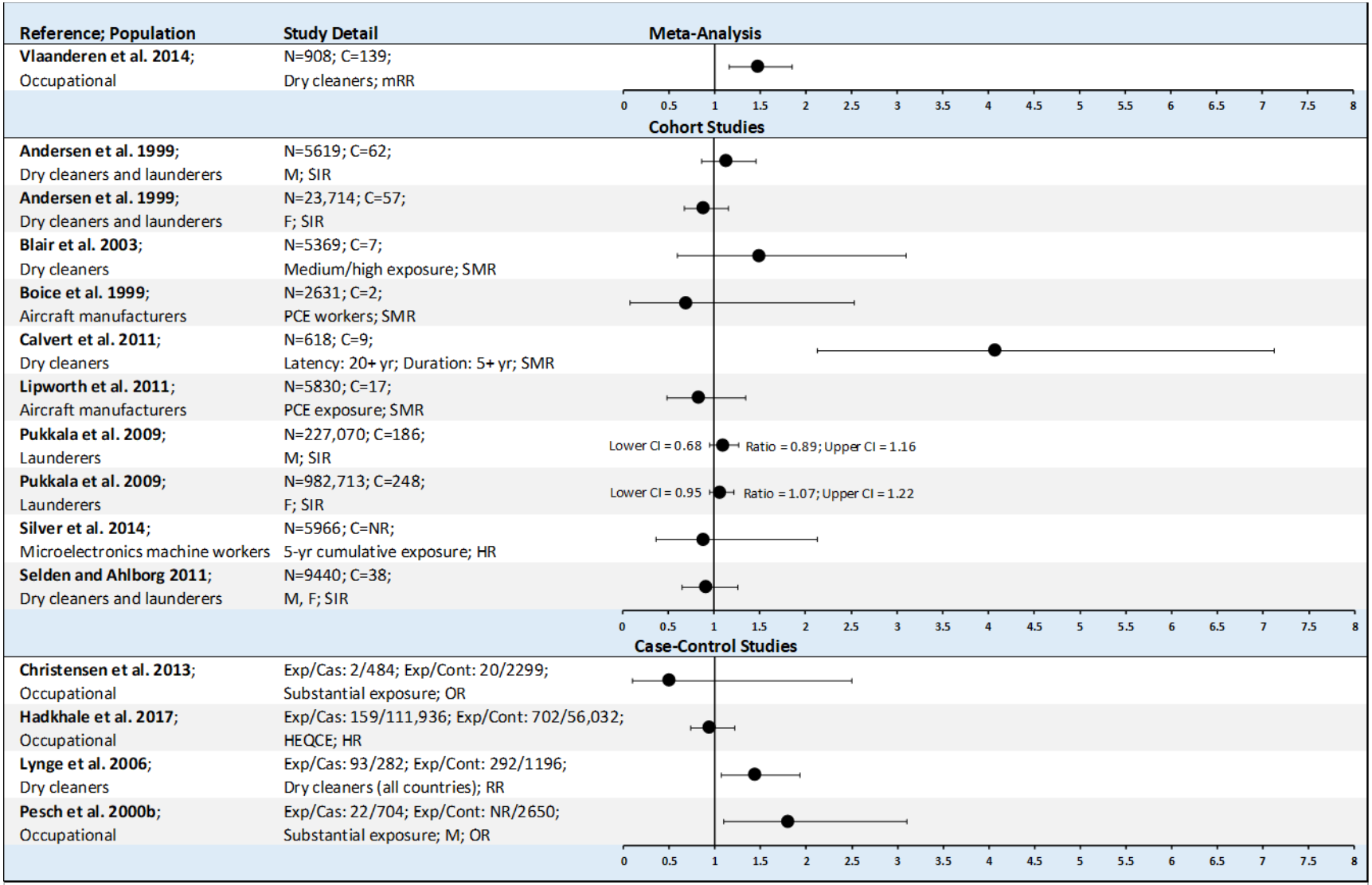
As summarized in Table 3-2, selected studies included 1 meta-analysis, 2 pooled case-control studies, 11 cohort studies, and 15 case-control studies. Study populations were from several countries, including the United States, Canada, Germany, France, and individual Nordic countries. In addition, several studies examined combined populations from multiple Nordic countries. Cohort studies evaluated dry cleaners and launderers, aircraft manufacturers and maintenance workers, machine workers, and general worker populations. Two cohort studies were follow-ups of other studies; Lipworth et al. (2011) is a follow-up of the Boice et al. (1999) study of aircraft workers, and Pukkala et al. (2009) is a follow-up of the Anderson et al. (1999) study, expanding the Nordic study population to include participants from Iceland. Case-control studies examined general worker populations with exposure to tetrachloroethylene, except for the study by Lynge et al. (2006), which examined dry cleaners and launderers.

Exposure assessment methods are listed in Table 3-2. It is important to note that none of the exposure assessments included individual monitoring data or rigorous monitoring of tetrachloroethylene concentrations in individual workplaces. A few case-control studies provided semi-quantitative estimates for cumulative exposure, based on JEM, with estimates of average exposure per specific occupation (Gold et al. 2010, 2011; Hadkhale et al. 2017; Talibov et al. 2017; Vlaanderen et al. 2013). The remaining studies provided qualitative descriptions of exposure (e.g., exposed/not exposed, probable, substantial, low-moderate-high) based on JEM and/or occupational history from union records, census records, and/or participant questionnaires. For most study participants, it is likely that exposure included other solvents or chemicals. For workers in the dry cleaning industry, exposure is primarily to tetrachloroethylene (Vlaanderen et al. 2014).

The potential influence of confounding factors is an important consideration in the interpretation of these epidemiological studies. As shown in Table 3-2, confounders were not consistently addressed across studies. Studies by Neta et al. (2012) and Vizcaya et al. (2013) provided the most comprehensive assessment of confounders, with other studies considering several confounders (Christensen et al. 2013; Hadkhale et al. 2017; Lipworth et al. 2011; Mattei et al. 2014; Silver et al. 2014). However, other studies considered only a few confounders or did not assess any confounders. For assessments of the carcinogenic potential of tetrachloroethylene, it is important to consider the potential influence of exposure to other solvents and chemicals, including smoking tobacco, an important confounder for bladder and lung cancer (EPA 2012a; Guyton et al. 2014). Studies by Christensen et al. (2013), Mattei et al. (2014), Neta et al. (2012), and Vizacya et al. (2013) considered both smoking and exposure to solvents and other chemicals. Other studies considered smoking (Dosemeci et al. 1999; Lynge et al. 2006; Pesch et al. 2000a, 2000b; Selden and Ahlborg 2011) or exposure to solvents and other chemicals (Hadkhale et al. 2017; Lipworth et al. 2011; Silver et al. 2014; Talibov et al. 2017).

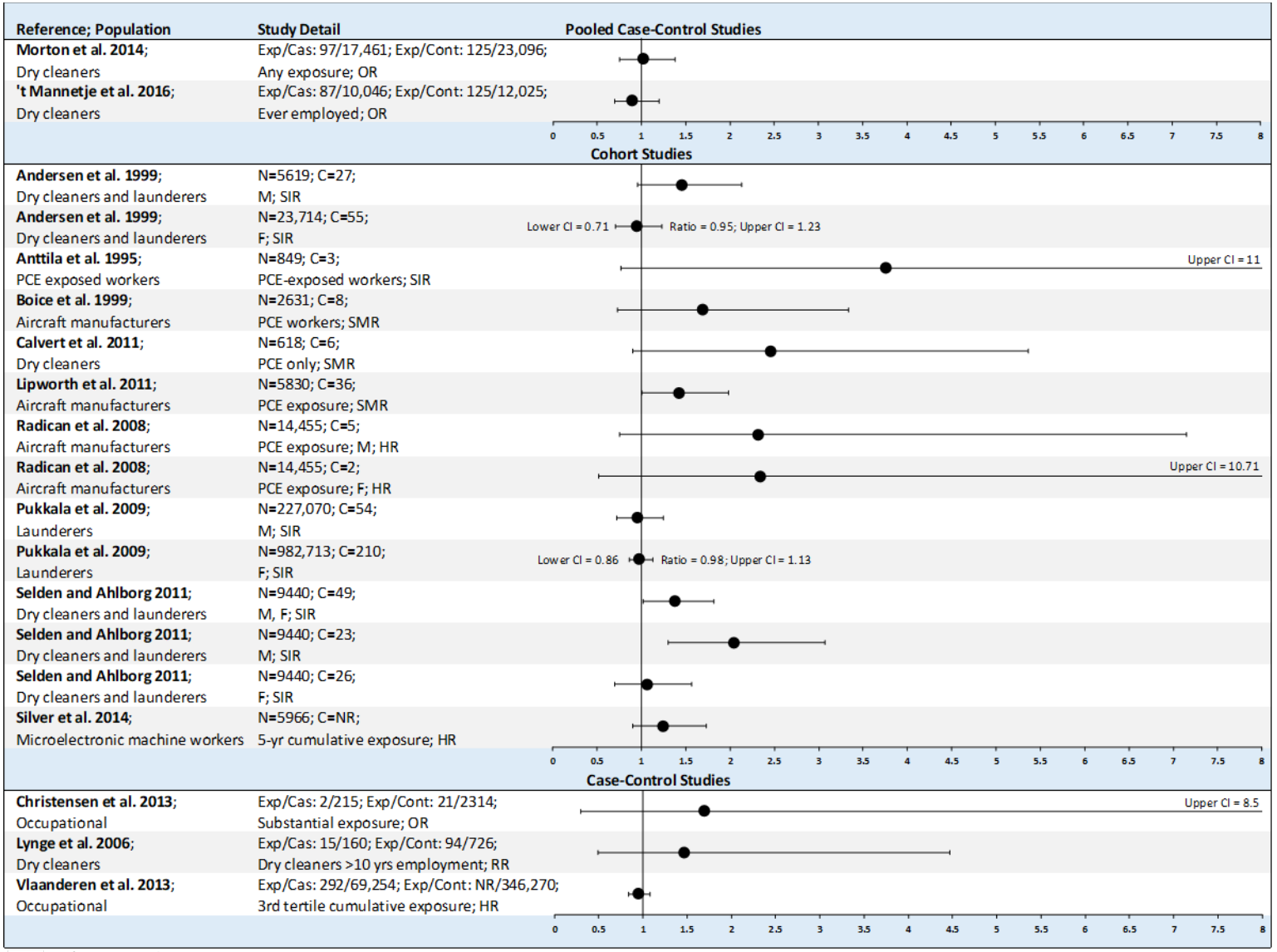
Study results based on cancer type are shown in the following figures: bladder cancer, Figure 3-2; non-Hodgkin's lymphoma, Figure 3-3; multiple myeloma, Figure 3-4; kidney cancer, Figure 3-5; leukemias/lymphomas, Figure 3-6; liver cancer, Figure 3-7; pancreatic cancer, Figure 3-8; prostate cancer, Figure 3-9; breast cancer, Figure 3-10; cervical cancer, Figure 3-11; esophageal cancer, Figure 3-12; rectal cancer, Figure 3-13; lung cancer, Figure 3-14; and cancer of the brain/central nervous system, Figure 3-15. These figures include information on exposure type (e.g., dry cleaners, general occupational exposure), number of participants, cancer incidence, and study statistics (e.g., risk values and confidence intervals) as reported by the study authors. For studies that evaluated males, females, and combined males and females, if risk values were similar, results for combined males and females are presented; however, if results differed between these groups, values for all groups are presented. For studies evaluating males and females separately (with no combined group), data for both are presented. Exposure classifications (e.g., qualitative exposure or classification of estimated cumulative exposure) for presented risk values also are included. If specific data were adjusted for exposure duration or latency period, this is noted.

Figure 3-2. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Bladder Cancer



C = number with bladder cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HEQCE = high estimated quantitative cumulative exposure; HR = hazard ratio; M = males; mRR = meta-relative risk; N = population size; NR = not reported; OR = odds ratio; PCE = tetrachloroethylene; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

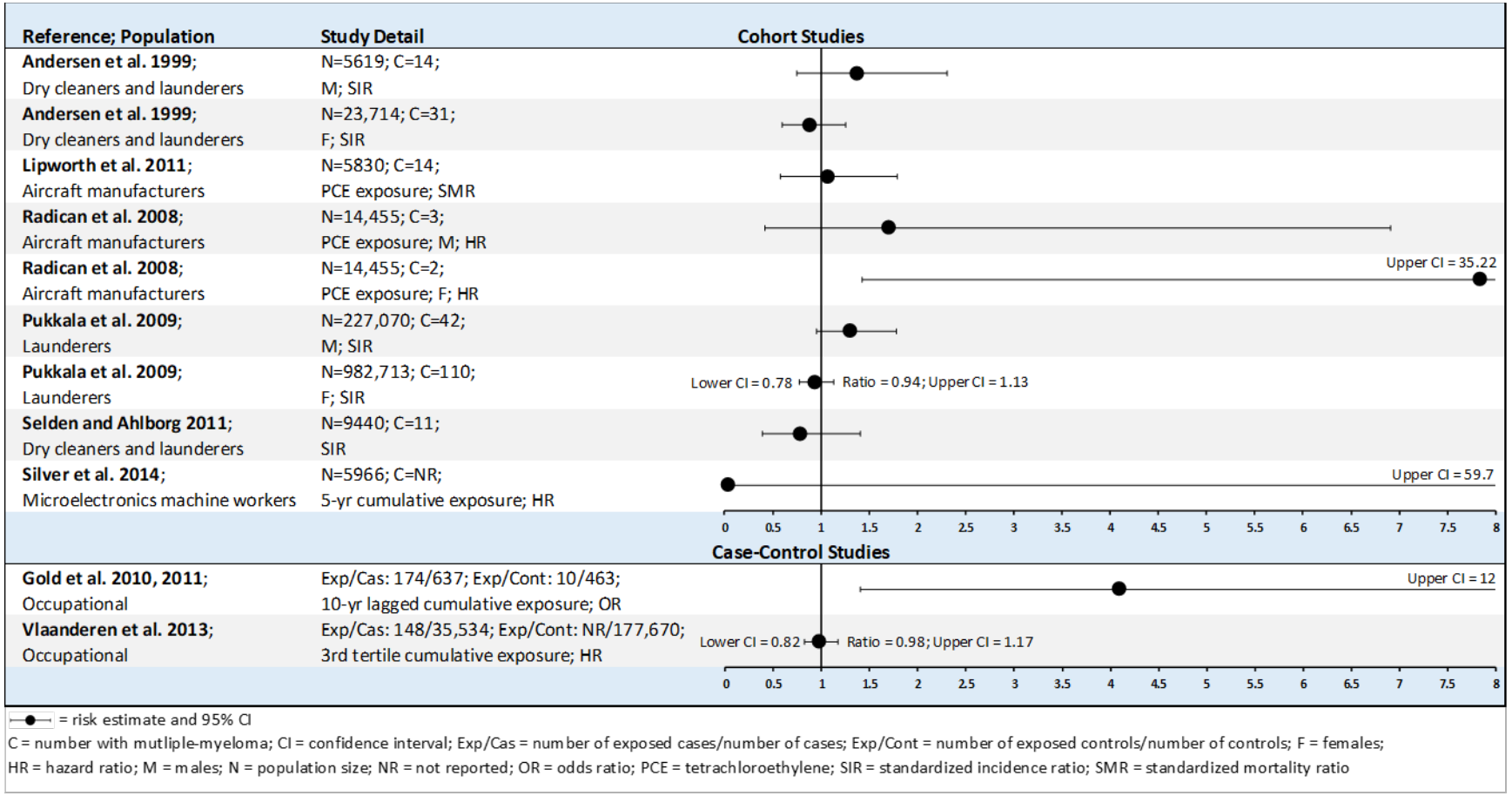
Figure 3-3. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Non-Hodgkin's Lymphoma



= risk estimate and 95% CI

C = number with non-Hodgkin's lymphoma; CI = confidence interval; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; N = population size; NR = not reported; OR = odds ratio; PCE = tetrachloroethylene; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-4. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Multiple Myeloma



= risk estimate and 95% CI

C = number with mutliple-myeloma; CI = confidence interval; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; N = population size; NR = not reported; OR = odds ratio; PCE = tetrachloroethylene; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-5. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Kidney Cancer

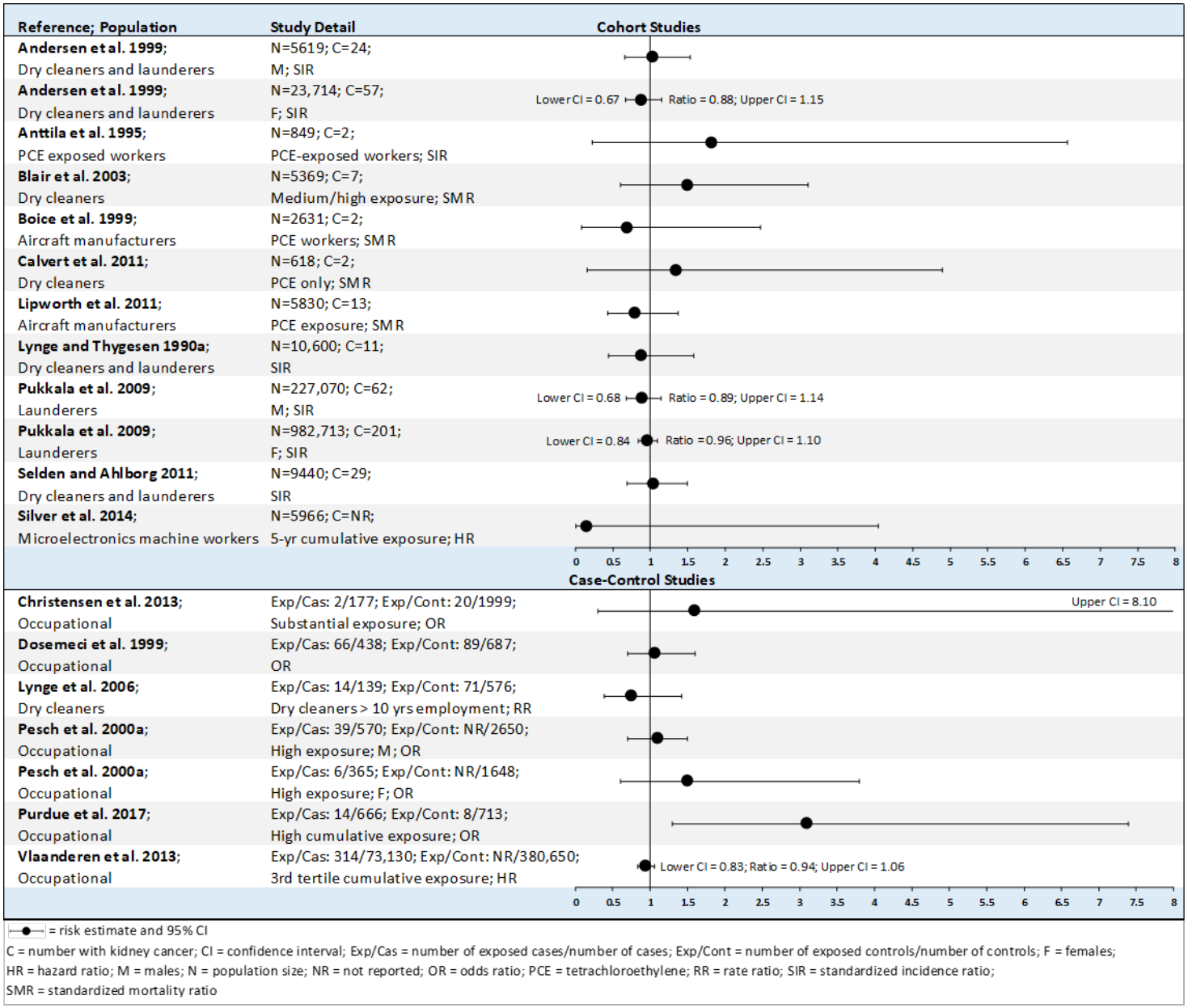


Figure 3-6. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Leukemia-Lymphoma

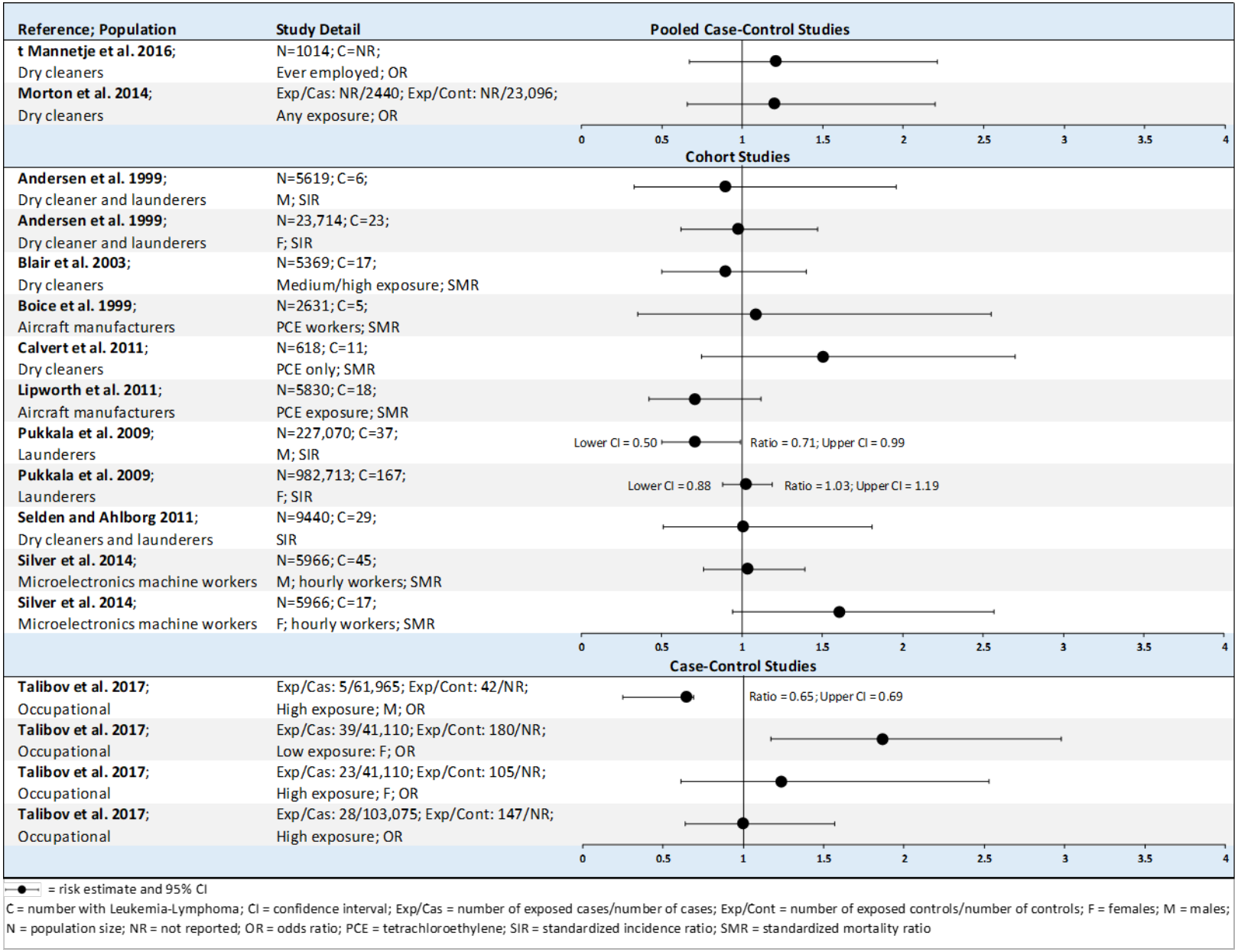
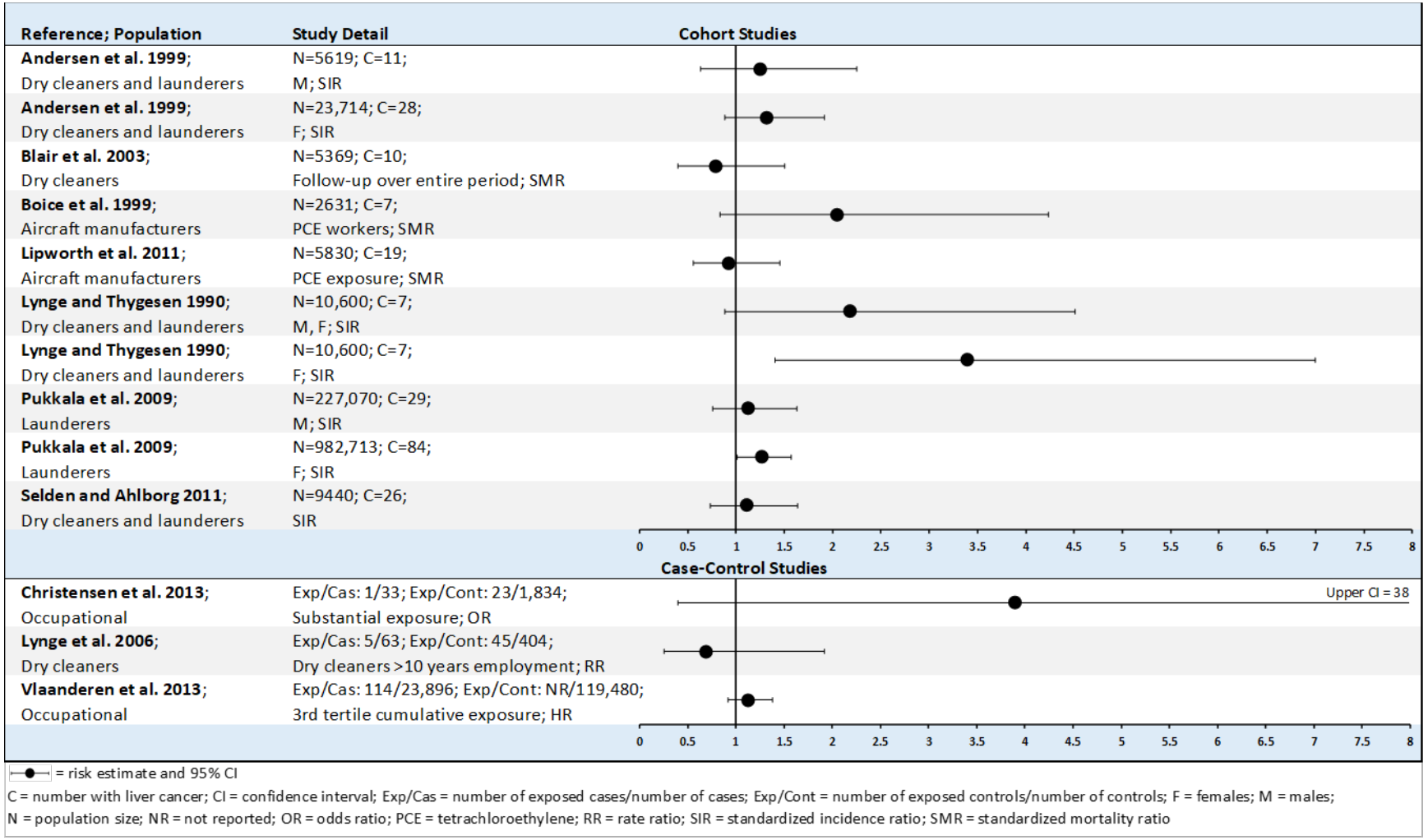
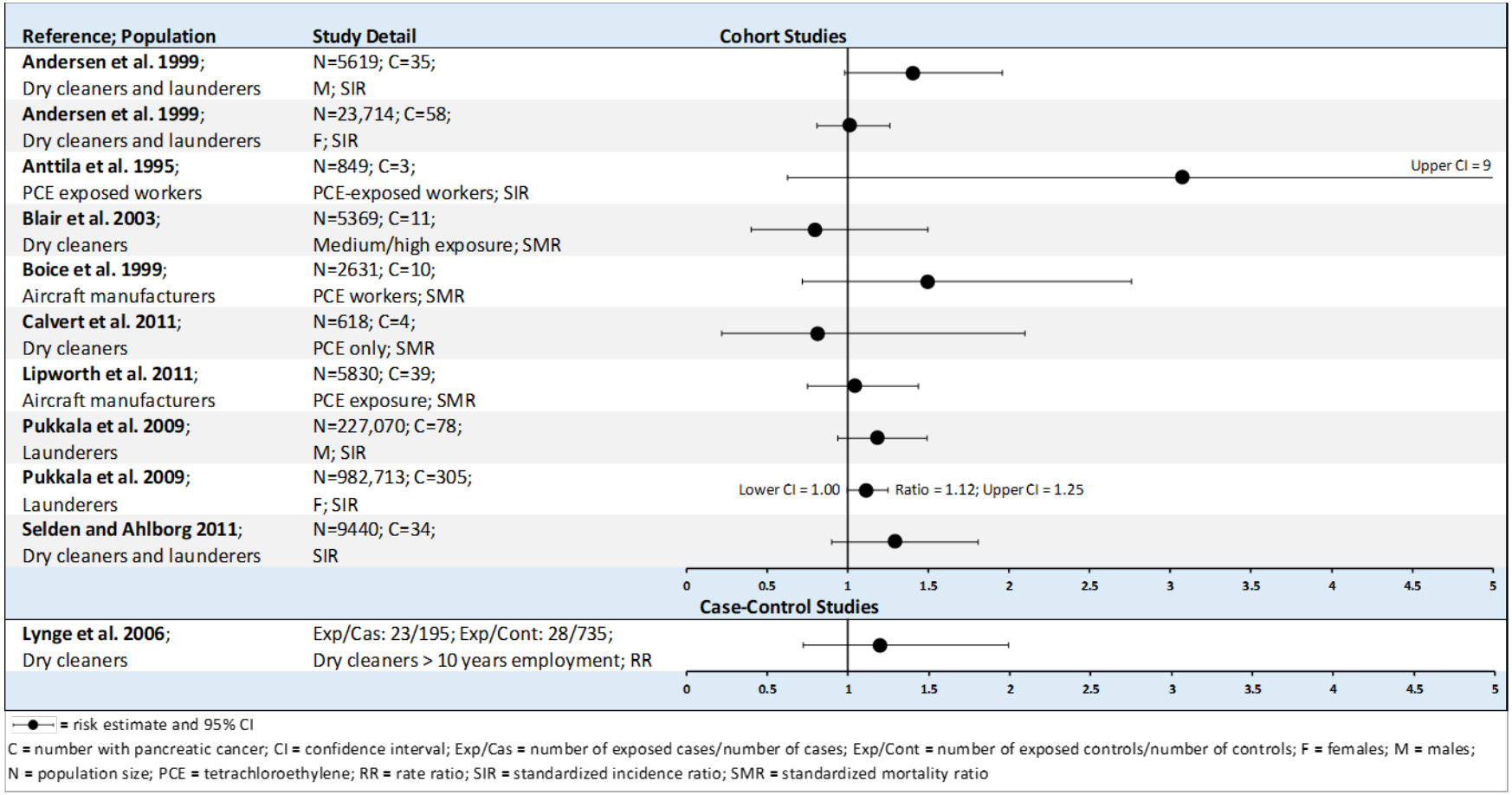


Figure 3-7. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Liver Cancer



C = number with liver cancer; CI = confidence interval; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; M = males; N = population size; NR = not reported; OR = odds ratio; PCE = tetrachloroethylene; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

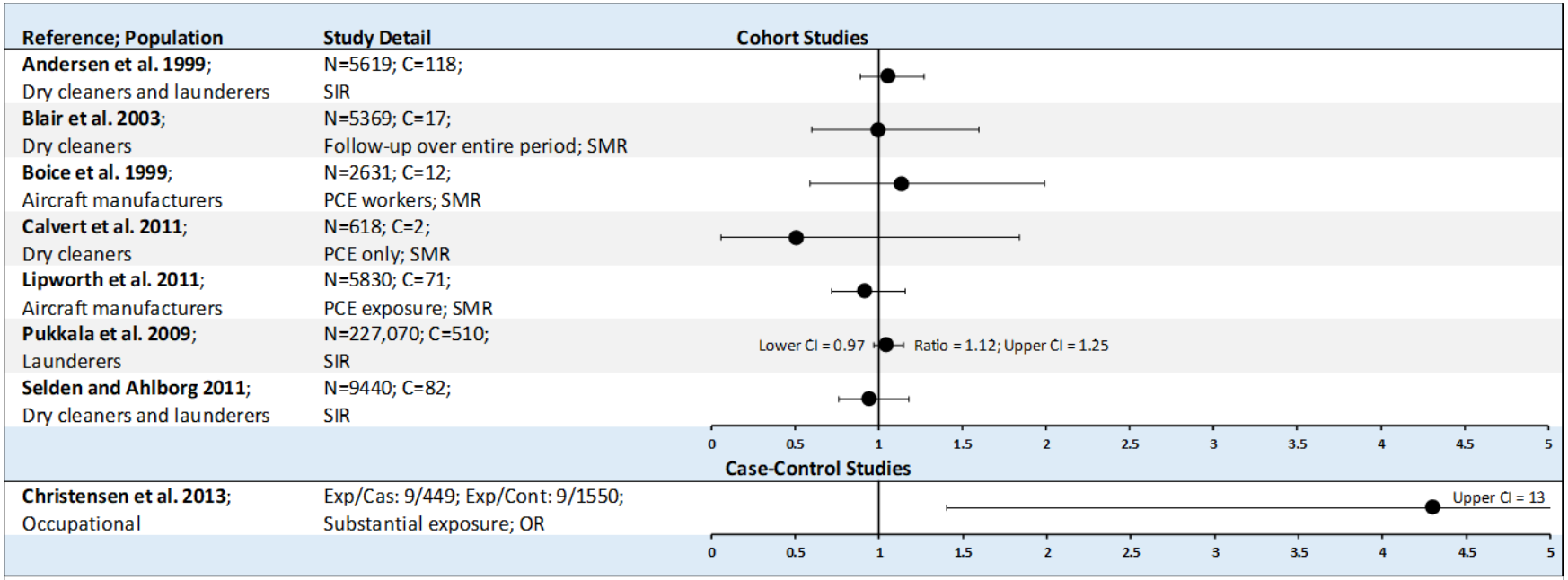
Figure 3-8. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Pancreatic Cancer



= risk estimate and 95% CI

C = number with pancreatic cancer; CI = confidence interval; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; M = males; N = population size; PCE = tetrachloroethylene; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-9. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Prostate Cancer

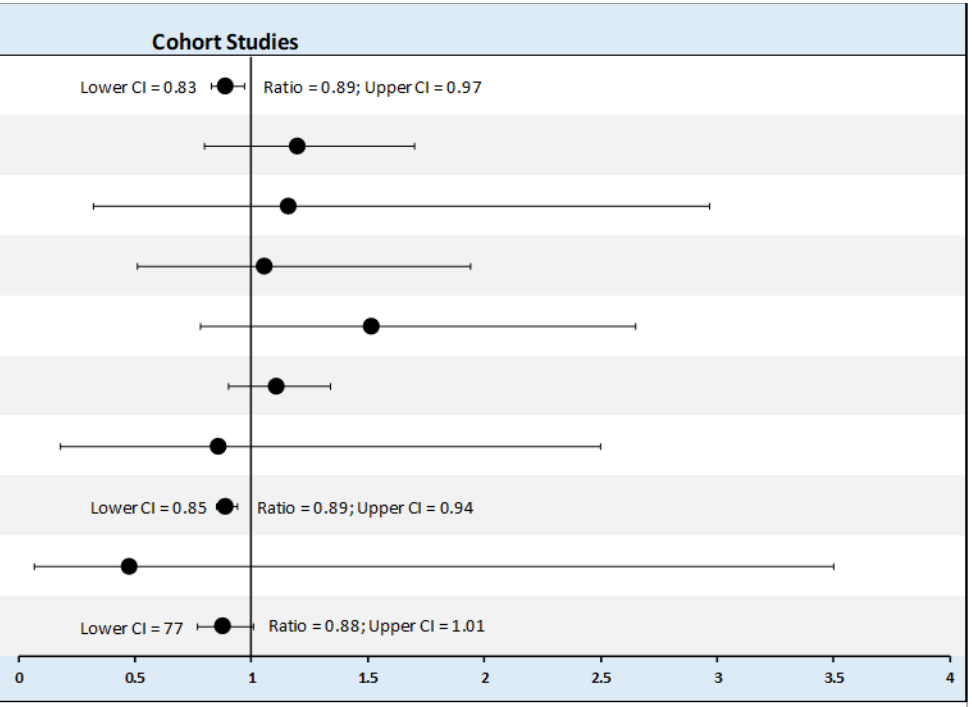


= risk estimate and 95% CI

C = number with prostate cancer; CI = confidence interval; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; M = males; N = population size; OR = odds ratio; PCE = tetrachloroethylene; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-10. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Breast Cancer

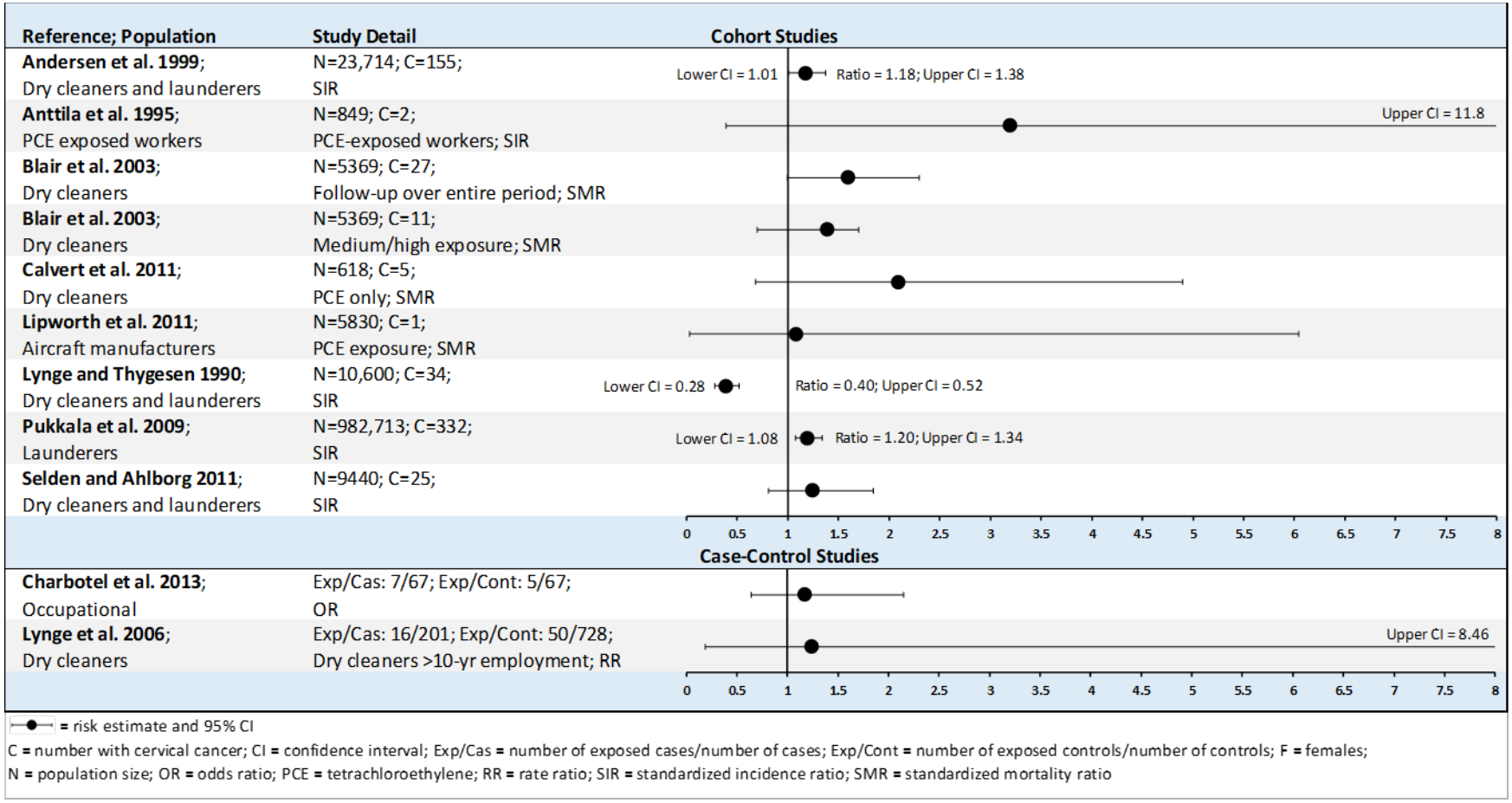
Reference; Population	Study Detail
Andersen et al. 1999; Dry cleaners and launderers	N=23,714; C=634; F; SIR
Blair et al. 2003; Dry cleaners	N=5369; C=29; Medium/high exposure; F; SMR
Boice et al. 1999; Aircraft manufacturers	N=2631; C=4; PCE workers; M, F; SMR
Calvert et al. 2011; Dry cleaners	N=618; C=10; PCE only; M, F; SMR
Lipworth et al. 2011; Aircraft manufacturers	N=5830; C=12; PCE exposure; M, F; SMR
Lynge and Thygesen 1990; Dry cleaners and launderers	N=10,600; C=94; F; SIR
Pukkala et al. 2009; Launderers	N=227,070; C=3; M; SIR
Pukkala et al. 2009; Launderers	N=982,713; C=1757; F; SIR
Radican et al. 2008; Aircraft manufacturers	N=14,455; C=1; PCE exposure; F; HR
Selden and Ahlborg 2011; Dry cleaners and launderers	N=9440; C=219; F; SIR



= risk estimate and 95% CI

C = number with breast cancer; CI = confidence interval; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; N = population size; PCE = tetrachloroethylene; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-11. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Cervical Cancer

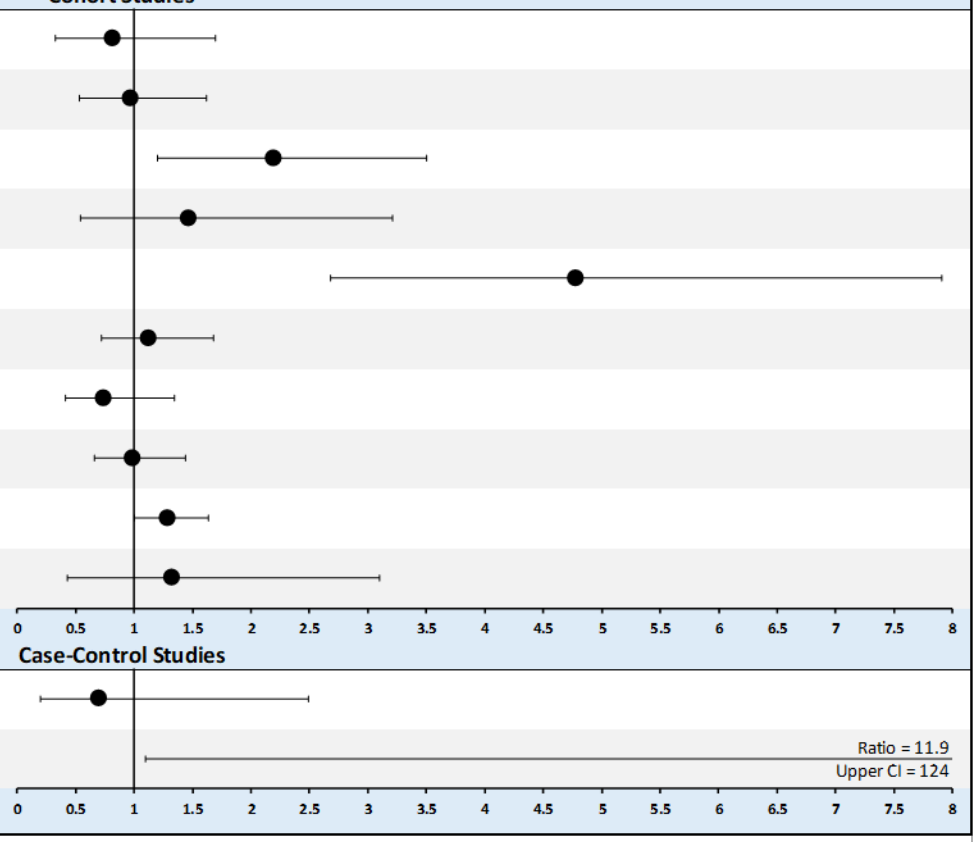


= risk estimate and 95% CI

C = number with cervical cancer; CI = confidence interval; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; N = population size; OR = odds ratio; PCE = tetrachloroethylene; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-12. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Esophageal Cancer

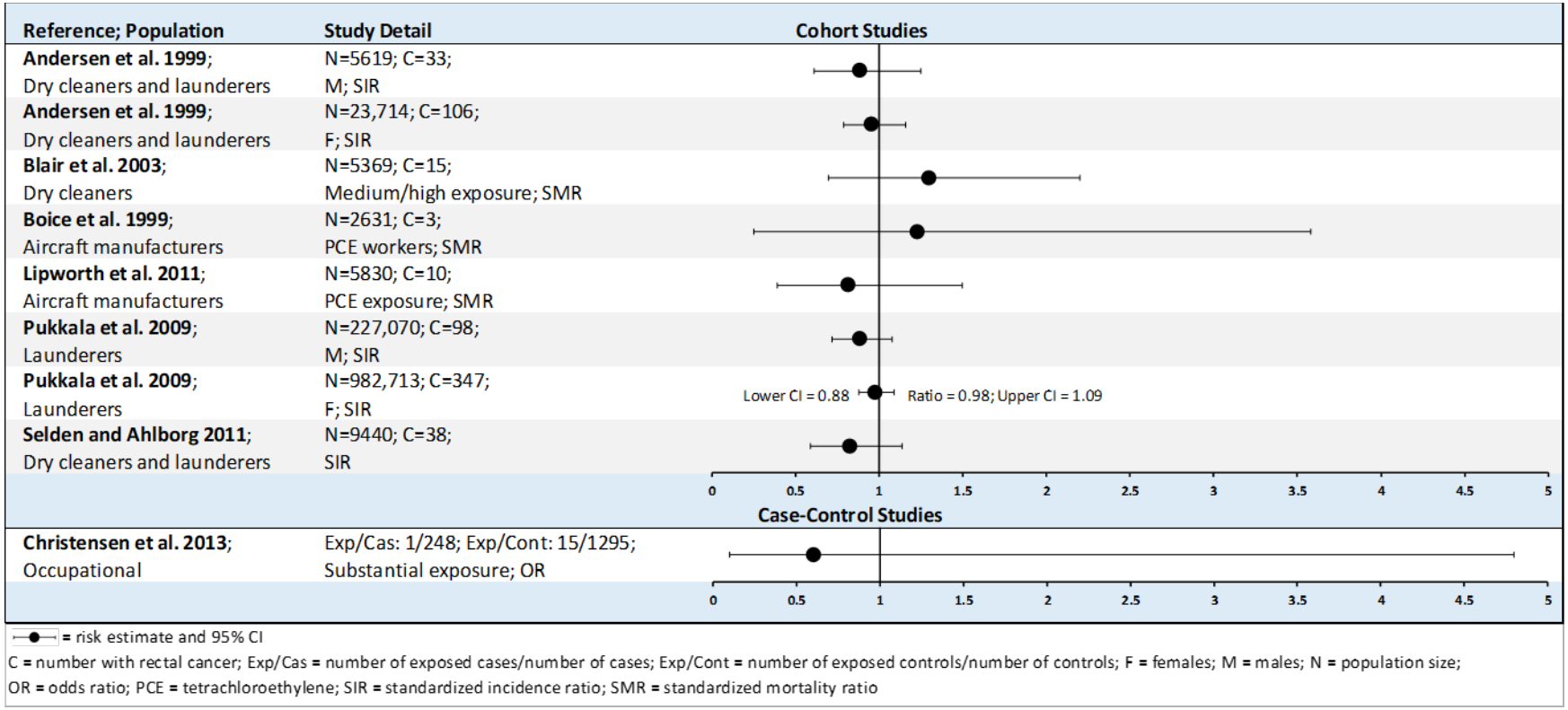
Reference; Population	Study Detail
Cohort Studies	
Andersen et al. 1999; Dry cleaners and launderers	N=5619; C=7; M; SIR
Andersen et al. 1999; Dry cleaners and launderers	N=23,714; C=14; F; SIR
Blair et al. 2003; Dry cleaners	N=5369; C=16; Medium/high exposure; SMR
Boice et al. 1999; Aircraft manufacturers	N=2631; C=6; PCE workers; SMR
Calvert et al. 2011; Dry cleaners	N=618; C=11; Latency: 20+ yr; Duration: 5+ yr; SMR
Lipworth et al. 2011; Aircraft manufacturers	N=5830; C=24; PCE exposure; SMR
Lynge and Thygesen 1990; laundry and dry cleaning workers	N=10,600; C=14; PCE exposure; M, F; SIR
Pukkala et al. 2009; Launderers	N=227,070; C=28; M; SIR
Pukkala et al. 2009; Launderers	N=982,713; C=67; F; SIR
Selden and Ahlborg 2011; Dry cleaners and launderers	N=9440; C=5; F; SIR
Case-Control Studies	
Lynge et al. 2006; Dry cleaners	Exp/Cas: 3/44; Exp/Cont: 27/288; Dry cleaners >10 years employment; RR
Vaughan et al. 1997; Dry cleaners	Exp/Cas: 2/109; Exp/Cont: 4/720; Cumulative exposure 1-29 ppm-yrs



= risk estimate and 95% CI

C = number with esophagael cancer; CI = confidence interval; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; M = males; N = population size; PCE = tetrachloroethylene; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

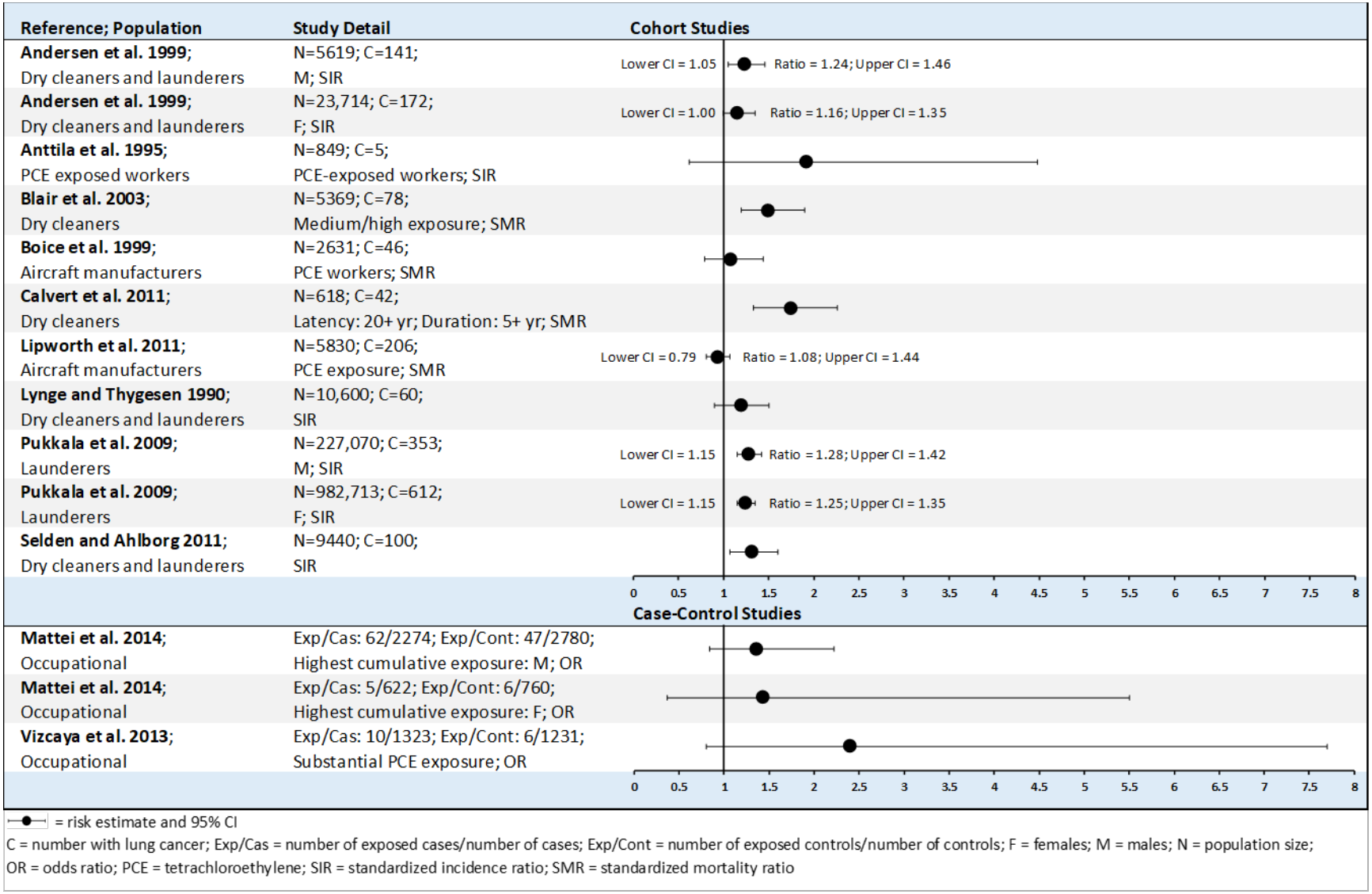
Figure 3-13. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Rectal Cancer



= risk estimate and 95% CI

C = number with rectal cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; M = males; N = population size; OR = odds ratio; PCE = tetrachloroethylene; SIR = standardized incidence ratio; SMR = standardized mortality ratio

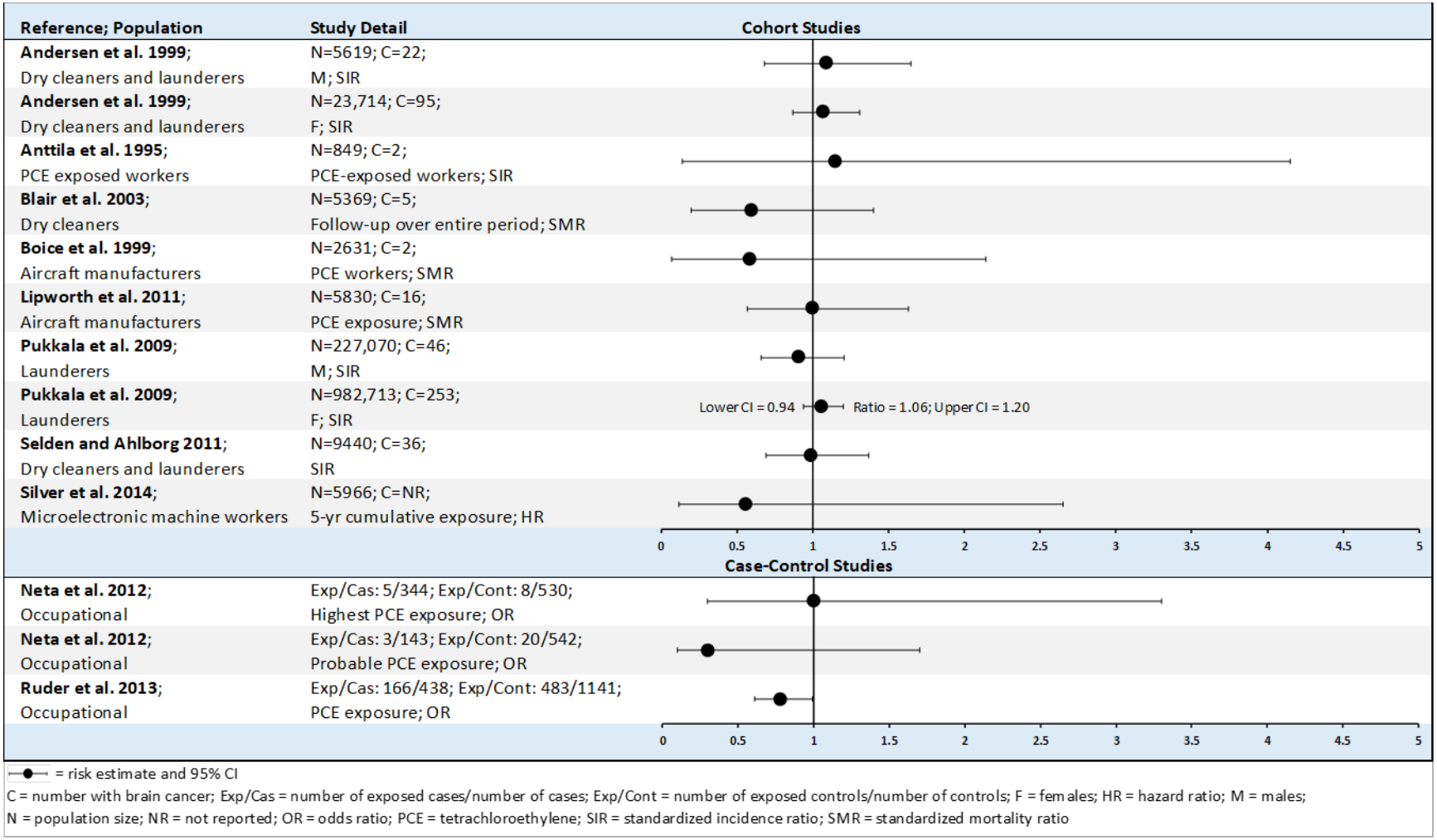
Figure 3-14. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Lung Cancer



= risk estimate and 95% CI

C = number with lung cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; M = males; N = population size; OR = odds ratio; PCE = tetrachloroethylene; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-15. Summary of Epidemiological Studies Evaluating Associations between Inhaled Tetrachloroethylene and Brain Cancer



= risk estimate and 95% CI

C = number with brain cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; N = population size; NR = not reported; OR = odds ratio; PCE = tetrachloroethylene; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Studies in Laboratory Animals. Studies in laboratory animals demonstrate increased risks of mononuclear cell leukemias (MCL) and liver tumors after chronic exposure to tetrachloroethylene (JISA 1993; NTP 1986). The cancer effect levels (CELs) for rats and mice are recorded in Table 3-1 and plotted in Figure 3-1.

Regarding the relevance of mononuclear cell leukemia in mice to humans, NRC (2010) noted that there is uncertainty regarding dose-response data in mice and the mode of action for mononuclear cell leukemia is poorly understood. Despite these concerns, NCR (2010) concluded that MCL in rats is relevant to humans. NRC (2010) also discussed relevance of liver tumors in mice to humans. Although the strain of mice (B6C3F1) used in NTP (1986) has a high background incidence of hepatic cancer, findings have been reproduced in different laboratories and data demonstrate a dose-response relationship. The NRC (2010) committee considered hepatic tumors in mice to be relevant to humans, although the mechanism of action needs to be established. The NTP (1986) and JISA (1993) studies are reviewed below.

A 103-week inhalation toxicity/carcinogenicity study of tetrachloroethylene was conducted using male and female F344 rats and B6C3F1 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 males and females (males: 28/50, 37/50, and 37/50 in control, 200 ppm, and 400 ppm groups, respectively; females: 18/50, 30/50, and 29/50 in control, 200 ppm, and 400 ppm groups, respectively). This neoplasm occurs spontaneously in F344 rats, and incidences of mononuclear cell leukemia 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 at that time concurred with NTP's (1986) conclusion that the incidence of rat leukemias was a valid basis for the characterization of "some evidence of carcinogenicity" in rats 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 (1/49, 3/49, and 4/50 in control, 200 ppm, and 400 ppm groups, respectively) 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 3-3).

Table 3-3. Hepatocellular Neoplasms in Mice Exposed to Tetrachloroethylene for 103 Weeks by Inhalation[a]

Study and tumor type	Control		100 ppm		200 ppm	
NTP 1986 (B6C3F1 mice)	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%)

	Control		10 ppm		50 ppm		250 ppm	
JISA 1993 (Crj:BDF1 mice)	Male	Female	Male	Female	Male	Female	Male	Female
Hepatocellular adenoma	7/50 (14%)	3/50 (6%)	13/50 (26%)	3/47(6%)	8/50 (16%)	7/49 (14%)	26/50 (52%)	16/49 (33%)
Hepatocellular carcinoma	7/50 (14%)	0/50	8/50 (16%)	0/47	12/50 (20%)	0/49	25/50 (50%)	14/49 (29%)
Hepatocellular adenoma or carcinoma	13/50 (26%)	3/50 (6%)	21/50 (42%)	3/47(6%)	19/50 (38%)	7/49 (14%)	40/50 (80%)	33/49 (67%)

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

Sources: JISA 1993; NTP 1986

NTP (1986) also reported increases in the incidence of testicular interstitial cell tumors and gliomas in rats. For testicular interstitial cell tumors, incidences in the control, 200 ppm, and 400 ppm groups were 35/50 (70%), 39/49 (80%), and 41/40 (82%), respectively, and showed a significant positive trend and statistically significant increases for each treatment group relative to controls. When interstitial cell tumors were combined with interstitial cell hyperplasia, the effect was "diminished," with combined incidences of 40/50 (80%), 45/49 (92%), and 45/90 (90%) in the control, 200 ppm, and 400 ppm groups, respectively. NTP (1986) concluded that the "marginal increase" in testicular interstitial cell tumors was not treatment-related because the incidences in all test groups were similar to historical controls (0). For gliomas in male rats, incidences in the control, 200 ppm, and 400 ppm groups were 1/50 (2%), 0/59 (0%), and 4/50 (8%), respectively, and showed a statistically significant positive trend, although the incidence of gliomas in 400 ppm group was not statistically increased compared to the control group. The time to first occurrence in males in the 400 ppm group was 88 weeks, compared to 104 weeks in controls. Gliomas were also observed in one female in the control group and two females in the 400 ppm group. Due to the lack of statistical significance in male rats exposed to 400 ppm compared to controls (pairwise test) and the occurrence of gliomas in the control group, NTP (1986) concluded that gliomas were not related to treatment with tetrachloroethylene.

Limitations of the NTP (1986) study include several instances of rats and mice loose from their cages within the exposure chambers, with the potential for small aberrations in exposure, as well as elevated incidences of mononuclear cell leukemia in control rats, and liver tumors in mice.

A similar 104-week inhalation toxicity/carcinogenicity study of tetrachloroethylene was conducted using male and female F344DuCrj rats and Crj:BDF1 mice (JISA 1993). Exposure levels were 0, 50, 200, or 600 ppm tetrachloroethylene for rats and 0, 10, 50, or 250 ppm tetrachloroethylene for mice. In rats, there was a dose-related trend in the incidence of monocytic leukemia of the spleen (males: 11/50, 14/50, 22/50, 27/50; females: 10/50, 17/50, 16/20, 19/50). This increase was statistically significant only in male rats exposed to 600 ppm. In mice, there was a dose-related trend in the incidences of hepatocellular adenoma (males 7/50, 13/50, 8/50, 26/50; females: 3/50, 3/47, 7/49, 16/49) and carcinoma (males: 7/50, 8/50, 12/50, 25/50; females: 0/50, 0/47, 0/49, 14/49). Increased incidences of hepatocellular adenoma and carcinoma were statistically significant in both sexes exposed to 250 ppm (see Table 3-3). Dose-related trends were also noted for incidences of tumors of the Harderian gland and hemangioendotheliomas of the liver and spleen in males, but the incidences in treatment groups were not significantly different compared to controls (pairwise test) at any exposure level.

3.2.2 Oral Exposure

3.2.2.1 Death

Oral exposure to large doses of tetrachloroethylene may lead to death from central nervous system depression. While no reliable information in humans is available, rats and mice have died after intermediate-duration exposures as low as 1,780 and 1,000 mg/kg/day, respectively (NCI 1977; Philip et al. 2007).

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 of the female rats treated with a single dose of 5,000 mg tetrachloroethylene/kg died (Berman et al. 1995). Philip et al. (2007) reported an oral LD_{50} of 4,500 mg/kg tetrachloroethylene when administered in 5% Emulphor to male Swiss-Webster mice; deaths occurred between 72 and 96 hours postdosing. An oral LD_{50} of 8,139 mg/kg was reported for mice treated with undiluted tetrachloroethylene (Wenzel and Gibson 1951).

A single death was observed among five female Wistar rats given daily gavage doses of 2,400 mg/kg/day tetrachloroethylene in corn oil in a 32-day study (Jonker et al. 1996). The timing and cause of death were not reported, but the rats in this group exhibited signs of severe central nervous system depression immediately after dosing.

When 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 (NCI 1977). Ten percent lethality (2/20) was observed in male Swiss Webster mice given daily gavage doses of 1,000 mg/kg/day tetrachloroethylene in 5% Emulphor for 1–30 days; no deaths occurred at the lower doses of 150 or 500 mg/kg/day (Philip et al. 2007). The timing of deaths was not reported, but the fatalities were attributed to central nervous system depression based on observations of tremors and ataxia prior to death.

In a chronic 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 1977). Increased deaths occurred in groups of male and female rats exposed to 471 and 474 mg/kg/day tetrachloroethylene, respectively, 5 days/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 (NCI 1977). This study is discussed in Sections 3.2.2.2 and 3.2.2.7.

All reliable LOAEL and LD_{50} values for death in each species are recorded in Table 3-4 and plotted in Figure 3-16.

3.2.2.2 Systemic Effects

The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-4 and plotted in Figure 3-16. No studies examining musculoskeletal or ocular effects in humans or animals after oral exposure to tetrachloroethylene were located.

Respiratory Effects. Studies of military personnel and civilian employees exposed to tetrachloroethylene-contaminated drinking water at the Marine Base at Camp Lejeune, North Carolina did not observe increased mortality due to chronic obstructive pulmonary disease (Bove et al. 2014a, 2014b). Study populations consisted of 154,932 military personnel (Bove et al. 2014a) and 4,647 civilian employees (Bove et al. 2014b) exposed to drinking water contaminated with tetrachloroethylene. Estimated monthly maximum average drinking water concentrations of tetrachloroethylene were 38.7 and 158.1 µg/L for the civilian and military populations, respectively. Estimated maximum concentrations of trichloroethylene, vinyl chloride, and benzene for both populations were 783, 67, and 12 µg/L, respectively. Military personnel and civilian employees were exposed during the time periods of 1975–1985 and 1973–1985, respectively; mortality follow-up for both populations was assessed from 1979 to 2008. SMRs (95% CI), adjusted for age, sex, race, occupation, and education level, were 0.87 (0.64–1.16) for military personnel and 1.33 (0.95–1.82) for civilian employees.

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 that were associated with increased mortality (NCI 1977).

Table 3-4 Levels of Significant Exposure to Tetrachloroethylene - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Fischer- 344)	once (GO)				5000 F (50% died)	Berman et al. 1995	
2	Rat (Fischer- 344)	single dose (G)		2500		3200 (increased mortality)	Dow Chemical 1983	
3	Rat (Sprague-Dawley)	once (G)				3835 M (LD50) 3005 F (LD50)	Hayes et al. 1986	
4	Rat (Fischer- 344)	single dose (G)				2500 M (increased mortality)	Wall and Carreon 1984	
5	Mouse (Swiss-Webster)	once (G)				4500 M (LD50)	Philip et al. 2007	
6	Mouse (Swiss-Webster)	once (G)				8139 M (LD50)	Wenzel and Gibson 1951	
Systemic								
7	Rat (Fischer- 344)	14 d (GO)	Hepatic	500 F	1500 F (increased relative liver weights; increased alanine aminotransferase; hepatocellular hypertrophy)		Berman et al. 1995	
			Renal	1500 F				
			Endocr	1500 F				

Table 3-4 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
8	Rat (Fischer- 344)	10 d 1x/d (GO)	Hepatic		1000 M (increased liver to body weight ratio)		Goldsworthy and Popp 1987	
			Bd Wt	1000 M				
9	Rat (Wistar)	5d (GO)	Hepatic	500 M	1000 M significatly increased liver weights; induction of CYP2B P450 enzymes; induction of phase II drug-metabolizing enzymes.		Hanioka et al. 1995	
			Bd Wt	1000 M	2000 M (body weights 16% lower than controls)			
10	Rat (Fischer- 344)	Gd 6-19 (GO)	Bd Wt			900 F (about 25% decrease in body weight gain)	Narotsky and Kavlock 1995	
11	Rat (Fischer- 344)	7 d (G)	Bd Wt	1000 M			Potter et al. 1996	
12	Rat (Wistar)	14 d 1x/d (G)	Hepatic		1000 F (increased serum enzymes and histopathology including minimal periportal lymphocytic infiltration, inflammation, and hepatocellular necrosis)		Rajamanikandan et al. 2012	

Table 3-4 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
13	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)		
14	Mouse (B6C3F1)	10 d 1x/d (G)	Hepatic		1000 M increased liver to body weight ratios; peroxisomal proliferation		Goldsworthy and Popp 1987	
			Renal		1000 M peroxisomal proliferation			
			Bd Wt	1000 M				
15	Mouse (Swiss-Webster)	14 days Daily (G)	Hepatic		150 M (>twofold increase in serum ALT)		Philip et al. 2007	
16	Mouse (B6C3F1)	11 d (GO)	Hepatic		100 M (hepatocellular swelling)		Schumann et al. 1980	
			Bd Wt	1000 M				
Immuno/ Lymphoret								
17	Rat (Fischer- 344)	14 d (GO)		1500 F			Berman et al. 1995	
18	Rat (Wistar)	5d (GO)		1000 M	2000 M (atrophy of the spleen and thymus)		Hanioka et al. 1995	

Table 3-4 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
19	Rat (Wistar)	2 wk (W)			0.0009 (increased dermal lymphocyte infiltration and perivascular mast cell accumulation)		Seo et al. 2008a	
20	Mouse (ICR)	2 wk (W)		0.26			Seo et al. 2012	
Neurological								
21	Human	once (C)				116 M (amnesia; dizziness; hallucinations)	Haerer and Udelman 1964	
22	Human	once				108 M (unconsciousness)	Kendrick 1929	
23	Rat (Sprague-Dawley)	once (GO)			50 M (increased seizure threshold)		Chen et al. 2002	
24	Rat (Fischer- 344)	single dose (G)			1300 (lethary, loss of coordination)		Dow Chemical 1983	
25	Rat (Fischer- 344)	once		500 F		1500 F (lacrimation and gait score significantly increased; motor activity significantly decreased)	Moser et al. 1995	

Table 3-4 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
26	Rat (Fischer- 344)	Gd 6-19 (GO)				900 F (ataxia that lasted about 4 hours after dosing)	Narotsky and Kavlock 1995	
27	Rat (Fischer- 344)	single dose (G)			1300 M (lethargy and loss of coordination)		Wall and Carreon 1984	
28	Rat (Sprague-Dawley)	Once (GO)		160 M	480 M (suppression of operant response behavior)		Warren et al. 1996	
Reproductive								
29	Rat (Fischer- 344)	Gd 6-19 (GO)				900 F (significant increase in resorptions)	Narotsky and Kavlock 1995	
Developmental								
30	Rat (Fischer- 344)	Gd 6-19 (GO)				900 F (increased postnatal deaths; increased micro/anophthalmia)	Narotsky and Kavlock 1995	
31	Mouse (NMRI)	7 d (GO)			5 M (increased activity at 60 days of age)		Fredriksson et al. 1993	
INTERMEDIATE EXPOSURE								
Death								
32	Rat (Wistar)	32 d Daily (GO)				2400 F (1/5 died)	Jonker et al. 1996	

Table 3-4 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
33	Rat (Osborne-Mendel)	6 wk 5d/wk (GO)					1780	(number of deaths not specified)	NCI 1977	
34	Mouse (Swiss-Webster)	30 days Daily (G)					1000 M	(2/20 died)	Philip et al. 2007	
Systemic										
35	Rat (Sprague-Dawley)	90 d (W)	Hemato	1400					Hayes et al. 1986	
			Hepatic	400	1400	increased liver/body weight ratio				
			Renal	14 M	400 M	increased kidney/body weight ratio				
			Bd Wt	14 F	400 F	(18% decrease in body weight gain)	1400 F	(24% decrease in body weight gain)		

Table 3-4 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Rat (Wistar)	32 d Daily (GO)	Hepatic	600 F	2400 F (increased relative liver weight; increased alanine aminotransferase and aspartate aminotransferase)		Jonker et al. 1996	
			Renal	600 F	2400 F (urinalysis changes, increased relative kidney weight, multifocal tubular vacuolation and karyomegaly)			
			Bd Wt	2400 F				
37	Rat (Osborne-Mendel)	6 wk 5d/wk (GO)	Bd Wt	1000			NCI 1977	
38	Rat (Osborne-Mendel)	7wk 5d/wk (GO)	Hepatic		995 M (increased liver weight; increased Type II GGT and foci with or without an initiator)		Story et al. 1986	
39	Mouse (Swiss- Cox)	6 wk 5d/wk (GO)	Hepatic	20 M	100 M (increased relative liver weight; increased liver triglycerides)	200 M (hepatic necrosis)	Buben and O'Flaherty 1985	

Table 3-4 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
40	Mouse (Swiss-Webster)	15 d Daily (GO)	Hepatic		3000 (increased relative liver weight, altered hepatic glycolytic and gluconeogenic enzyme activities, and liver histopathology)		Ebrahim et al. 1996	
			Renal		3000 (increased relative kidney weight; hypercellular glomeruli)			
			Bd Wt	3000				
41	Mouse (Swiss-Webster)	15 d Daily (GO)	Hemato		3000 M (decr Hb, Hct, RBC and platelet counts; incr WBC count)		Ebrahim et al. 2001	
42	Mouse (B6C3F1)	6 wk 5d/wk (GO)	Bd Wt			562 F (30% decrease in body weight gain)	NCI 1977	
43	Mouse (Swiss-Webster)	30 days Daily (G)	Hepatic	150 M	500 M (centrilobular fatty degeneration and single cell necrosis)		Philip et al. 2007	
			Renal	1000 M				

Table 3-4 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
44	Rat (Wistar)	4 wk (W)			0.0009 (increased relative weight of mesenteric lymph nodes; enlargement of lymphoid nodules with clearly visible germinal centers)		Seo et al. 2008a	
45	Mouse (ICR)	4 wk (W)			0.0025 (enhancement of passive cutaneous anaphylaxis reaction)		Seo et al. 2012	
Neurological								
46	Rat (Sprague-Dawley)	8 wk 5 d/wk (GO)			5 M (impaired nociception and increased seizure threshold)		Chen et al. 2002	
47	Rat (Wistar)	32 d Daily (GO)				2400 F (severe but transient signs of CNS depression)	Jonker et al. 1996	
CHRONIC EXPOSURE								
Death								
48	Rat (Osborne-Mendel)	78 wk 5d/wk (GO)				471 M (decreased survival) 474 F (decreased survival)	NCI 1977	
49	Mouse (B6C3F1)	78 wk 5d/wk (GO)				536 M (reduced survival) 386 F (reduced survival)	NCI 1977	

Table 3-4 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
50	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				
			Dermal	941				
			Bd Wt	941				
51	Mouse (B6C3F1)	78 wk 5d/wk (GO)	Resp	1072			NCI 1977	
			Cardio	1072				
			Gastro	1072				
			Hepatic	1072				
			Renal			536 M nephropathy		
						386 F nephropathy		
			Endocr	1072				
			Dermal	1072				
			Bd Wt	1072				

Table 3-4 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
52	Human	106 mo average			2.3[b]		Cavalleri et al. 1994	POD (2.3 mg/kg/day) derived from PBPK model-based route-to-route extrapolation
Cancer								
53	Mouse (B6C3F1)	78 wk 5d/wk (GO)				536 M CEL: hepatocellular carcinomas	NCI 1977	
						386 F CEL: hepatocellular carcinomas		

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

b Used to derive a chronic-duration oral minimal risk level (MRL) of 0.008 mg/kg/day for tetrachloroethylene; the MRL is based on the equivalent continuous exposure LOAEL of 1.7 ppm from an inhalation study; a PBPK model was employed to determine the equivalent oral dose (2.3 mg/kg/day) using an internal dose metric of 24-hour AUC of the tetrachloroethylene blood concentration-time curve. The route-to-route extrapolated LOAEL of 2.3 mg/kg/day was divided by an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL), and a modifying factor of 3 for database deficiencies (for inadequate information on potential low-dose immune system effects). ATSDR has adopted the chronic-duration oral MRL as the acute-duration and intermediate-duration oral MRLs. See Appendix A for detailed discussion of the oral MRLs for tetrachloroethylene.

ad lib = ad libitum; B = both sexes; Bd Wt = body weight; BUN = blood urea nitrogen; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LC50 = lethal concentration, 50% kill; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Metab = metabolism; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Occup = occupational; Pmd = pre-mating day; Pnd = post-natal day; Ppd = post-parturition day; Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s); yr = year(s)

Figure 3-16 Levels of Significant Exposure to Tetrachloroethylene - Oral

Acute (≤14 days)

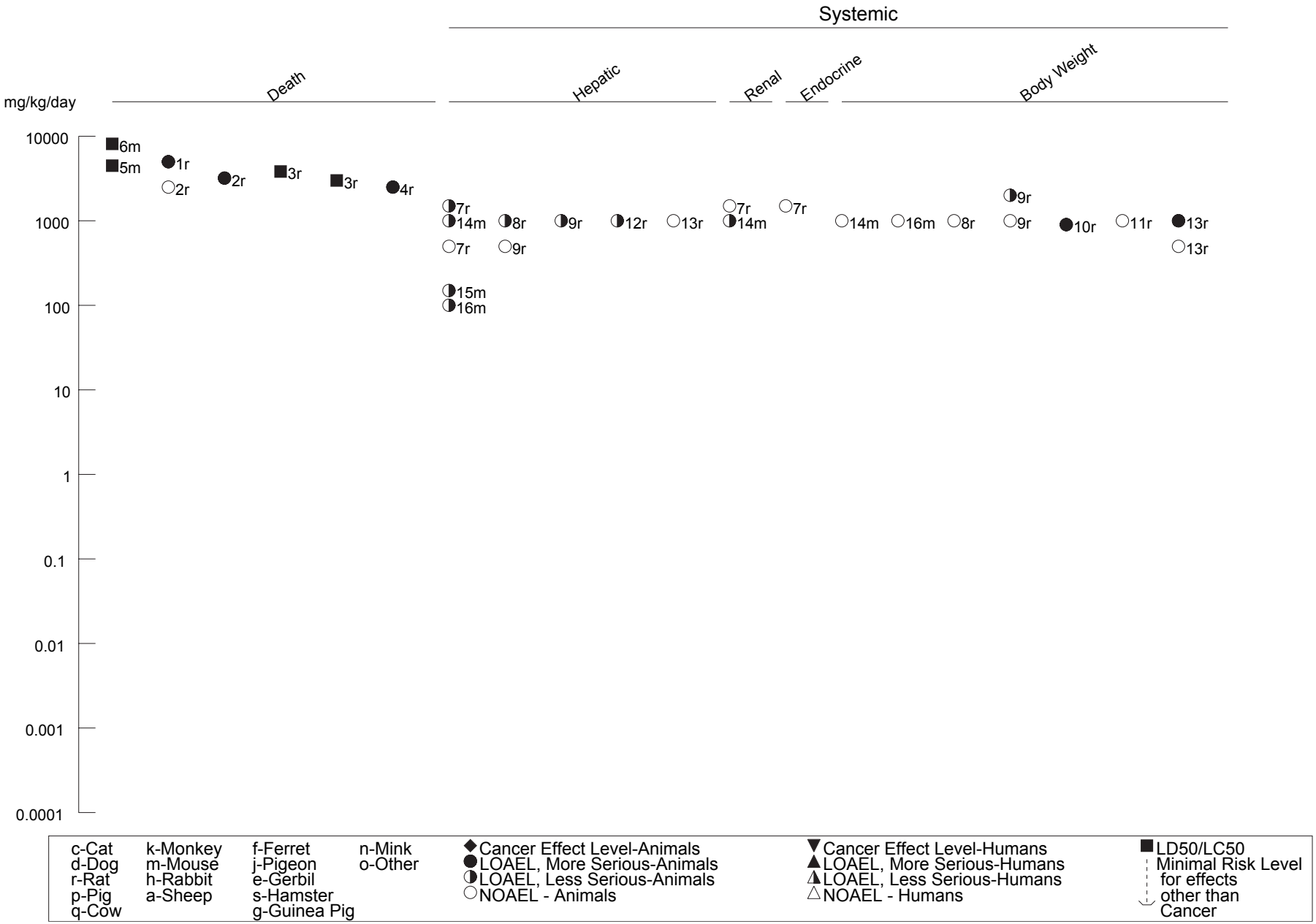


Figure 3-16 Levels of Significant Exposure to Tetrachloroethylene - Oral *(Continued)*

Acute (≤14 days)

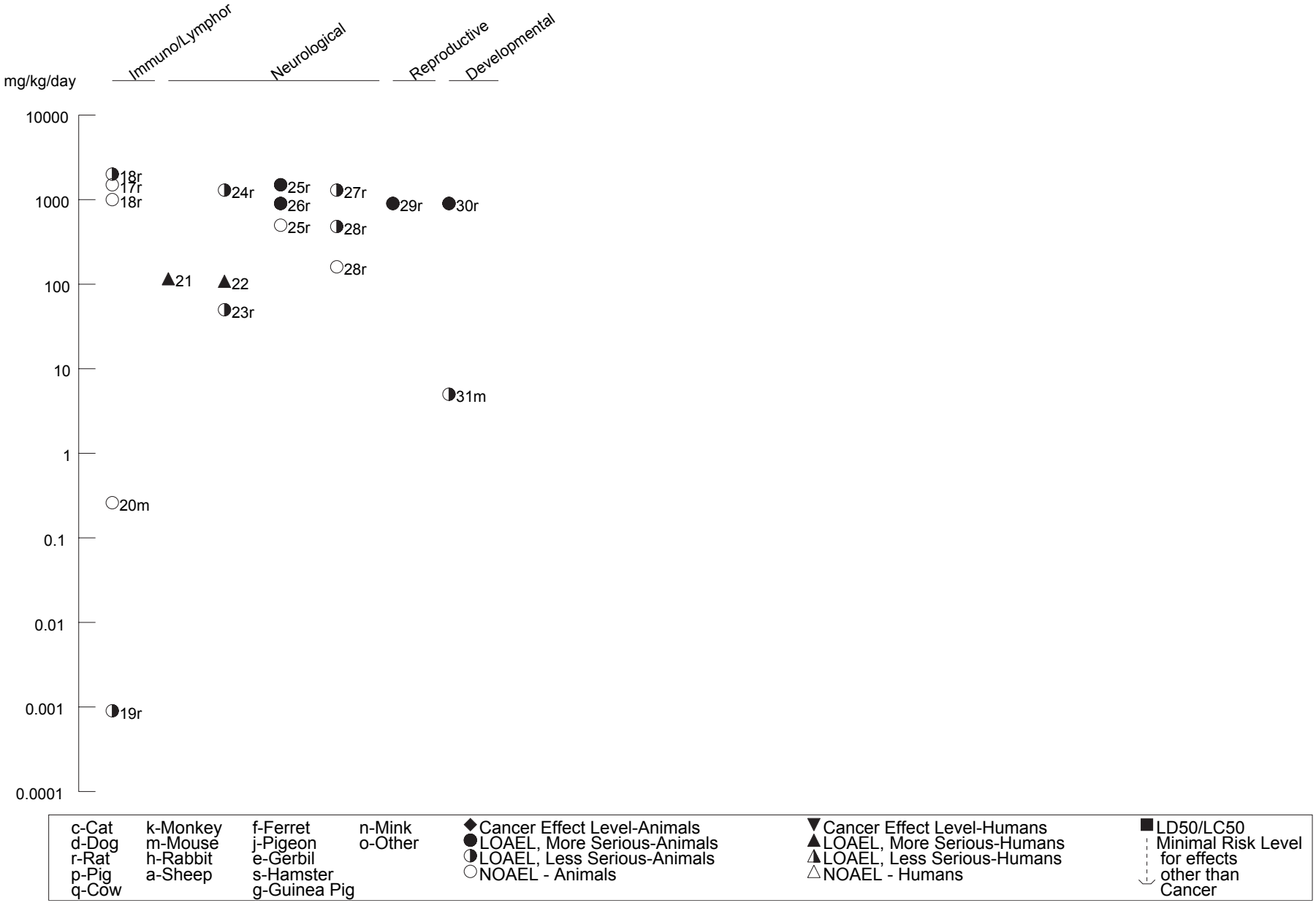


Figure 3-16 Levels of Significant Exposure to Tetrachloroethylene - Oral *(Continued)*

Intermediate (15-364 days)

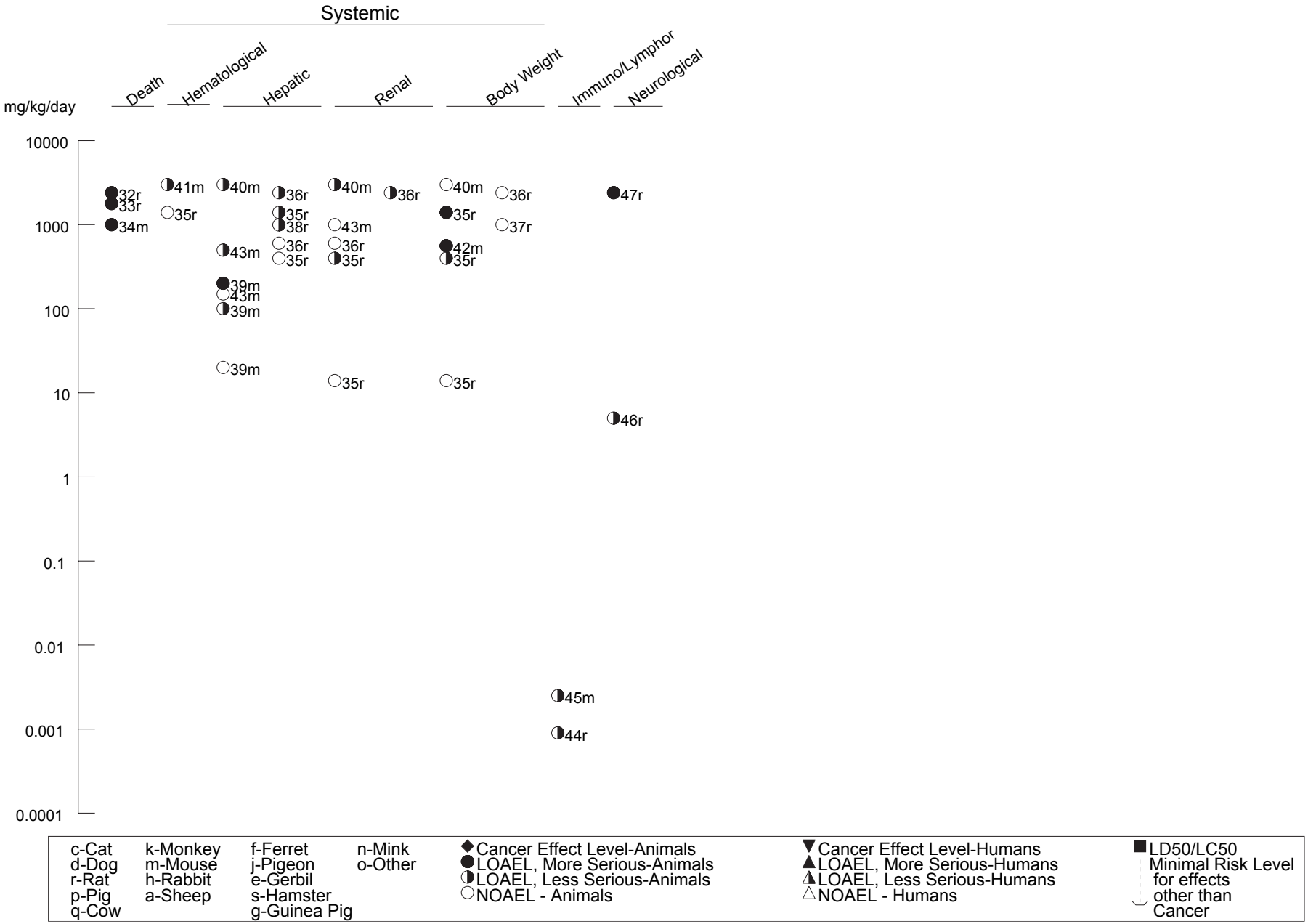
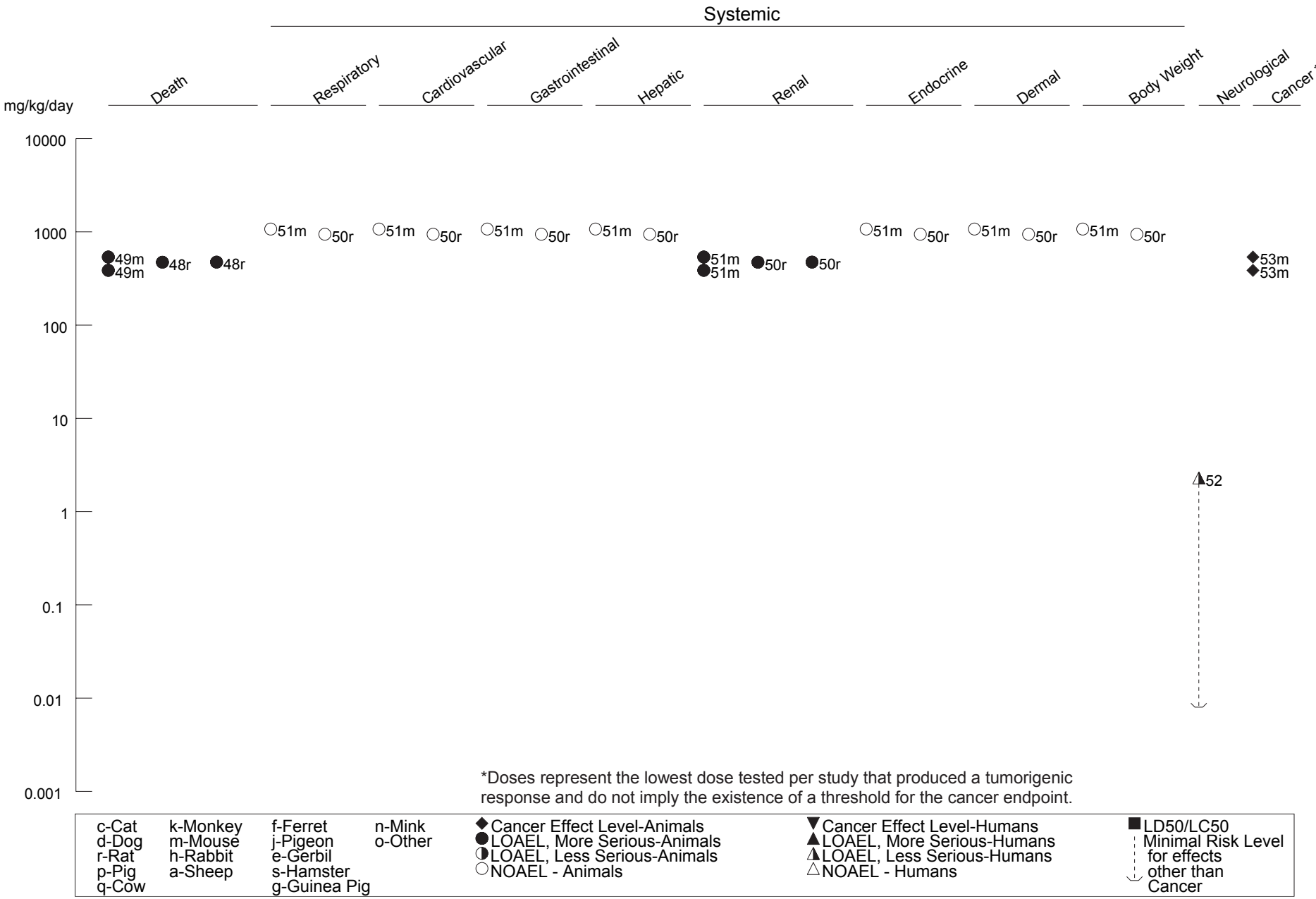


Figure 3-16 Levels of Significant Exposure to Tetrachloroethylene - Oral *(Continued)*

Chronic (≥365 days)



Cardiovascular Effects. Studies of military personnel and civilian employees exposed to tetrachloroethylene-contaminated drinking water at the Marine Base at Camp Lejeune, North Carolina did not observe increased mortality due to all cardiovascular disease (specific cardiovascular diseases not specified) (Bove et al. 2014a, 2014b). Details of these studies are provided above in Section 3.2.2.2 (Oral, Systemic Effects, Respiratory Effects). SMRs (95% CI) were 0.78 (0.74–0.82) for military personnel and 0.86 (0.75–0.98) for civilian employees. 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 of 25 adults complained of cardiac symptoms of tachycardia at rest, palpitations, or near syncope. Eleven of these were selected for detailed testing, which included resting and exercise tolerance electrocardiograms, Holter monitoring, echocardiograms, and serum lipid levels. Of these 11 people, 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 people given extensive testing. No background information on family history of heart disease, smoking habits, or occupational history was provided 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).

Hematological Effects. Little information was located regarding hematological effects in humans after oral exposure to tetrachloroethylene. The odds of aplastic anemia were not increased in 50,684 marines exposed to tetrachloroethylene in drinking water at Camp Lejeune, North Carolina (23 cases) for any cumulative exposure tertile, compared to 8,615 marines stationed at Camp Pendleton (5 cases). The OR for the highest cumulative exposure tertile (≥711 ppb-months) was 1.28 (95% CI 0.33–4.94), with only four marines in this exposure group diagnosed with aplastic anemia. Study details are provided below in Section 3.2.2.2 (Oral, Systemic Effects, Hepatic Effects).

Data on the hematologic effects of tetrachloroethylene in laboratory rodents exposed orally are limited to intermediate-duration studies in mice yielding uncertain findings.

In a 15-day study of male Swiss mice exposed to tetrachloroethylene in sesame oil via gavage dosing at 3,000 mg/kg/day, hematologic changes included significantly decreased hemoglobin (17% less than controls), hematocrit (23% lower), and erythrocyte (21%) and platelet counts (32%), as well as increased leukocyte count (42% higher than controls; Ebrahim et al. 2001).

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 tetrachloroethylene in the spleen, increased spleen weight, increased splenic hemosiderin deposits and congestion of red pulp, increased serum 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 8-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 occurred in B6C3F1 mice exposed via drinking water to tetrachloroethylene plus 24 other groundwater contaminants (Germolec et al. 1989). This study is discussed in more detail in Section 3.2.2.3.

Hepatic Effects. There is little information on the potential hepatic effects in humans exposed orally to tetrachloroethylene. A 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. Three studies examined hepatic effects of exposure to tetrachloroethylene-contaminated drinking water at the Marine Base at Camp Lejeune, North Carolina; one morbidity study (ATSDR 2018) and two mortality studies (Bove et al. 2014a, 2014b). ATSDR (2018) is a retrospective cohort study of 50,684 marines exposed to drinking water containing

tetrachloroethylene, trichloroethylene, and benzene; Marines stationed at Camp Pendleton, California (n=8,615), not exposed to contaminated drinking water, served as the reference group. Exposure groups for Camp Lejeune marines were stratified by cumulative exposure tertiles in terms of ppb-months (low: >0–<36; medium: ≥36–<711; high: ≥711); the number of marines in each tertile was not reported. The Camp Lejeune study population was exposed from 1975 to 1985. This paper reports ORs (95% CI) of all liver disease in the medium and high exposure groups as 1.54 (1.11–2.13) and 1.56 (1.03–2.35), respectively. Odds ratios (95% CI) for cirrhosis and fatty liver in the medium exposure group were 2.17 (1.04–4.53; n=36) and 1.68 (1.15–2.44; n=158), respectively. With 47 instances of fatty liver reported in the high exposure group, the OR (95% CI) was 1.86 (1.17–2.94; n=47). In contrast, mortality studies of military personnel and civilian employees exposed to tetrachloroethylene-contaminated drinking water at the Camp Lejeune did not observe increased mortality due to all liver disease (specific liver diseases not specified) (Bove et al. 2014a, 2014b). SMRs (95% CI) were 0.61 (0.53–0.71) for military personnel and 0.48 (0.22–0.91) for civilian employees. Details of the Bove (2014a, 2014b) studies are provided above in Section 3.2.2.2 (Oral, Systemic Effects, Respiratory 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 trichloroacetic acid—as discussed in Section 3.4. Hepatic effects in mice have occurred after acute- and intermediate-duration exposures to doses ≥100 mg/kg/day (Buben and O'Flaherty 1985; Schumann et al. 1980). Chronic-duration oral bioassays of tetrachloroethylene in rats and mice have been conducted (NCI 1977). No nonneoplastic hepatic lesions were observed, but these studies had significant limitations, as discussed further in Section 3.2.2.7.

Acute-duration studies have shown liver changes after only a single dose of tetrachloroethylene. Exposure of Swiss mice to 500 or 1,000 mg/kg/day tetrachloroethylene via gavage resulted in histopathology changes including centrilobular fatty degeneration and necrosis, with cytoplasmic vacuolization at the higher dose, after only 1 day of exposure (Philip et al. 2007). In this study, serum ALT was significantly increased (>2-fold) at exposures ≥150 mg/kg/day after 1 day of exposure. Tetrachloroethylene administered by gavage at a dose of 1,000 mg/kg/day for 10 days to male B6C3F1 mice increased relative liver weights and elevated cyanide-insensitive palmitoyl CoA oxidase levels, indicative of peroxisomal proliferation (Goldsworthy and Popp 1987). Schumann et al. (1980) reported hepatocellular swelling in mice given 11 daily gavage doses of 100 mg tetrachloroethylene/kg.

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 uridine 5'diphosopho (UDP)-glucuronyltransferase activity at all doses tested (≥125 mg/kg/day). Tetrachloroethylene administered by gavage at a dose of 1,000 mg/kg/day for 10 days to F344 rats did not elevate cyanide-insensitive palmitoyl CoA oxidase levels significantly above controls, although relative liver weights were increased (Goldsworthy and Popp 1987). Schumann et al. (1980) observed no liver changes in rats given 11 daily gavage doses up to 1,000 mg/kg/day. Increased relative liver weights, increased serum ALT, and hepatocellular hypertrophy were observed in female rats treated by gavage with tetrachloro-ethylene in corn oil at a dose of 1,500 mg/kg/day for 14 days, but not at 500 mg/kg/day (Berman et al. 1995). Rajamanikandan et al. (2012) observed increased serum AST, ALT, and alkaline phosphatase, along with histopathology changes (minimal periportal lymphocytic infiltration, inflammation, and hepatocellular necrosis; incidences not reported) in female Wistar rats given 14 consecutive daily gavage doses of 1,000 mg/kg/day tetrachloroethylene. The authors also measured increased levels of hepatic lipid oxidation as well as decreased antioxidant levels (Rajamanikandan et al. 2012).

Similar liver effects are seen after intermediate-duration exposure to tetrachloroethylene. When male and female Swiss mice were given tetrachloroethylene via gavage in sesame oil at a dose of 3,000 mg/kg/day for 15 consecutive days, hepatic effects included increased relative liver weight (in the absence of body weight change), altered glycolytic and gluconeogenic enzyme activities, and focal necrosis with hydropic changes (Ebrahim et al. 1996). In a similar study, groups of four male Swiss mice received daily gavage doses of 150, 500, or 1,000 mg/kg/day for 1, 7, 14, or 30 consecutive days (Philip et al. 2007). Serum ALT was significantly increased (>2-fold) in all exposure groups after 1 and 14 days of exposure, but groups exposed for 30 days exhibited no difference from control in serum ALT levels. Histopathology changes observed after exposure to 500 or 1,000 mg/kg/day included centrilobular fatty degeneration and necrosis, with cytoplasmic vacuolization at the higher dose; these changes were less pronounced after 30 days of exposure than after 1 day (Philip et al. 2007). 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/day, and hepatocellular lesions at

≥200 mg/kg/day. Lesions consisted of centrilobular hepatocellular hypertrophy, karyorrhexis, centrilobular necrosis, polyploidy, and hepatocellular vacuolization. All of 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).

Exposure to gavage doses of 2,400 mg/kg/day tetrachloroethylene in corn oil for 32 days resulted in increased relative liver weights as well as increased levels of serum AST and ALT in female Wistar rats; no hepatic effects were seen in the group exposed to 600 mg/kg/day (Jonker et al. 1996). 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 the 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 (10/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 GGT activity).

Chemically-related nonneoplastic liver lesions were not reported for Osborne-Mendel rats or B6C3F1 mice given tetrachloroethylene by gavage in a chronic bioassay (NCI 1977). This study, including its limitations, is discussed in Section 3.2.2.7.

Renal Effects. A morbidity study of military personnel (n=50,684) exposed to tetrachloroethylene-contaminated drinking water at the Marine Base at Camp Lejeune showed increased ORs for all renal disease in the medium exposure tertile (cumulative exposure ≥36–<711 ppb-months; OR 1.79; 95% CI 1.15–2.77) and high cumulative exposure tertile (cumulative exposure ≥711 ppb-months; OR 2.00; 95% CI 1.18–3.39) (ATSDR 2018). Odds ratios above 2 were reported for nephrotic syndrome in all

tetrachloroethylene exposure groups of Camp Lejeune military personnel, although only the highest cumulative exposure group had an equivalent or higher risk for renal failure (OR 2.36; 95% CI 1.17–4.77). However, morbidity studies of military personnel and civilian employees at Camp Lejeune, did not observe increased mortality due to all kidney diseases (specific renal diseases not specified) (Bove et al. 2014a, 2014b). SMRs (95% CI) were 0.78 (0.34–1.54) for civilian employees and 0.50 (0.35–0.68) for military personnel. Details of the ATSDR (2018) study are provided above in above Section 3.2.2.2 (Oral, Systemic Effects, Hepatic Effects) and details of the Bove (2015a, 2014b) studies are provided above in Section 3.2.2.2 (Oral, Systemic Effects, Respiratory Effects).

Acute-duration studies measuring renal effects in animals have not used doses lower than 1,000 mg/kg/day. At this dose, male, but not female, rats exhibited renal changes characteristic of α-2u-globulin nephropathy (Berman et al. 1995; Goldsworthy et al. 1988; Potter et al. 1996), while male mice exhibited peroxisomal proliferation in the kidneys (Goldsworthy and Popp 1987). The lowest dose resulting in renal effects in intermediate-duration studies was 400 mg/kg/day; rats exposed to this dose for 90 days showed increased relative kidney weights (Hayes et al. 1986). In chronic oral studies, toxic nephropathy, which contributed to early mortality, was observed in both sexes of mice and rats at TWA doses ≥386 mg/kg/day; these studies had significant limitations, as discussed in Section 3.2.2.7.

Daily gavage administration of 1,000 mg/kg tetrachloroethylene to male F344 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-2u-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 F344 rats receiving daily gavage doses of 1,000 mg/kg/day tetrachloroethylene in 4% Emulphor exhibited increased numbers of hyaline droplets in renal tubules, also consistent with α-2u-globulin accumulation, after 1, 3, or 7 days of exposure (Potter et al. 1996). Kidney weight, renal cell proliferation rate, and frequency of DNA strand breaks in the kidney were not altered by exposure (Potter et al. 1996). 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 B6C3F1 mice exposed to 1,000 mg/kg/day by gavage for 10 days had peroxisomal proliferation, as evidenced by elevated cyanide-insensitive palmitoyl CoA oxidase levels (Goldsworthy and Popp 1987).

Increased relative kidney weights (in the absence of body weight changes) were observed in male and female Swiss mice given gavage doses of 3,000 mg/kg/day tetrachloroethylene in sesame oil for 15 consecutive days (Ebrahim et al. 1996). Histopathology examination of the kidneys showed hypercellular glomeruli. In male Swiss mice given daily gavage doses of 150, 500, or 1,000 mg/kg/day for 1, 7, 14, or 30 consecutive days, cell proliferation was increased in the kidneys after 30 days of exposure, but no histopathology changes were seen, and no change in BUN was observed at any time point (Philip et al. 2007).

Male rats exposed to 1,500 mg/kg/day tetrachloroethylene by gavage for 42 days developed typical α-2u-globulin nephropathy (Green et al. 1990). Male rats, but not female rats, also developed α-2u-globulin nephropathy following daily gavage treatment with tetrachloroethylene at 500 mg/kg/day for 4 weeks (Bergamaschi et al. 1992). Exposure of female Wistar rats to gavage doses of 2,400 mg/kg/day tetrachloroethylene in corn oil for 32 days resulted in urinalysis changes including increased urine volume, and increased protein, GGT, ALP, LDH, and NAG excretion. Increased relative kidney weights were also noted, and histopathology examination revealed increased incidences of mild multifocal tubular vacuolation and karyomegaly (Jonker et al. 1996). Rats exposed to a lower dose of 600 mg/kg/day did not exhibit renal effects (Jonker et al. 1996).

Hypercellular glomeruli and congestion of the convoluted tubules were observed in the kidneys of male 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-Mendel rats and B6C3F1 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 3.2.2.7. 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 hyaline intraluminal 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, and few data are available in animals. 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 1–2 years after cessation of exposure to contaminated water (Byers et al. 1988). There is no conclusive evidence that skin lesions were related to solvent exposure in general or to tetrachloroethylene specifically.

Few data on dermal effects after oral exposure are available in animals. 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. No studies of body weight effects in humans orally exposed to tetrachloroethylene were identified in the available literature. Body weight effects observed in studies of animals exposed orally are not consistent across study or species/strain of animal. At the end of a 5-day study, body weights of male Wistar 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 F344 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 F344 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 F344 rats treated by gavage with tetrachloroethylene at 1,000 mg/kg/day for 7 or 10 days (Goldsworthy and Popp 1987; Potter et al. 1996), in female Wistar rats given gavage doses of 2,400 mg/kg/day tetrachloroethylene for 32 days (Jonker et al. 1996), or in B6C3F1 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).

In intermediate-duration studies, no effect on body weight was observed in male and female Swiss mice treated by gavage with tetrachloroethylene at 3,000 mg/kg/day for 15 days (Ebrahim et al. 2001), in female Wistar rats given gavage doses of 2,400 mg/kg/day tetrachloroethylene for 32 days (Jonker et al. 1996), or in Osborne-Mendel rats treated by gavage with tetrachloroethylene at doses ≤1,000 mg/kg/day for 6 weeks (NCI 1977). Hayes et al. (1986) reported 18 and 24% decreases in body weight gain in female Sprague-Dawley 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 B6C3F1 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.

An explanation for the differences in effect on body weight in rats in the studies was not readily apparent; the differences do not appear to be related to strain or sex of the animals or to exposure duration. Changes in body weight in the available chronic-duration oral studies are also not consistent. Changes in body weight were not observed in Osborne-Mendel rats or B6C3F1 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).

3.2.2.3 Immunological and Lymphoreticular Effects

Little information regarding immunological and lymphoreticular effects in humans after oral exposure to tetrachloroethylene was located. In a morbidity study of 50,684 military personnel exposed to tetrachloroethylene in drinking water at Camp Lejeune, North Carolina, the OR (95% CI) for lupus was reported as 1.50 (0.54–4.18) for the highest cumulative exposure group (≥711 ppb-months). Study details are provided in Section 3.2.2.2 (Oral, Systemic Effects, Hepatic Effects).

A study suggesting immunological effects in humans with chronic exposure to a solvent-contaminated domestic water supply was conducted by Byers et al. (1988). Several wells in Woburn, 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). A potential association between water contamination in Woburn and cases of childhood leukemia is discussed in Section 3.2.2.7.

Some immunological abnormalities were found in 23 adults in Woburn 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% (11/23) of the adults tested. In the Woburn 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 and an increased risk of developing leukemia. Other limitations of this study are described in Section 3.2.2.7.

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).

Enhanced antigen-stimulated allergic responses have been demonstrated following small oral doses of tetrachloroethylene in both rats (Seo et al. 2008a) and mice (Seo et al. 2012). In addition, rats exposed to tetrachloroethylene displayed enhanced inflammatory responses (Seo et al. 2008a). Wistar rats and ICR mice were exposed to drinking water containing 0, 0.01, or 1 mg/L tetrachloroethylene for 2 or 4 weeks (estimated doses of 0, 0.0009, or 0.09 mg/kg/day in rats; 0, 0.0025, or 0.26 mg/kg/day in mice). Rats and mice were sensitized by intraperitoneal injection of anti-dinitrophenol IgE antibody 2 days or 1 day prior to the end of exposure, respectively. The passive cutaneous anaphylaxis (PCA) reaction was significantly increased in rats treated with 0.09 mg/kg/day and mice treated with 0.0025 and 0.26 mg/kg/day for 4 weeks, in a dose-dependent manner. Neither species demonstrated enhanced PCA reactions after exposure for 2 weeks. However, microscopic examination of skin demonstrated that all rats exposed for 2 weeks demonstrated increased lymphocyte infiltration (~1.2-fold more lymphocytes in treated groups compared with controls) and perivascular mast cell accumulation (~2-fold more). In addition, rats

exposed to 0.09 mg/kg/day for 2 weeks demonstrated significantly increased (~1.3-fold) histamine release from antigen-stimulated peritoneal mast cells. These assays were not conducted following the 4-week exposure in rats or any exposure duration in mice. There was no treatment-related change in the relative weights of the spleen, thymus, and cervical lymph nodes of rats exposed for 4 weeks (not assessed at 2 weeks in rats or any duration in mice), but the relative mesenteric lymph node weight was significantly increased at both exposure levels. Microscopic examination of the mesenteric lymph nodes showed enlarged lymphoid nodules with clearly visible germinal centers; the study authors did not indicate the incidence or severity of this effect in the two treated groups.

Immunological effects were detected in a study exposing female B6C3F1 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, natural killer 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 3-4 and plotted in Figure 3-16.

3.2.2.4 Neurological Effects

Neurological Effects in Humans. Acute neurological effects in humans after ingesting tetrachloroethylene are similar to those seen after inhalation, such as dizziness, loss of coordination, and narcosis, in some cases leading to coma; however, available data are limited to a small number of case reports. 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).

A series of retrospective cohort studies examining brain structure, neurobehavioral and developmental end points, and cancer was conducted on residents of Cape Cod, Massachusetts who were exposed to tetrachloroethylene leaching from the lining of vinyl-lined asbestos-cement water supply pipes (Aschengrau et al. 1998, 2003, 2008, 2009, 2011, 2012; Getz et al. 2012; Janulewicz et al. 2008, 2012; 2013; Paulu et al. 1999; Vieira et al. 2005). The exposure, discovered in 1980, had been occurring for the preceding 15 years; concentrations in the water in 1980 ranged from 1.5 to 7,750 μg/L. Exposure to other water contaminants was considered by the study authors to be rare, limiting confounding by coexposures. Most of the studies examined effects in children who had been exposed *in utero* or during the first 5 years of life. In these studies, residential histories were obtained by questionnaire, and locations of affected pipes were collected from municipalities. Total exposure for each individual subject was then estimated as the total amount (in grams) of tetrachloroethylene delivered to the subject's residence by modeling leaching of tetrachloroethylene from the pipes and subsequent transport to households (using EPANET water distribution modeling software). The studies did not include estimates of tetrachloroethylene intake, as they considered information on water consumption and bathing habits obtained by questionnaire to be of limited reliability. Exposure to tetrachloroethylene in this cohort likely included oral, inhalation, and dermal routes, but oral exposure is considered to be the dominant exposure route.

No structure abnormalities of the brain were observed in 26 adults exposed to tetrachloroethylene-contaminated drinking water in Cape Cod during prenatal and early postnatal periods, compared to controls (n=16) (Janulewicz et al. 2013). The exposed group was identified through birth records from 1969 to 1983. Brain structure was examined by structural magnetic resonance imaging (MRI). No differences were observed between groups for white matter hypodensities, white matter volume, or grey matter volume.

Studies examining neurobehavioral end points of learning, attention, and behavior in the Cape Cod cohort were conducted (Janulewicz et al. 2008, 2012). Janulewicz et al. (2008) used parental questionnaires to compare academic difficulties, diagnoses of attention deficit disorder or hyperactive disorder, and behavioral problems among 1,910 exposed and 1,928 unexposed children whose mothers lived on Cape Cod during pregnancy or the first 5 years after birth. "Low" and "high" cumulative exposure categories were defined as <10 and >10 g tetrachloroethylene over 9 months of gestation, respectively, for prenatal exposure assessments, and <66.7 and >66.7 g tetrachloroethylene over 9 months of gestation, respectively, for postnatal exposure assessments. The results showed no associations between "low" and "high" prenatal exposure and diagnosis of attention deficit disorder (ADD) (low: OR 1.4; 95% CI 0.9–2.0; high: OR 1.0; 95% CI 0.7–1.6), hyperactive disorder (HD) (low: OR 1.5; 95% CI 0.9–2.7; high: OR 0.8; 95% CI 0.4–1.6), or special educational class placement (low: OR 1.3; 95% CI 0.9–1.7; high: OR 0.8; 95% CI 0.6–1.2). Similarly, risks were not increased for postnatal exposure and ADD (low: OR 1.3; 95% CI 0.9–1.9; high: OR 1.0; 95% CI 0.6–1.7), HD (low: OR 1.4; 95% CI 0.8–2.5; high: OR 0.7; 95% CI 0.3–1.6), or special educational class placement (low: OR 1.2; 95% CI 0.9–1.7; high: OR 0.7; 95% CI 0.5–1.1).

A follow-up study examining neuropsychological end points in adults was performed (Janulewicz et al. 2012); participation in this study was very low, with only 35 exposed and 28 unexposed subjects agreeing to neuropsychological testing of the original cohort. This study also reported no evidence ($p>0.05$) of an association between exposure and neuropsychological tests for omnibus intelligence, academic achievement, or language end points using either crude analysis or multivariate analysis considering likely confounders (Janulewicz et al. 2012). The study authors stated that suggestive associations were noted between exposure and decrements in visuospatial functioning, learning and memory, motor speed, attention, and mood; however, the differences were not statistically significant (Janulewicz et al. 2012). The small group sizes in this study represent a significant limitation.

Aschengrau et al. (2011) examined the frequency of risky behaviors (including cigarette smoking, alcohol consumption, and drug use) during the teenage and young adult years among exposed and unexposed members of the cohort (exposure occurred during gestation and early childhood). A total of 831 exposed and 547 unexposed subjects with adequate information for exposure assessment provided information by questionnaire. Tetrachloroethylene exposure categories were defined as any tetrachloroethylene exposure and tetrachloroethylene tertiles: >0–<33rd percentile (lowest exposure tertile), 33rd–<67th percentile, and ≥67th percentile (highest exposure tertile). Increased risks were only observed in the ≥67th percentile category; no elevated risks (e.g., the lower 95th CI was ≤1.0) were observed in the lower exposure

categories or for the "any exposure" category. An association was observed for teen use of alcohol (relative risk 1.6; 95% CI 1.1–2.3), cocaine (risk ratio 2.1; 95% CI 1.4–3.0), psychedelics/hallucinogens (risk ratio 1.4; 95% CI 1.1–1.8), Ritalin without a prescription (risk ratio 2.1; 95% CI 1.4–3.3), and two or more illicit drugs (relative risk 1.6; 95% CI 1.2–2.2), and for adult drug use (relative risk 1.5; 95% CI 1.2–1.9) in the highest exposure tertile. The same subjects also responded to questions on mental illness, and results of this evaluation were published by Aschengrau et al. (2012). An association for bipolar disorder was observed for the highest exposure category (risk ratio 2.7; 95% CI 1.3–5.6), but not for the "any exposure" category (risk ratio 1.8; 95% CI 0.9–3.5) or for the lowest exposure tertile: 0–<33rd (risk ratio 1.6; 95% CI 0.7–3.7) or the mid exposure tertile: 33rd–<67th percentiles (risk ratio 1.1; 95% CI 0.4–2.7). No associations were observed for depression or stress disorder, with risk ratios for the highest exposure tertile of 1.1 (95% CI 0.8–1.5) and 1.7 (95% CI 0.9–3.2), respectively. No increases were observed for risks of post traumatic stress (risk ratio 1.5; 95% CI 0.9–2.5) or schizophrenia (risk ratio 2.1; 95% CI 0.2–20.0) for the "any exposure" category (risk ratios not reported for other exposure categories).

Getz et al. (2012) examined visual acuity, contrast sensitivity, and color discrimination in a small subset of the Cape Cod cohort (n=29 exposed and 25 unexposed) who agreed to vision testing. The testing revealed a decrease in contrast sensitivity and an increase in color confusion measured by the Farnsworth test (mean difference of 0.05; 95% CI 0.003–0.10), but not when measured by Lanthony's D-15d test. While limited by the small group sizes, the suggestive findings in this study are supported by studies of occupational and residential exposures to inhaled tetrachloroethylene that also observed decreased contrast sensitivity and color discrimination (Gobba et al. 1998; Schreiber et al. 2002; Storm et al. 2011; see Section 3.2.1.4).

Studies of military personnel and civilian employees exposed to tetrachloroethylene-contaminated drinking water at the Marine Base at Camp Lejeune, North Carolina evaluated morbidity and mortality due to amyotrophic lateral sclerosis (ALS), multiple sclerosis, and Parkinson's disease (ATSDR 2018; Bove et al. 2014a, 2014b). The ATSDR (2018) morbidity study of 50,684 military personnel reported ORs (95% CI) for the high cumulative exposure group (≥711 ppb-months) as 1.86 (0.71–4.85; n=10) for ALS, 0.63 (0.25–1.60; n=6) for multiple sclerosis, and 1.22 (0.57–2.61; n=13) for Parkinson's disease. Study details are provided above in Section 3.2.2.2 (Oral, Systemic Effects, Hepatic Effects). Similar results were observed in mortality studies on Camp Lejeune military personnel and civilian workers (Bove et al. 2014a, 2014b). For ALS, SMRs (95% CI) for military personnel and civilian employees were 1.14 (0.70–1.74) and 0.44 (0.01–2.44), respectively. For multiple sclerosis, SMRs (95% CI) for military personnel and civilian employees were 0.81 (0.42–1.42) and 0.53 (0.01–2.95), respectively. For

civilian employees, the SMR (95% CI) for Parkinson's disease was 2.19 (0.71–5.11). Details of the Bove (2014a, 2014b) studies are provided above in Section 3.2.2.2 (Oral, Systemic Effects, Respiratory Effects).

Neurological Effects in Animals. Most of the limited available animal data on neurological effects of oral exposure to tetrachloroethylene come from acute-duration studies; the lowest LOAEL in these studies was for suppression of operant behavior response in rats exposed to single gavage doses of 480 mg/kg (Warren et al. 1996). A single intermediate-duration study observed impairments in nociception and an increased threshold for seizure initiation in rats exposed to 5 mg/kg/day for 8 weeks (Chen et al. 2002). Chronic studies of effects on neurological function in animals exposed orally are not available.

When female Wistar rats received daily gavage doses of 2,400 mg/kg/day tetrachloroethylene in corn oil in a 32-day study, severe but transient signs of central nervous system depression were noted immediately after dosing (Jonker et al. 1996). 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 that 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). Operant response behavior was suppressed in male Sprague-Dawley rats tested immediately after a single gavage dose of 480 mg/kg tetrachloroethylene in polyethoxylated vegetable oil (Warren et al. 1996). The rats were trained for 2–3 weeks prior to dosing to press a lever for a milk reward. Rats exposed to 480 mg/kg tetrachloroethylene exhibited suppressed (4/6 rats) or nonexistent (2/6) operant responses after dosing. In the four rats that did respond, response rates returned to normal levels 15–30 minutes postdosing. No effect on operant response was noted in the group exposed to 120 mg/kg tetrachloroethylene (Warren et al. 1996).

A single intermediate-duration study of neurological effects in animals is available. Chen et al. (2002) observed impairments in nociception (increased latency to tail withdrawal from hot water and response

latency to hot plate exposure) as well as an increased threshold for seizure initiation when male Sprague-Dawley rats were given gavage doses of 5 or 50 mg/kg/day tetrachloroethylene for 8 weeks (5 days/week). At the higher dose of 50 mg/kg/day, reduced locomotor activity was also observed.

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 LOAELs for nervous system effects identified in human and animal studies and the NOAEL in rats are indicated in Table 3-4 and Figure 3-16.

3.2.2.5 Reproductive Effects

Two studies examining reproductive effects in humans after oral exposure to tetrachloroethylene were identified; data in animals are very limited. A retrospective cohort study examined the association between maternal exposure to tetrachloroethylene in drinking water and ischemic placental diseases, including placental abruption, preeclampsia, and small for gestational age in Cape Cod, Massachusetts (Carwile et al. 2014). The cohort consisted of 1,091 exposed and 1,019 unexposed births from 1,766 women, and included at total of 2,110 pregnancies. Exposures, which occurred during the period 1969–1990, were estimated using water distribution system modeling software. For exposed pregnancies, estimated cumulative monthly exposures were divided into two groups: 0.00012–0.57 and 0.57–89.2 g. Data for birth certificates for birth weight and gestational age were obtained from birth certificates; pregnancy complications were self-reported. Data were adjusted based on outcome assessed, and included hypertension before or during pregnancy, smoking, previous ischemic placental disease, maternal age during last menstrual period, birth year, and gestational weight gain. The risk of stillbirth was increased for the high exposure group based on a risk ratio of 2.38 (95% CI 1.01–5.59), but not the low exposure group (risk ratio 0.98; 95% CI 0.30–3.14). Risk was not increased for placental abruption, preeclampsia, or small for gestational age, with risk ratios for the highest exposure group of 1.35 (95% CI 0.68–2.67), 0.36 (95% CI 0.12–1.07), and 0.98 (95% CI 0.66–1.45), respectively. An important limitation of this study is the lack of water sampling.

A recent retrospective cohort study of 50,684 military personnel exposed to tetrachloroethylene in drinking water at Camp Lejeune, North Carolina examined male and female reproductive function (ATSDR 2018); study details are provided in Section 3.2.2.2 (Oral, Systemic Effects, Hepatic Effects).

All three tetrachloroethylene exposure groups had ORs above 2 for male infertility at Camp Lejeune (n=129 total) when compared with the reference population (n=7). However, no exposure-related increase in risk was observed, as would be expected, in the Camp Lejeune cohort when exposure increased (medium exposure OR 0.74, 95% CI 0.51–1.09, n=44; high exposure OR 0.74, 95% CI 0.39–1.42, n=11). The OR (95% CI) for low testosterone was 1.18 (0.31–4.43; n=4). For female reproductive function, ORs (95% CI) in the high exposure group were 1.59 (0.753.37; n=11) for infertility and 1.67 (0.76–3.65; n=10) for endometriosis.

A retrospective cohort study of 500 exposed and 331 control women examined potential associations between prenatal and early life exposure to tetrachloroethylene and polycystic ovary syndrome and other adverse reproductive system effects (endometriosis, difficulty conceiving, miscarriage) in Cape Cod, Massachusetts (Mahalingaiah et al. 2016). Study subjects resided in the Cape Cod area from 1969 to 1983. The relative delivered dose (RDD) of tetrachloroethylene was estimated using RDD estimated by an algorithm developed by Webler and Brown (1993) algorithm, using a water distribution model (EPANET 2.0). The study authors concluded that there were no associations between early life tetrachloroethylene exposure and polycystic ovary syndrome (adjusted risk ratio: 0.9; 95% CI 0.5–1.6), endometriosis (adjusted risk ratio: 1.00; 95% CI 0.5–1.8), difficulty conceiving (adjusted risk ratio: 1.0; 95% CI 0.6–1.6), or miscarriage (adjusted risk ratio: 0.9; 95% CI 0.6–1.4).

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 decreased body weight gain of 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 3-4 and plotted in Figure 3-16.

3.2.2.6 Developmental Effects

A large study of was conducted comparing birth weights and gestational ages of infants born to mothers who had lived in a Marine base housing area (Tarawa Terrace at Camp Lejeune, North Carolina) with a contaminated water supply well with infants of other housing areas on the base that did not receive contaminated water (Sonnenfeld et al. 2001). The well contamination was believed to originate from a dry cleaning facility near the well. Contaminants measured during the winter of 1985 in the affected supply well (not at the tap) at Camp Lejeune, North Carolina included tetrachloroethylene (1,580 ppb), trichloroethylene (57 ppb), 1,2-dichloroethylene (92 ppb), and vinyl chloride (27 ppb); the well was shut down shortly thereafter. Birth weight and gestational age were obtained from the review of birth certificates of 6,117 exposed and 5,681 unexposed infants, and mean difference in birth weight, OR for small for gestational age, and preterm birth were assessed. The mean difference in birth weight was -26 g (90% CI -43 – -9) when exposed and unexposed infants were compared. The OR for small for gestational age was 1.2 (90% CI 1.0–1.3). Similar results (data not reported) were observed after adjustment for potential confounders. No clear indication of an effect on preterm birth was seen. When the groups were stratified on maternal age and on number of prior fetal losses, a larger effect was seen among mothers ≥35 years old and among mothers who had two or more prior fetal losses; adjusted birth weight differences were -236 and -104 g, respectively, and adjusted ORs for small for gestational age were 2.1 (90% CI 0.9–4.9) and 2.5 (90% CI 1.5–4.3), respectively. The study authors suggested that the findings included a weak association between tetrachloroethylene exposure and small for gestational age, but no association with preterm birth or mean birth weight (Sonnenfeld et al. 2001). Limitations of the study include potential for exposure misclassification due to limited water sampling data, intermittent well use, and lack of information on water use habits among exposed persons, as well as lack of control for potential confounders including maternal smoking and maternal height.

An association was observed between tetrachloroethylene exposure and preterm birth, and possibly low birth weight and small for gestational age, in a cross-sectional study of pregnant women exposed to contaminated drinking water at the Camp Lejeune Marine Corps Base (North Carolina) during 1968–1985 (Ruckart et al. 2014). A total of 11,896 births were included in the study, with data obtained from birth certificates. Modeling, based on extensive hydrogeological information, pollution source, well pumping schedules, and water distribution system, was conducted for a historical reconstruction of tetrachloroethylene concentrations in drinking water; monthly average estimates were stratified into exposure quartiles and included a no exposure group (Q1: >0–<35.8 µg/L: Q2: ≥35.8–<52.7 µg/L; Q3: ≥52.7–<81.4 µg/L; Q4: ≥81.4 µg/L). Odds ratios for preterm birth were 1.0 (95% CI 0.9–1.2),

0.9 (95% CI 0.7–1.1), 0.8 (95% CI 0.6–1.0), and 1.3 (95% CI 1.0–1.6) for the Q1, Q2, Q3, and Q4 exposure groups, respectively. The study authors noted that study limitations included lack of detailed information on maternal characteristics (e.g., alcohol consumption, smoking status) and residential history and measured tetrachloroethylene concentrations. In addition, the study population was also exposed to trichloroethylene and benzene.

Aschengrau et al. (2008) examined birth weight and gestational duration among 1,353 exposed and 772 nonexposed members of the Cape Cod cohort exposed to tetrachloroethylene in drinking water (see Section 3.2.2.4 for further description of the cohort and exposure conditions). The study authors stated that "in general, birth weights of exposed infants were greater than those of unexposed infants." Gestational duration for exposed subjects was slightly lower than in unexposed subjects, although the decrease was ≤0.2 weeks. Odds ratios for gestational duration were 1.1–1.9 (CIs not reported). The study authors concluded that prenatal exposure to tetrachloroethylene did not have an adverse effect on birth weight or pre-term birth. A later study of congenital anomalies in the Cape Cod cohort (Aschengrau et al. 2009) reported ORs for all congenital anomalies, neural tube defects, and oral cleft defects as 1.2 (95% CI 0.8–1.7), 3.5 (95% CI 0.8–14.0), and 3.2 (95% CI 0.7–15.0), respectively. The study authors noted that the results were limited by the small numbers of children with anomalies and the fact that the anomalies were identified by maternal report and not independently verified.

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 (ORs and CIs not reported) (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 (OR 3.54; 90% CI 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.

Ruckart et al. (2013) conducted a case-control study of exposure of a community to tetrachloroethylene and other chemicals in drinking water to determine if children born during 1968–1985 to mothers with

residential exposure to contaminated drinking water during the first trimester of pregnancy were more likely to have childhood hematopoietic cancers, neural tube defects (NTDs), or oral clefts. The residential community was located at the Marine Corps Base at Camp Lejeune North Carolina. Monthly levels of drinking water contaminants at mothers' residences were estimated using groundwater contaminant fate and transport and distribution system models. Exposures were stratified into the following exposure groups: >0–≤5 (low exposure) and ≥5 ppb (high exposure) for neural tube defects; >0–≤44 (low exposure) and ≥44 ppb (high exposure) for oral cleft and childhood cancers. A total of 51 cases and 536 controls were included in the analysis. No increased risk was observed for oral cleft defects (low OR 0.6; 95% CI 0.2–2.0; p=0.43; ≥44 ppb: OR 0.5; 95% CI 0.1–1.7; p=0.25), or childhood cancers (childhood leukemia and childhood non-Hodgkin's lymphoma; >0–≤44 ppb: OR 1.8; 95% CI 0.5–6.6; ≥44 ppb; p=0.36: OR 1.4; 95% CI 0.3–5.6; p=0.66). For neural tube defects, ORs were 3.7 (95% CI 1.0–14.1; p=0.06) and 0.4 (95% CI 0.1–1.8; p=0.23) in the low and high exposure groups, respectively.

A study examining the association between prenatal and early childhood exposure to tetrachloroethylene in drinking water and cancer is reviewed in Section 3.2.2.7 (Aschengrau et al. 2015).

Increased numbers of postnatal deaths, and increased micro/anophthalmia were observed in offspring of rats treated by gavage with 900 mg/kg/day tetrachloroethylene in corn oil on gestation days 6–19 (Narotsky and Kavlock 1995). This dose also resulted in maternal toxicity (ataxia and decreased body weight gain of approximately 25% less than controls). 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 ($p<0.001$; Narotsky and Kavlock 1995). 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 <0.01) and total activity ($p<0.01$) was observed at both doses.

All reliable LOAELs values identified in rats and mice are recorded in Table 3-4 and plotted in Figure 3-16.

3.2.2.7 Cancer

Cancer Classifications. Cancer classifications for tetrachloroethylene by the HHS (NTP 2016), IARC (2014), and EPA (2012a) are reviewed in Section 3.2.1.7 (Inhalation, Cancer). Conclusions made in comprehensive reviews (EPA 2012a; IARC 2014; NRC 2010) regarding associations between tetrachloroethylene exposure and specific cancer types also are summarized.

Epidemiological Studies. The epidemiological data on cancers among humans exposed orally to tetrachloroethylene is much more limited than the inhalation data due to small numbers of studies and small population/cohort sizes, as well as potential confounding by co-exposure to other chlorinated solvents. Table 3-5 provides an overview of selected epidemiological studies, including information on study types (cohort, case-control), study populations (specific geographic locations), exposure assessments (qualitative versus semi-quantitative, assessment methods), consideration of confounders, and study strengths and limitations. Studies were selected based on the following considerations: studies that EPA (2012a) relied upon to support conclusions regarding associations between tetrachloroethylene exposure and specific cancer types; studies that EPA (2012a) considered to have higher quality exposure assessments; and studies published after EPA (2012a), with higher quality exposure assessments (as defined by EPA 2012a). For oral exposure, EPA (2012a) considered higher quality exposure assessments to include the following: biological monitoring data; estimated exposure through use of statistical models of the water distribution system; and consideration of confounders. For additional details and reviews of these and other epidemiological studies assessing the potential carcinogenicity of tetrachloroethylene, the EPA IRIS Toxicological Review for Tetrachloroethylene (EPA 2012a), IARC (2014), and NRC (2010) may be consulted.

Selected studies include five retrospective cohort studies, eight case-control studies, and one ecological study, with populations exposed through contaminated drinking water. Several studies conducted by the same research group examined a population from Cape Cod, Massachusetts exposed to tetrachloro-ethylene in drinking water that was contaminated through leaching from the vinyl lining of distribution pipes from the late 1960s to the early 1980s (Aschengrau et al. 1993, 1998, 2015; Gallagher et al. 2011; Paulu et al. 1999; Vieira et al. 2005). Two studies of this population (Aschengrau et al. 1998, 2003) are follow-ups of an earlier study (Aschengrau et al. 1993), and the Gallagher et al. (2011) study was a reanalysis of data from Aschengrau et al. (1998, 2003) and Paulu et al. (1999). One study of the Cape Cod population examined cervical cancer in adult women exposed prenatally and during early childhood

Table 3-5. Overview of Epidemiological Studies Evaluating Associations between Oral Tetrachloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Cohort studies			
Aschengrau et al. 2015; Cape Cod, Massachusetts; prenatal and early childhood exposures; outcome measured in adults	Semi-quantitative; RDD estimated by Webler and Brown (1993) algorithm, based on leaching model by Demond (1982)	Sex; race; age; education; employment status; marital status; smoking; alcoholic use; illicit drug use; history of solvent related jobs and hobbies; family history of cancer and other diseases; parental characteristics and behaviors during the subject's pregnancy	Strengths[b]: authors did not note any specific strengths Limitations[b]: low response rate; potential exposure misclassification; young age of the participants (mean age exposed: 29.6 years; mean age unexposed: 29.2 years
ATSDR 2018; Camp Lejeune, North Carolina; military personnel	Historical reconstruction of drinking water levels using groundwater fate and transport and water-distribution system models	Sex; age at diagnosis	Strengths[b]: very large cohort (n=50,684); small percentage of loss to follow-up; rigorous reconstruction of historical levels of drinking water contamination; confirmation of diagnosis decreased over-reporting bias Limitations[b]: numbers of participants in each exposure category were not reported; exposure misclassification bias; data on water consumption were not collected
Bove et al. 2014a; Camp Lejeune, North Carolina; military personnel	Historical reconstruction of drinking water levels using groundwater fate and transport and water-distribution system models	Age; sex; race; calendar period	Strengths[b]: large cohort; small percentage of loss to follow-up; rigorous reconstruction of historical levels of drinking water contamination. Limitations[b]: exposure misclassification bias; disease misclassification bias

Table 3-5. Overview of Epidemiological Studies Evaluating Associations between Oral Tetrachloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Bove et al. 2014b; Camp Lejeune, North Carolina; civilian employees	Historical reconstruction of drinking water levels using groundwater fate and transport and water-distribution system models	Age; sex; race; calendar period	Strengths[b]: small percentage of loss to follow-up; rigorous reconstruction of historical levels of drinking water contamination Limitations[b]: exposure misclassification bias; lack of information on water usage; small numbers of some cancers resulted in wide CIs; not possible to evaluate exposure-response relationships due to small incidence numbers; lack of information on smoking and other risk factors
Cohn et al. 1994; New Jersey; adults	Qualitative; exposure potential based on water monitoring data	Sex; age	Strengths: none noted by study authors or EPA (2012a) Limitations: lack of adjustment for possible confounders; potential misclassification of exposure; lack of information on individual exposure potential
Case-control studies			
Aschengrau et al. 1993; Cape Code, Massachusetts; adults	Semi-quantitative; RDD estimated by Webler and Brown (1993) algorithm, based on leaching model by Demond (1982)	Sex; age at diagnosis (cases) or index year (controls); vital status; education; occupational exposures; smoking; irradiation treatment; previous UTI and kidney stones	Strengths: considered confounders, including occupational exposures; examined the effect of latency periods. Limitations: small bladder cancer sample size; unknown levels of exposures; nonblinded interviews
Aschengrau et al. 1998; Cape Code, Massachusetts; adults	Semi-quantitative; RDD estimated by Webler and Brown (1993) algorithm, based on leaching model by Demond (1982)	Age at diagnosis (cases) or index year (controls); family history of breast cancer; age at first live birth or stillbirth; personal history of prior breast cancer and benign breast disease; occupational exposure to solvents	Strengths: consideration of several confounders Limitations: potential error in exposure estimates; small numbers of participants; possible misclassification due to inaccurate reporting on death certificates

Table 3-5. Overview of Epidemiological Studies Evaluating Associations between Oral Tetrachloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Aschengrau et al. 2003; Cape Cod, Massachusetts; adults	Semi-quantitative; RDD estimated by Webler and Brown (1993) algorithm, based on leaching model by Demond (1982)	Age at diagnosis (cases) or index year (controls); family and personal history of breast cancer; age at first live birth or stillbirth, occupational exposure to tetrachloroethylene	No strengths or limitations noted by study authors or EPA (2012a)
Gallagher et al. 2011; Cape Cod, Massachusetts; adults	Semiquantitative; RDD estimated by Webler and Brown (1993) algorithm, using a water distribution model (EPANET 2.0) that replaced the Webler-Brown flow model component	Age at diagnosis (cases) or index year (controls); vital status; family and personal history of breast cancer; age at first live birth or stillbirth; occupational exposure to tetrachloroethylene; study of origin	Strengths[b]: refined exposure assessment Limitations[b]: none noted by the study author
Paulu et al. 1999; Cape Cod, Massachusetts; adults	Semi-quantitative; RDD estimated by Webler and Brown (1993) algorithm, based on leaching model by Demond (1982)	Sex, age at diagnosis (cases) or index year (controls); vital status; education; occupational exposures; colorectal cancer further adjusted for history of polyps, inflammatory bowel disease, and occupational history; lung cancer further adjusted for smoking, living with a smoker, and occupational history associated with lung cancer	Strengths: consideration of several confounders and latency period Limitations: lack of measured tetrachloroethylene levels; low number of cases for brain and pancreatic cancer
Ruckart et al. 2013; Camp Lejeune, North Carolina; childhood cancer	Historical reconstruction of drinking water levels using groundwater	Maternal age and education; use of prenatal vitamins; working; smoking; alcohol use; 1st trimester fever; child's sex;	Strengths[b]: none noted by the study author Limitations[b]: small number of cases; case information obtained from surveys; non-participation of 20% of pregnancies occurring at Camp Lejeune during the study

Table 3-5. Overview of Epidemiological Studies Evaluating Associations between Oral Tetrachloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
	fate and transport and water-distribution system models	paternal occupational exposure to solvents	time period; interviews conducted from 20 to 37 years after the births that likely contributed to recall errors; due to small number of cases, could not distinguish effects of one chemical independent of the others; incomplete data on gestational age at birth; possible exposure misclassification
Ruckart et al. 2015; Camp Lejeune, North Carolina; adults	Historical reconstruction of drinking water levels using groundwater fate and transport and water-distribution system models	Age at diagnosis; race; service in Vietnam	Strengths[b]: none noted by the study author Limitations[b]: findings based on a small number of cases resulting in wide CIs for the estimated risk estimates; due to small numbers of cases, could not distinguish effects of one chemical independent of the others
Vieira et al. 2005; Cape Cod, Massachusetts; adults	Semiquantitative; PDD model that considered three exposure routes: inhalation, dermal absorption, and ingestion	History of benign breast disease; past use of diethylstilbestrol, oral contraceptives, and menopausal hormones; smoking history; alcohol use; history of ionizing radiation treatment; obesity; race; marital status; religion; education level; physical activity level	Strengths: incorporation of personal behaviors in estimating exposure; examination of non-proxy respondents to reduce misclassification bias; comparison of results from only non-proxy respondents to results of all subjects Limitations: use of cumulative exposures, which could mask the effect of intensity of exposure; recall bias for behavioral data; smaller sample size due to the use of non-proxy respondents only

Table 3-5. Overview of Epidemiological Studies Evaluating Associations between Oral Tetrachloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Ecological study			
Vartiainen et al. 1993; Finland	Qualitative; urine tetrachloroethylene and metabolites (yes/no exposure)	None	Strengths: use of the Finnish Cancer Registry (contained all cancer cases since 1953 and increased the confidence in calculated estimates) Limitations: extended latency time between exposure to tetrachloroethylene and cancer diagnosis; ambiguity related to the time-period within which cases were exposed; likely exposure misclassification due to ecologic study design; exposure classification not validated for cases or controls

[a]Unless otherwise noted, study strengths and limitations were noted by EPA (2012a).
[b]Study strengths and limitations were noted by the study authors.

CI = confidence interval; EPA = U.S. Environmental Protection Agency; PDD = personal delivered dose; RDD = relative delivered dose; UTI = urinary tract infection

(Aschengrau et al. 2015). Studies have also evaluated military personnel and civilians from the Marine Corps Base at Camp Lejeune, North Carolina (ATSDR 2018; Bove et al. 2014a, 2014b; Ruckert et al. 2013, 2015). The Ruckart et al. (2013) study examined childhood hemopoietic cancers in children exposed prenatally and in early childhood. Other drinking water studies examined populations from New Jersey (Cohn et al. 1994) and Finland (Vartiainen et al. 1993).

Exposure assessment methods are listed in Table 3-5. It is important to note that none of the exposure assessments included individual monitoring data or rigorous monitoring to determine individual tetrachloroethylene intake. Most studies provided a semi-quantitative estimate of oral exposure based on exposure and leaching models. One study (Vieira et al. 2005) used an exposure model that considered combined exposure by oral, inhalation, and dermal routes through ingestion and bathing. Vartiainen et al. (1993) determined exposure by measurement of urinary tetrachloroethylene and metabolites, however, outcomes were not linked to individual urinary measurements (exposure was qualified as yes/no).

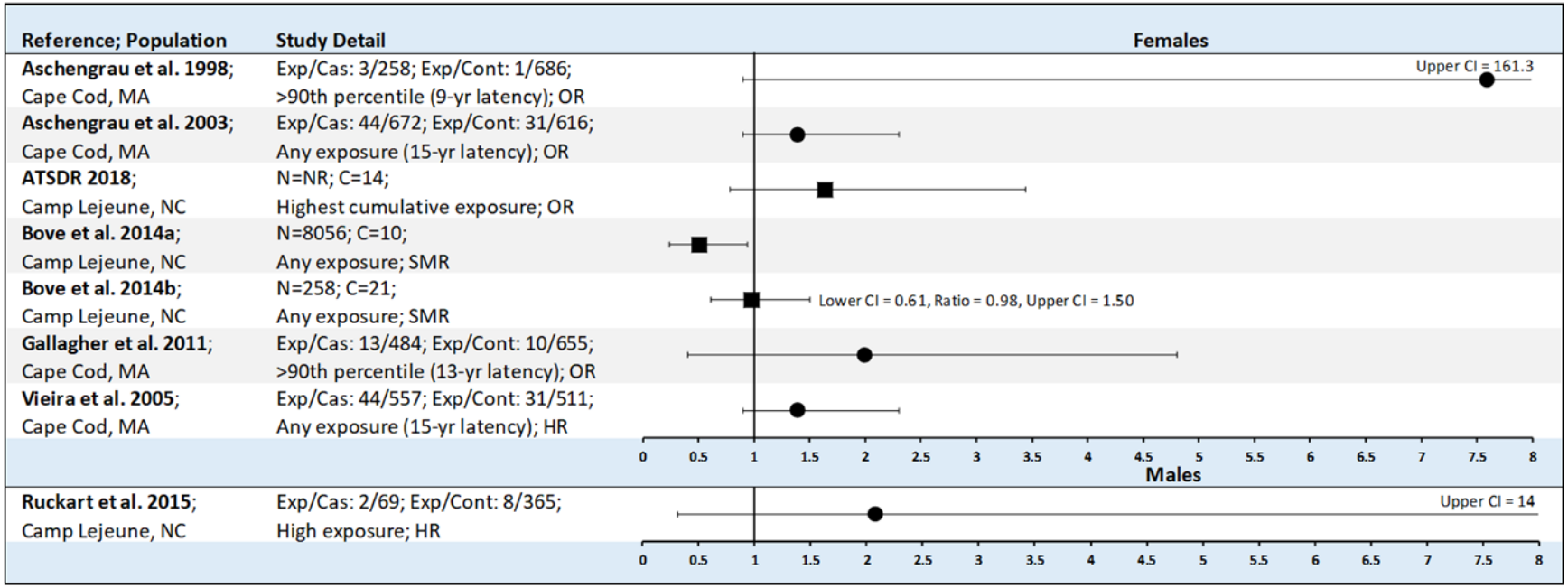
The potential influence of confounding factors is an important consideration in the interpretation of these epidemiological studies. As summarized in Table 3-5, consideration of confounders was not consistent across studies. Studies of the Cape Cod population evaluated numerous confounders; in contrast, other studies considered no confounders (Vartiainen et al. 1993) or a smaller number of confounders (Ruckert et al. 2013, 2015). Lack of consideration of confounding factors may add uncertainty to interpretation of study results. For assessments of the carcinogenic potential of tetrachloroethylene, it is important to consider the potential influence of exposure to other solvents and chemicals. In all studies, drinking water contained multiple contaminants. For example, drinking water at the Camp Lejeune was contaminated with tetrachloroethylene benzene, vinyl chloride, and trans-1,2-dichloroethylene (Cohn et al. 1994; Ruckert et al. 2013). In the Vartiainen et al. (1993) study, drinking water was contaminated with both trichloroethylene and tetrachloroethylene. Although most studies considered co-contaminants as confounders, it is difficult to rule out potential contributions of other chemicals, especially when studies have small numbers of cases. In addition, smoking should be considered as an important confounder for bladder and lung cancer (EPA 2012a; Guyton et al. 2014). All studies relied on qualitative or semi-quantitative methods to assign exposure histories to subjects. Semi-quantitative methods included the use of leaching and transport models to estimate amounts of tetrachloroethylene delivered to residential supply lines along with self-reported information on residence addresses during the applicable exposure period (e.g., Aschengrau et al. 2015). Exposure misclassification is possible from use of these models because they do not estimate individual tetrachloroethylene intakes and the amounts of tetrachloroethylene delivered to each residence may not reflect long-term drinking water exposure

concentrations or tetrachloroethylene intakes. Non-differential exposure misclassification (misclassification rate is the same among exposure groups) will tend to bias the estimates of relative risk downward. However, differential exposure misclassification could bias the risk estimates in the up or down direction.

Study results based on cancer end points are shown in figures as noted below. These figures include information on geographic location of the population (e.g., Cape Cod, Camp Lejeune), number of participants/cases, cancer incidence, and study statistics (e.g., risk values and CIs) as reported by the study authors. For studies that evaluated males, females, and combined males and females, if risk values were similar, results for combined males and females are presented; however, if results differed between these groups, values for all groups are presented. For studies evaluating males and females separately (with no combined group), data for both are presented. Exposure classifications (e.g., qualitative or semiquantitative exposure) for presented risk values also are included.

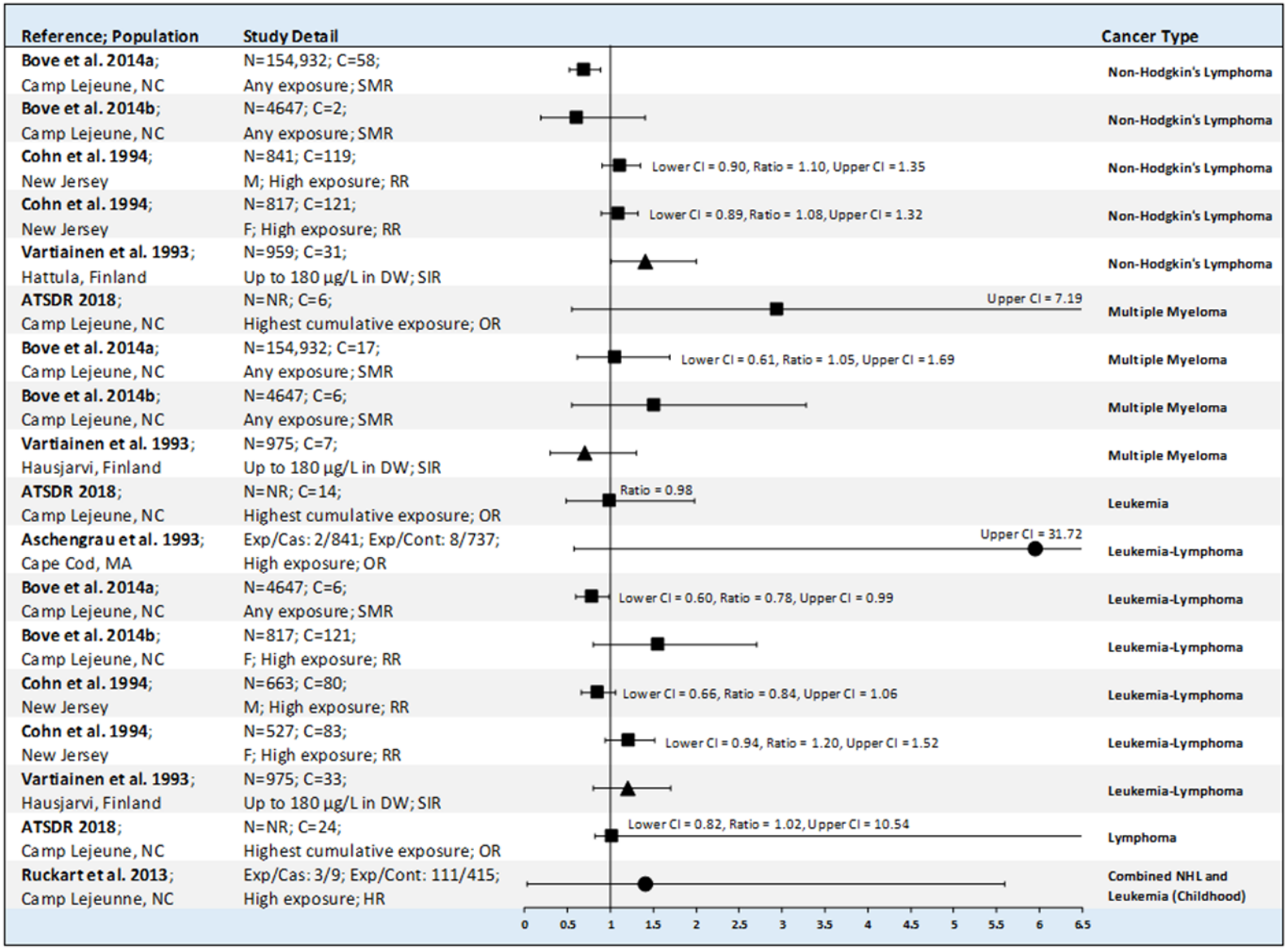
The most studied cancer end points for populations exposed to tetrachloroethylene in drinking water are breast cancer and hematopoietic cancers (non-Hodgkin's lymphoma, multiple myeloma, and leukemia/lymphoma). Studies examining breast cancer were conducted in women (Aschengrau et al. 1998, 2003; ATSDR 2018; Gallagher et al. 2011), except for one study that examined breast cancer in males (Ruckert et al. 2015); data are shown in Figure 3-17. For hematopoietic cancers, five studies were conducted in adults (ATSDR 2018; Bove et al. 2014a, 2014b; Cohn et al. 1994; Vartianinen et al. 1993) and one study examined children (Ruckart et al. 2013). Study results for hematopoietic cancers are shown in Figure 3-18. Less data are available for other cancer types (and all cancers and cancers of the bladder, kidney, liver, pancreas, lung, colon, rectum, brain/central nervous system, cervix, and prostate). Results of studies examining these cancer types are shown in Figure 3-19.

Figure 3-17. Summary of Epidemiological Studies Evaluating Associations between Oral Tetrachloroethylene and Breast Cancer



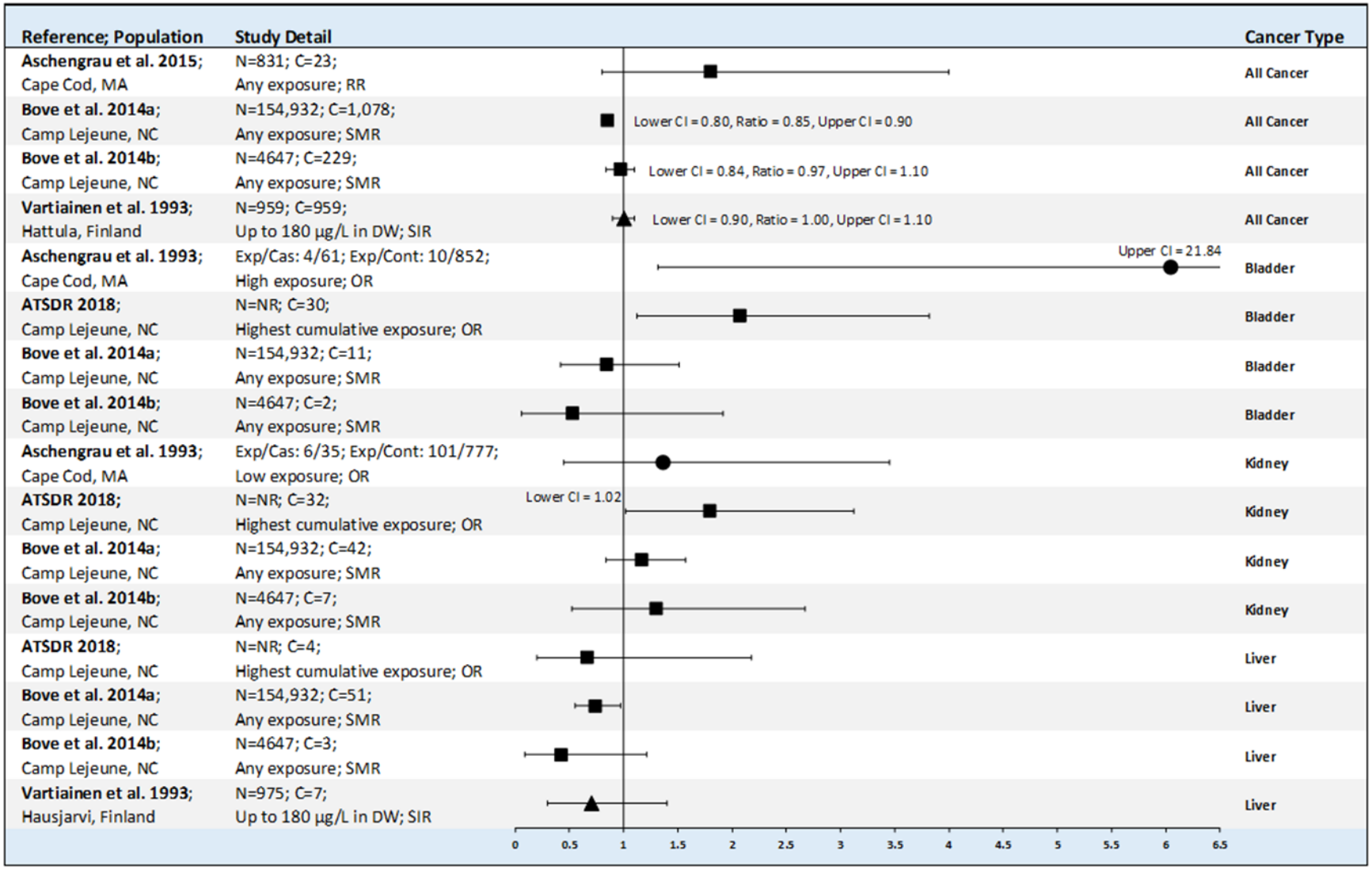
= risk estimate and 95% CI for cohort studies; = risk estimate and 95% CI for case-control studies; C = number with cancer; CI = confidence interval; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; HR = hazard ratio; N = population size; OR = odds ratio

Figure 3-18. Summary of Epidemiological Studies Evaluating Associations between Oral Tetrachloroethylene and Hematopoietic Cancers



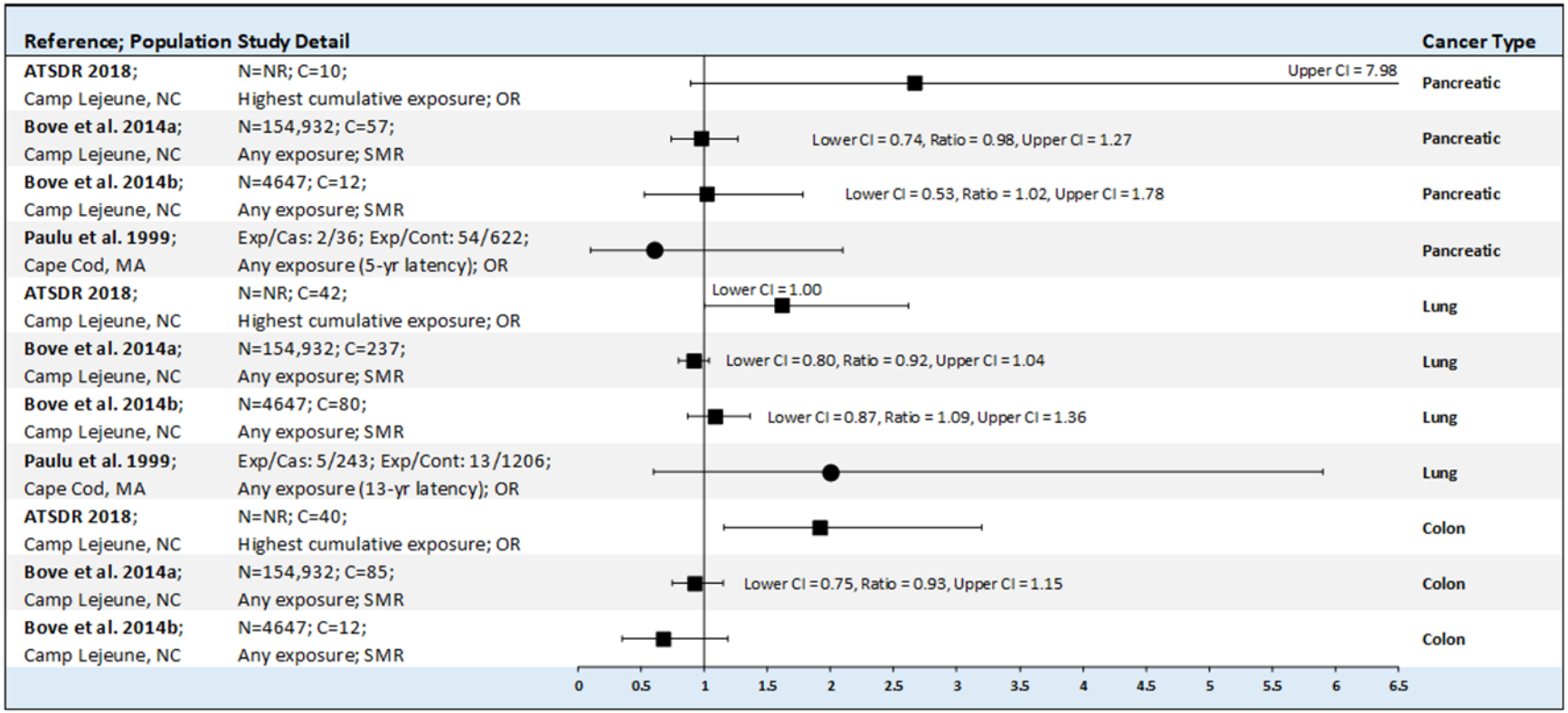
= risk estimate and 95% CI for cohort studies; = risk estimate and 95% CI for case-control studies; = risk estimate and 95% CI for ecological studies;
C = number with cancer; CI = confidence interval; DW = drinking water; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; N = population size; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-19. Summary of Epidemiological Studies Evaluating Associations between Oral Tetrachloroethylene and Other Cancers



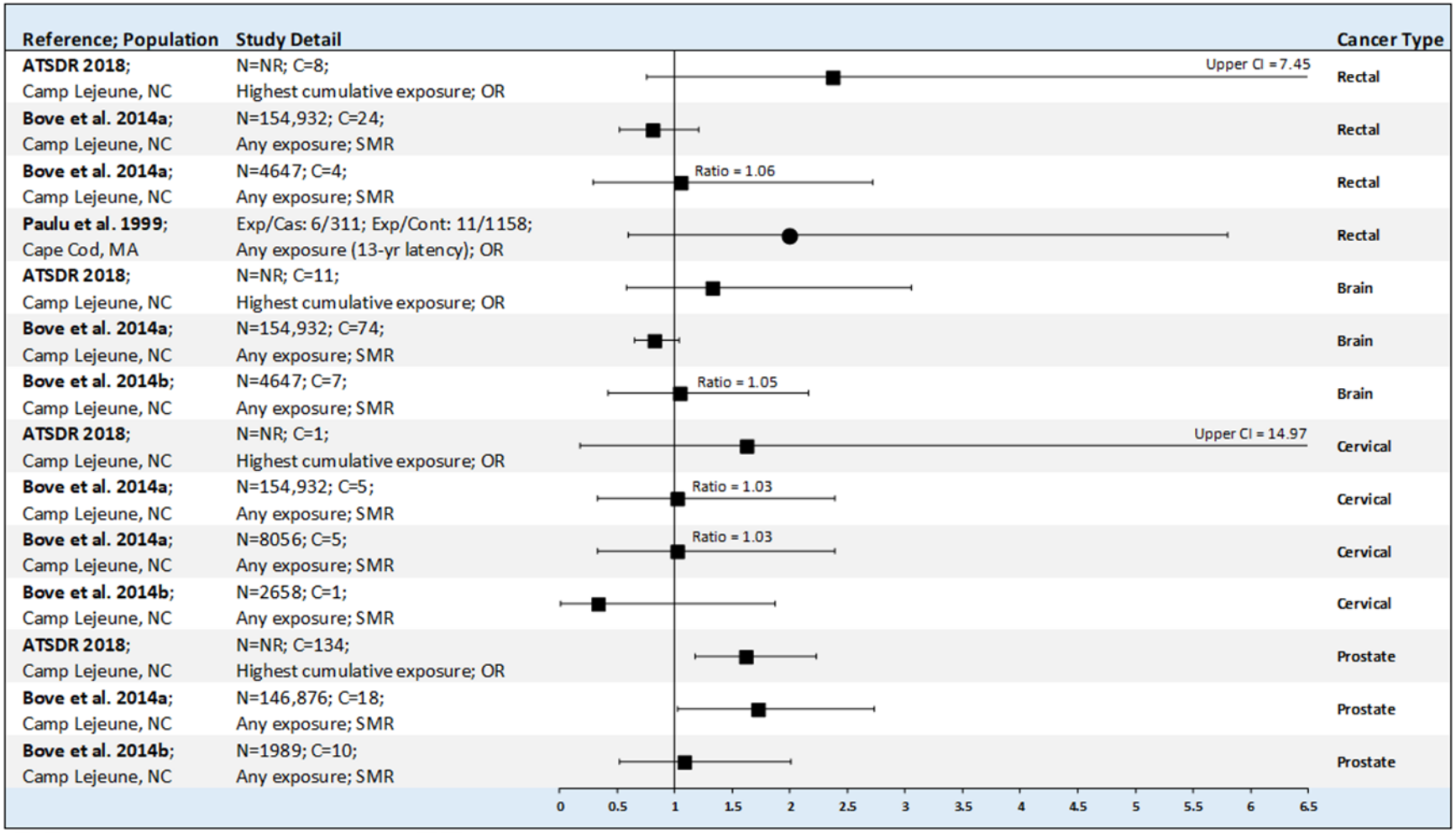
= risk estimate and 95% CI for cohort studies; = risk estimate and 95% CI for case-control studies; = risk estimate and 95% CI for ecological studies; C = number with cancer; CI = confidence interval; DW = drinking water; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; N = population size; OR = odds ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-19. Summary of Epidemiological Studies Evaluating Associations between Oral Tetrachloroethylene and Other Cancers *(continued)*



= risk estimate and 95% CI for cohort studies; = risk estimate and 95% CI for case-control studies; C = number with cancer; CI = confidence interval; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; N = population size; OR = odds ratio; SMR = standardized mortality ratio

Figure 3-19. Summary of Epidemiological Studies Evaluating Associations between Oral Tetrachloroethylene and Other Cancers *(continued)*



= risk estimate and 95% CI for cohort studies; = risk estimate and 95% CI for case-control studies; C = number with cancer; CI = confidence interval; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; N = population size; OR = odds ratio; SMR = standardized mortality ratio

Studies in Laboratory Animals. Cancer has been reported in experimental animals after oral exposure to tetrachloroethylene. Osborne-Mendel rats and B6C3F1 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 3.2.2.2). 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, respectively, in male mice, and 2/20, 0/20, 19/48, and 19/48, respectively, 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 GGT-positive type I altered foci. Tetrachloroethylene did promote the appearance of type II altered foci, both in the presence and absence of an initiator (in this case, diethylnitrosamine) (Story et al. 1986).

All reliable CELs are recorded in Table 3-4 and plotted in Figure 3-16.

3.2.3 Dermal Exposure

3.2.3.1 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.

3.2.3.2 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 tetrachloroethylene for 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 1–2 hours after exposure, was present in all cases. Chemical burns characterized by severe cutaneous erythema, blistering, and sloughing 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 (Kinkead and Leahy 1987).

Ocular Effects. Intense ocular irritation has been reported in humans after acute exposure to tetrachloroethylene vapor at concentrations >1,000 ppm (Carpenter 1937; Rowe et al. 1952). Vapors of tetrachloroethylene at 5 or 20 ppm were irradiated along with nitrogen dioxide in an 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.

3.2.3.3 Immunological and Lymphoreticular Effects

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

3.2.3.4 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.

3.2.3.5 Reproductive Effects

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

3.2.3.6 Developmental Effects

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

3.2.3.7 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).

3.2.4 Other Routes of Exposure

3.2.4.1 Immunological and Lymphoreticular Effects

Seo et al. (2008b, 2012) showed that tetrachloroethylene, administered intraperitoneally at 0.1 mg/kg in rats or ≥0.01 mg/kg in mice, significantly enhanced the passive cutaneous anaphylazis reaction in rats and mice.

3.3 GENOTOXICITY

The results of *in vitro* and *in vivo* genotoxicity studies are summarized in Tables 3-6 and 3-7, respectively. Data from these assays indicate that tetrachloroethylene has the potential to be genotoxic. Results of studies on lymphocytes of humans occupationally exposed to tetrachloroethylene provide mixed results for DNA and chromosome damage. In other *in vivo* assays (in rats, mice, and *Drosophila*), mixed results were shown for gene mutation, DNA binding and/or damage, chromosomal aberrations, and induction of micronuclei. An evaluation of the genotoxic potential of tetrachloroethylene *in vitro* suggests that tetrachloroethylene is unlikely to induce reverse mutations in *Salmonella typhimurium*; however, positive responses have been observed under some conditions (possibly due to metabolites and/or contaminants). Assays for chromosomal aberrations and DNA damage in mammalian cells have also shown mixed results, and most positive results required the presence of metabolic activation.

Table 3-6. 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; Emmert et al. 2006; Haworth et al. 1983; NTP 1986; Watanabe et al. 1998
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:				
Fisher rat embryo cells	Cell transformation	+	NR	Price et al. 1978
BALB/C3T3 mouse cells		–	NR	Tu et al. 1985
		–	–	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
Human lymphocytes	DNA damage	–	–	Hartman and Speit 1995
Human lymphocytes	Sister chromatid exchange	–	–	Hartman and Speit 1995
Chinese hamster ovary cells	Sister chromatid exchange	–	–	NTP 1986
Human MCL-5 cells (metabolically enhanced)	Micronucleus	NR	+	White et al. 2001
Chinese hamster lung cells	Micronucleus	–	–	Matsushima et al. 1999
Chinese hamster ovary (CHO-K1) cells	Micronucleus	NT	+	Wang et al. 2001

— = negative result; +/– = mixed results; + = positive result; DNA = deoxyribonucleic acid; NR = not reported; NT = not tested

Table 3-7. Genotoxicity of Tetrachloroethylene *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Human lymphocytes	Sister chromatid exchange	–	Ikeda et al. 1980; Seiji et al. 1990
Human lymphocytes	Chromosomal aberrations	–	Tucker et al. 2011
Human lymphocytes	Chromosome aberrations	(+/–)	Everatt et al. 2013
Human lymphocytes	DNA damage	+	Tucker et al. 2011
Human lymphocytes	DNA damage	+	Everatt et al. 2013
Human leukocytes	DNA damage	+	Azimi et al. 2017
Human leukocytes and urine	DNA damage	–	Toraason et al. 2003
Human lymphocytes	Micronucleus	+	Everatt et al. 2013
Rat/lymphocytes, liver, urine	DNA damage	–	Toraason et al. 1999
Mouse	DNA damage/induction of single strand breaks	+	Walles 1986
Mouse/hepatocytes	DNA damage	+/–	Cederberg et al. 2010
Mouse/kidney	DNA damage	–	Cederberg et al. 2010
Mouse/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, before partial hepatectomy	Micronucleus	–	Murakami and Horikawa 1995
Mouse/reticulocytes, after partial hepatectomy	Micronucleus	+	Murakami and Horikawa 1995
Hot-mediated assays:			
Drosophila melanogaster/ sex-linked recessive lethal mutation	Gene mutation	–	NIOSH 1980; Valencia et al. 1985
Rat bone marrow cells	Chromosomal aberrations	–	NIOSH 1980
Human lymphocytes	Chromosomal aberrations	–	Ikeda et al. 1980
D. melanogaster/sex-linked recessive lethal mutation	Gene mutation	–	NTP 1986

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

Assays in humans following occupational exposure to tetrachloroethylene via inhalation have provided mixed results regarding genotoxicity (Table 3-7).

Everatt et al. (2013) reported increased DNA damage and increased frequency of micronuclei formation in peripheral lymphocytes of dry cleaning workers exposed to tetrachloroethylene. The study population consisted of 30 workers and 29 controls; no differences between groups were observed for age, smoking, or alcohol consumption. Exposure monitoring was conducted by sampling of personal breathing zone air on two consecutive work days, with a mean tetrachloroethylene concentration of 31.40 mg/m^3. DNA damage, as assessed by comet assay, was significantly increased in workers compared to controls (workers: 10.45; controls: 5.77; $p<0.05$). Results of assays to assess chromosome damage yielded mixed results. The frequency of micronuclei formation, an indicator of chromosome damage, was significantly increased in workers compared to controls (workers: 11.36; controls: 6.96; $p<0.05$). However, the chromosome aberration frequency was not significantly increased in workers, although multiple regression analysis showed associations between employment duration ($p=0.015$) and frequency of exposure ($p=0.019$) and chromosome aberrations.

Azimi et al. (2017) evaluated DNA damage, assessed by comet assay parameters, in 33 dry cleaners. The median duration of employment was 8 years, with a minimum duration of 3 months. Compared to controls (n=26), workers exposed to tetrachloroethylene had significantly ($p<0.001$) increased tail length (median workers: 25.85; median controls: 5.61), percent DNA in tail (median workers: 23.03; median controls: 8.77), and tail moment (median workers: 7.07; median controls: 1.03).

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 the 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).

In a study of 18 dry cleaning workers exposed to tetrachloroethylene at TWA concentrations >3.8 ppm for at least 1 year, no significant effect on the frequency of chromosome translocations in peripheral blood lymphocytes was observed in comparison to 18 control laundry workers (Tucker et al. 2011). Chromosomal damage was not significantly changed based on cigarette smoking or alcohol consumption. Evidence of transient chromosomal damage, namely increased frequencies of acentric fragments, was observed; TWA blood levels of tetrachloroethylene in dry cleaners significantly ($p=0.0026$) correlated with the frequency of these fragments. Although the sample sizes were small, no acentric fragments were observed in unexposed laundry workers. Using 8-hydroxydeoxyguanosine (8OHdG) as a marker for oxidative DNA damage and repair, Toraason et al. (2003) found no significant increase in DNA damage in the leukocytes or urine of 18 dry cleaner workers (exposed to TWA concentration of tetrachloroethylene of 3.8 ppm) compared to 20 laundry workers. While there was an association between blood tetrachloroethylene levels and urinary 8OHdG ($r=0.4661$; $p<0.044$), there was no association between exposure indices and biomarkers after adjustments for age, body mass index, race, smoking status, and blood levels of antioxidants.

In vivo animal assays likewise showed mixed results for the induction of DNA damage or micronucleus formation. In male CD-1 mice administered tetrachloroethylene at 1,000 or 2,000 mg/kg/day via gavage for 2 days, there was equivocal evidence for the induction of DNA damage (Cederburg et al. 2010). In comet assays, a weak but significant, dose-related increase in tail intensity, but not tail moment, was reported in hepatocytes ($p=0.041$ in one-sided Jonckheere-Terpstra test); no significant effects associated with DNA damage were observed in the kidney. Although the study authors classified the response in the liver as "positive," these data, when analyzed in the context of biological relevance by the lab that conducted the experiment and by Lillford et al. (2010), Lovell (2010), and Struwe et al. (2011), were classified as "negative." The bases for classification of the response in the liver as negative included the small magnitude of the response, interanimal variability, the order of analysis of biological samples, responses that fell within the range of historical controls, and the lack of a statistical effect using other statistical tests (Dunnett's test for pairwise comparisons). Although 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 in one study (Walles 1986), Toraason et al. (1999) found no significant increase in oxidative DNA damage (using 8OHdG as a biomarker) in the livers of rats administered a single intraperitoneal injection of tetrachloroethylene at up to 1,000 mg/kg. With

respect to micronucleus induction, 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 Horikawa 1995). Micronuclei were increased in hepatocytes at 1,000 and 2,000 mg/kg when mice were treated after partial hepatectomy. Additional *in vivo* studies showed no evidence of germ cell chromosomal damage and equivocal evidence of mutation in germ cells (positive in males, but not females, after one-time exposure only) of Sprague-Dawley rats exposed to tetrachloroethylene via inhalation for up to 5 days (NIOSH 1980).

In a study by Schumann et al. (1980), no DNA binding was observed in B6C3F1 mice exposed to tetrachloroethylene a single time via the inhalation or oral route of exposure. 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 after a single intraperitoneal injection (Mazzullo et al. 1987), providing some evidence that the glutathione metabolites of tetrachloroethylene may be mutagenic.

A large number of studies of *in vitro* genotoxicity of tetrachloroethylene have been performed using prokaryotic, eukaryotic, and mammalian cells (Table 3-6). Most of the studies using the Ames test with *S. typhimurium* have indicated that tetrachloroethylene itself is not a mutagen (Bartsch et al. 1979; Emmert et al. 2006; Haworth et al. 1983; NTP 1986; Watanabe et al. 1998). 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* TA1535 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 glutathione *S*-transferases in the presence of glutathione and rat kidney fraction resulted in the formation of the conjugate, *S*-(1,2,2-trichlorovinyl)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 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 vitro* 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. Other investigators found no effects on the DNA of rat and mouse hepatocytes or human lymphocytes (Costa and Ivanetich 1980; Hartman and Speit 1995). Most data do not support a directly mutagenic effect of tetrachloroethylene itself. The inconsistent results could be due to differences between tested species in metabolism or activation, protocol differences, or purity of the compound tested.

There are few data on clastogenic effects of tetrachloroethylene following *in vitro* exposure. When human lymphocytes and Chinese hamster ovary cells were assayed for sister chromatid exchanges, no increase in frequency was found (Hartman and Speit 1995; NTP 1986). Mixed results have been reported for micronucleus induction in human lymphocytes and Chinese hamster cell lines. There was no significant induction of micronuclei in Chinese hamster lung cells following exposure to tetrachloroethylene at up to 250 μg/mL in the presence or absence of metabolic activation (Matsushima et al. 1999). Wang et al. (2001) reported a dose-related, significant ($p<0.001$) increase in micronuclei in Chinese hamster ovary (CHO-K1) cells exposed to tetrachloroethylene at 63 ppm in a closed system. A dose-related increase ($p<0.05$) in micronuclei induction was likewise reported in human MCL-5 cells (metabolically enhanced to express human cytochrome P-450 enzymes) exposed to tetrachloroethylene at concentrations up to 2.0 mM (White et al. 2001). 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 (Price et al. 1978).

3.4 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, the duration of exposure, and at lower concentrations, 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 affinity 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 1–3% of the absorbed tetrachloroethylene is metabolized to trichloroacetic acid by humans, and the metabolism of tetrachloroethylene is saturable. Compared to humans, rodents, especially mice, metabolize more tetrachloroethylene to trichloroacetic acid. Geometric mean V_{max} values for the metabolism of tetrachloroethylene of 13, 144, and 710 nmol/(minute/kg) have been reported for humans, rats, and mice, respectively. Trichloroacetic acid produced from tetrachloroethylene is excreted in the urine, and in humans, trichloroacetic acid 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, 30–40, and 55 hours, respectively.

A PBPK model for tetrachloroethylene toxicokinetics in mice, rats, and humans was published in Chiu and Ginsberg (2011); this model built upon previous PBPK models for tetrachloroethylene and for the related compound, trichloroethylene.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

The primary route of human exposure to tetrachloroethylene is inhalation. In humans, tetrachloroethylene is readily absorbed into the blood through the lungs. The blood:gas partition coefficient of tetrachloroethylene in humans exposed for 4–6 hours to concentrations between 1 and 70 ppm ranged between 9.4 and 12.54 during exposure and between 15.74 and 23.65 after exposure (Chiu et al. 2007; Monster et al. 1979). Estimates of human blood:air partition coefficients from *in vitro* methods are shown in Table 3-8; in large part, these estimates are consistent with the *in vivo* values. *In vitro* blood:gas partition coefficients obtained by Mahle et al. (2004) suggest no gender- or age-related differences in partitioning between males and females or between pediatric and adult human blood.

Available data suggest that 64–100% of inhaled tetrachloroethylene is taken up from the lungs (Chiu et al. 2007; Monster et al. 1979). Pulmonary uptake of tetrachloroethylene is proportional to ventilation rate,

Table 3-8. Partition Coefficients for Tetrachloroethylene in Mice, Rats, Dogs, and Humans

Partition coefficients[a]	Mouse	Rat	Dog	Human	Method[b]	Reference
Blood/air	16.9	18.9		10.3	Vial equilibration	Ward et al. 1988
Blood/air	21.5			11.6	Smear method	Gearhart et al. 1993
Blood/air		33.5		19.8	Smear method	Byczkowski and Fisher 1994
Blood/air		19.8			Intraarterial dosing	Dallas et al. 1994b
Blood/air		19.6	40.5		Oral dosing	Dallas et al. 1994a
Blood/air				16.67	Vial equilibration	Fisher et al. 1997
Blood/air					Vial equilibration	Mahle et al. 2004
males		12.8		15.8		
females				15.3		
Liver/air	70.3	70.3		70.3	Vial equilibration	Ward et al. 1988
Liver/air		62			Vial equilibration	Gearhart et al. 1993
Liver/air	48.8	50.2		61.1	Smear method	Gearhart et al. 1993
Liver/air		33.5			Vial equilibration	Mahle et al. 2004
Fat/air	2,060	2,300		1,638	Vial equilibration	Ward et al. 1988
Fat/air		1,237			Vial equilibration	Gearhart et al. 1993
Fat/air	1,510	1,437		1,450	Smear method	Gearhart et al. 1993
Fat/air		1,474			Vial equilibration	Mahle et al. 2004
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
Muscle/air		18.1			Vial equilibration	Gearhart et al. 1993
Muscle/air	79.1	21.7		70.5	Smear method	Gearhart et al. 1993
Muscle/air		25.0			Vial equilibration	Mahle et al. 2004
Kidney/air		51.7			Vial equilibration	Gearhart et al. 1993
Kidney/air	79.1	51.3		58.6	Smear method	Gearhart et al. 1993
Kidney/air		30.6			Vial equilibration	Mahle et al. 2004
Brain/air		38.6			Vial equilibration	Mahle et al. 2004
Milk/air				59.27	Vial equilibration	Fisher et al. 1997
Liver/blood	2.3			5.28	Smear method	Gearhart et al. 1993
Liver/blood		1.9		6.83	Smear method	Byczkowski and Fisher 1994
Liver/blood		5.3			Intraarterial dosing	Dallas et al. 1994b
Liver/blood		5.0	2.4		Oral dosing	Dallas et al. 1994a
Fat/blood	70.4			125	Smear method	Gearhart et al. 1993
Fat/blood		42.4		159	Smear method	Byczkowski and Fisher 1994
Fat/blood		152			Intraarterial dosing	Dallas et al. 1994b
Fat/blood		150.5	71.4		Oral dosing	Dallas et al. 1994a
Muscle/blood	3.69			6.11	Smear method	Gearhart et al. 1993
Muscle/blood		3.0			Intraarterial dosing	Dallas et al. 1994b
Muscle/blood		2.4	2.4		Oral dosing	Dallas et al. 1994a
Kidney/blood	2.3			5.1	Smear method	Gearhart et al. 1993

Table 3-8. Partition Coefficients for Tetrachloroethylene in Mice, Rats, Dogs, and Humans

Partition coefficients[a]	Mouse	Rat	Dog	Human	Method[b]	Reference
Kidney/blood		4.5			Intraarterial dosing	Dallas et al. 1994b
Kidney/blood		3.2	2.1		Oral dosing	Dallas et al. 1994a
Lung/blood		2.5			Intraarterial	Dallas et al. 1994b
Lung/blood		1.9	1.3		Oral dosing	Dallas et al. 1994a
Brain/blood		4.4			Intraarterial dosing	Dallas et al. 1994b
Brain/blood		4.1	4.1		Oral dosing	Dallas et al. 1994a
Heart/blood		2.7			Intraarterial dosing	Dallas et al. 1994b
Heart/blood		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/pediatric (pups, infants, children)						
Blood/air		24.3		8	Smear method	Byczkowski and Fisher 1994
Blood/air					Vial equilibration	Mahle et al. 2004
males		15.1		15.7		
females		15.8		15.7		
Liver/air					Vial equilibration	Mahle et al. 2004
males		42.2				
females		40.0				
Fat/air					Vial equilibration	Mahle et al. 2004
males		945.0				
females		1,014				
Muscle/air					Vial equilibration	Mahle et al. 2004
males		95.1				
females		126.7				
Kidney/air					Vial equilibration	Mahle et al. 2004
males		31.8				
females		30.6				
Brain/air					Vial equilibration	Mahle et al. 2004
males		28.9				
females		29.7				
Other tissues/ blood		4.5		6.6	Smear method	Byczkowski and Fisher 1994
Aged/elderly						
Blood/air		20.9			Vial equilibration	Mahle et al. 2004
Liver/air		65.9			Vial equilibration	Mahle et al. 2004
Fat/air		2,002			Vial equilibration	Mahle et al. 2004
Muscle/air		60.4			Vial equilibration	Mahle et al. 2004

Table 3-8. Partition Coefficients for Tetrachloroethylene in Mice, Rats, Dogs, and Humans

Partition coefficients[a]	Mouse	Rat	Dog	Human	Method[b]	Reference
Kidney/air		37.7			Vial equilibration	Mahle et al. 2004
Brain/air		58.3			Vial equilibration	Mahle et al. 2004

[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 tetrachloroethylene. 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 three dogs were sacrificed 1, 4, 12, 24, 48, and 72 hours after dosing.

duration of exposure, and at lower atmospheric concentrations of tetrachloroethylene, concentration of tetrachloroethylene in the inspired air (Hake and Stewart 1977; Stewart et al. 1981). In addition, a study of male volunteers showed higher total uptake of inhaled tetrachloroethylene with higher lean body mass; minute volume and adipose tissue did not influence uptake (Monster et al. 1979).

The rate of tetrachloroethylene uptake by the lungs is initially high, but decreases during exposure (Monster et al. 1979); this pattern is common for lipophilic compounds. The concentration of tetrachloroethylene in the venous blood of six male volunteers peaked near the end of a 6-hour exposure to 1 ppm, and declined thereafter (Chiu et al. 2007).

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 dependent on ventilation and retention index, 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 also indicate that tetrachloroethylene is readily absorbed through the lungs into the blood. Total recovery of radioactivity from expired air and urine was 90–95% when measured up to 72 hours after male Sprague-Dawley rats were exposed for 6 hours to 10 or 600 ppm tetrachloroethylene (Pegg et al. 1979). 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. Near steady-state 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 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 from the lungs was not proportional to inhaled concentration, possibly as a consequence of saturable metabolism (see Section 3.4.3).

3.4.1.2 Oral Exposure

Tetrachloroethylene was found in the blood of a 6-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. Recovery of tetrachloroethylene from expired air and urine was 90.5–95% (up to 72 hours postdosing) in Sprague-Dawley rats given a single gavage dose of 1 or 500 mg/kg tetrachloroethylene in corn oil (Pegg et al. 1979). The peak blood tetrachloroethylene concentration of 40 μg/mL was measured 1 hour after dosing at 500 mg/kg tetrachloroethylene (Pegg et al. 1979); the analytical technique used lacked the sensitivity to precisely measure blood levels following administration of 1 mg/kg tetrachloroethylene. In Sprague-Dawley rats and Beagle dogs given a single oral dose of tetrachloroethylene (10 mg/kg in polyethylene glycol 400) by gavage, the absorption constants were estimated to be 0.025/minute for rats and 0.34/minute for dogs (Dallas et al. 1994a). Maximum blood concentrations of tetrachloroethylene were reached 20–40 and 15–30 minutes in rats and dogs, respectively, after a single oral dose of tetrachloroethylene (1, 3, or 10 mg/kg) (Dallas et al. 1994a).

3.4.1.3 Dermal Exposure

Dermal absorption of tetrachloroethylene may occur with exposure to the vapor form as well as the liquid form. When volunteers' forearms and hands were exposed to tetrachloroethylene vapor (6.68 mmol/L) in a dynamic exposure chamber for 20 minutes, the concentration of tetrachloroethylene in exhaled air peaked approximately 45 minutes after exposure began (Kezic et al. 2000). The study authors estimated the tetrachloroethylene skin permeation rate to be 0.054 cm/hour. 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.

Animal studies also indicate that dermal uptake of tetrachloroethylene 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 exposures of 1,000 and 3,000 ppm, respectively. Tetrachloroethylene exposure (12,500 ppm) of F344 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).

Dermal uptake of liquid tetrachloroethylene may be enhanced by its lipophilic properties; lipophilic compounds may lead to defatting of the skin and disruption of the stratum corneum, increasing absorption. Dermal flux of neat liquid tetrachloroethylene was estimated to be 69 nmol/cm^2/minute in volunteers when each person's forearm skin (27 cm^2) was exposed to liquid tetrachloroethylene for 3 minutes (Kezic et al. 2001). The maximal rate of absorption, estimated based on measurements of tetrachloroethylene in expired air, occurred 20 minutes after the exposure began. Dermal absorption of tetrachloroethylene in liquid form 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). A peak concentration of 0.31 ppm in exhaled air was reached after 40 minutes of exposure. Subjects in this study exhibited erythema and reported a burning sensation, indicating injury to the skin surface.

Application of undiluted tetrachloroethylene to the shaved backs of guinea pigs (strain not specified) resulted in blood concentrations of 1.1 µg/mL at the end of 30 minutes of exposure and 0.63 µg/mL at the end of 6 hours of exposure (Jakobson et al. 1982). The peak blood concentration of ~1.5 µg/mL tetrachloroethylene occurred approximately 30 minutes after the commencement of the 6-hour exposure (time-course data were not shown for the 30-minute exposure). The lower tetrachloroethylene blood level observed at the end of the longer exposure duration (6 hours) compared with the 30-minute exposure was attributed to local vasoconstriction of the exposed skin or rapid transport of the compound from the blood to adipose tissue.

Tetrachloroethylene applied in a volume of 0.5 mL to a 2.92 cm^2 patch of abdominal skin of ICR mice for 15 minutes yielded an estimated absorption rate of 24.4 nmol/minute/cm^2 (Tsuruta 1975). An *in vitro* study in which 1 mL of tetrachloroethylene was applied to 3.7 cm^2 of excised rat (SD-JCL) skin for 2–6 hours and penetration into a sodium chloride solution was measured resulted in an estimated penetration rate of 0.554 nmol/minute/cm^2 for tetrachloroethylene. The penetration rate estimated from the *in vitro* method was much slower than that observed *in vivo*. The authors suggested that the difference may result

from the lower solubility of tetrachloroethylene in 0.9% sodium chloride compared to its solubility in body fluids (Tsuruta 1977).

Only one study examined uptake of tetrachloroethylene in an aqueous solution. Bogen et al. (1992) immersed anesthetized female hairless guinea pigs in water containing 27–64 ppb tetrachloro[14C]ethylene for 70 minutes, and the disappearance of radioactivity from the water was determined as a means of estimating dermal uptake. 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 from the water in an hour. When an animal was not present in the chamber, about 1.3% of the radioactivity was lost from the water. 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.

3.4.2 Distribution

Studies in animals, and autopsy findings in human cases of accidental death, demonstrate that absorbed tetrachloroethylene is distributed throughout the body regardless of the route of exposure, with highest concentrations measured in the adipose tissue, liver, and kidney (Dallas et al. 1994a, 1994b; Levine et al. 1981; Lukaszewski 1979; Pegg et al. 1979; Savolainen et al. 1977). Tetrachloroethylene has been shown to cross the placenta and distribute to the fetus and amniotic fluid of mice (Ghantous et al. 1986). In addition, tetrachloroethylene has been detected in goat's milk after oral exposure (Hamada and Tanaka 1995).

Organ:blood partition coefficients from *in vitro* and *in vivo* determinations can also inform the distribution of a chemical within the body. Organ:blood partition coefficients that exceed 1 suggest organs that can accumulate the compound of interest. Examples of organ:blood partition coefficients from experiments in four species are shown in Table 3-8. Regardless of the methods and in all species, partitioning from blood into fat was the greatest (partition coefficients ranged from 42.4 to 159), consistent with tetrachloroethylene's high lipophilicity. A marked species difference was observed in the milk:blood partition coefficients, which were reported to be 12 in Sprague-Dawley rats and 2.8 in humans (Byczkowski and Fisher 1994), possibly reflecting a greater fat content in the rat milk that was tested compared to the human milk.

3.4.2.1 Inhalation Exposure

Repeated inhalation exposure to tetrachloroethylene results in the accumulation of this compound in the body, as evidenced by increasing concentrations of tetrachloroethylene in expired air and blood. When experimental subjects were exposed by inhalation to 100 ppm tetrachloroethylene 7 hours/day for 5 days, the concentration of tetrachloroethylene in exhaled breath increased as the 5-day week progressed (Stewart et al. 1977). Following termination of exposure, additional accumulation of the compound was suggested by the prolonged decline (>14 days) in the concentration of tetrachloroethylene in exhaled air. The study authors suggested that tetrachloroethylene's affinity for fat tissue probably accounted for the protracted period of clearance from the lungs. Altmann et al. (1990) measured blood concentrations of tetrachloroethylene in volunteers before and after each of four daily 4-hour exposures to 10 or 50 ppm, as well as 1 day after the end of exposure. Even at these relatively low air concentrations and brief exposure durations, tetrachloroethylene levels in the blood increased from one exposure day to the next; blood levels increased from 36 to 56 μg/L after 1–4 days of exposure to 10 ppm, and from 59 to 153 μg/L after 1–4 days of exposure to 50 ppm tetrachloroethylene.

Autopsy data after accidental human poisonings have demonstrated distribution of inhaled tetrachloroethylene to various organs, including liver, kidney, brain, lung, and heart. The highest concentrations have generally been seen in the liver, kidney, and brain; however, the autopsy results did not include analysis of adipose tissue for tetrachloroethylene. In one human fatality due to tetrachloroethylene inhalation, the highest concentration of tetrachloroethylene was measured in the brain (36 mg/kg) and the lowest was in the lung (3 mg/kg) (Lukaszewski 1979). 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 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 (Garnier et al. 1996). Tetrachloroethylene was measured in the liver and lung of a 26-year-old male found dead after intentional inhalation of a pressurized tire repair product containing tetrachloroethylene; concentrations were 341 mg/kg in liver and 47 mg/kg in lung (Isenschmid et al. 1998). Tetrachloroethylene concentrations of 0.751 μg/g in muscle, 1.195 μg/g in kidney, 1.678 μg/g in myocardium, 1.855 μg/g in brain stem, and 1.95 μg/g in liver were reported at autopsy of a 45-year-old woman who was found unconscious in a laundry area and was transported to the hospital where she subsequently died (Dehon et al. 2000).

Studies measuring radioactivity in animals after inhalation exposure to radiolabeled tetrachloroethylene confirm the distribution of tetrachloroethylene or its metabolites throughout the body, with the fat, liver, and kidney accumulating the highest concentrations. In rats exposed for 6 hours to 600 ppm tetrachloro-[1,2-14C]ethylene, the concentrations in kidney, liver, fat, lung, and heart were 0.167, 0.096, 0.082, 0.066, and 0.045 μmol eq/g, respectively, 72 hours after exposure; radioactivity was not detected in the brain or adrenal glands (Pegg et al. 1979). The distribution of the compound in Sprague-Dawley rats following exposure to 200 ppm tetrachloroethylene vapor (four daily 6-hour periods followed by 1 day of exposure for 0, 2, 3, 4, or 6 hours) was characterized by Savolainen et al. (1977). Tetrachloroethylene was found to have distributed primarily to perirenal fat. In rats receiving five 6-hour exposures, concentrations of tetrachloroethylene in perirenal fat, liver, cerebrum, and lungs were 1,724.8, 160.7, 142.5, and 74.0 nmol/g (Savolainen et al. 1977). Dallas et al. (1994b) exposed Sprague-Dawley male rats to tetrachloroethylene at 500 ppm for up to 2 hours. At specified times during and after exposure (up to 72 hours after exposure), groups of five rats were sacrificed and tetrachloroethylene residues in the perirenal fat, brain, liver, kidneys, heart, lung, skeletal muscle and blood were measured. The maximum tetrachloroethylene concentrations measured at any time point in these tissues were 1,536.3, 173.9, 152.4, 107.5, 106.6, 94.6, 87.3, and 44 μg/g (respectively). Half-lives for elimination from these tissues ranged from 322 minutes in blood to 578 minutes in fat. High levels of radioactivity were also observed in maternal body fat, brain, nasal mucosa, blood, and well-perfused organs such as the liver, kidneys, and lungs (concentrations were not reported) when pregnant 657BL/6N mice were exposed to radiolabeled (14C) tetrachloroethylene for 10 minutes or 1 hour (Ghantous et al. 1986). The exposure concentration was not reported; 100 μCi of tetrachloroethylene was dissolved in oil and heated to generate the exposure.

The Ghantous et al. (1986) study in pregnant mice also showed that tetrachloroethylene can cross the placenta and distribute to the fetus and amniotic fluid. Unmetabolized tetrachloroethylene (measured as volatile radioactivity) was detected in the fetoplacental unit following inhalation exposure of pregnant 657BL/6N mice to radiolabeled (14C) tetrachloroethylene for 10 minutes or 1 hour (Ghantous et al. 1986). Nonvolatile radioactivity, measured to approximate the proportion of metabolized tetrachloro-ethylene, was higher in fetuses sacrificed later in gestation than those sacrificed early, consistent with increasing maternal metabolism of tetrachloroethylene over time.

3.4.2.2 Oral Exposure

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

The distribution of tetrachloroethylene in animals exposed orally is similar to that seen after inhalation exposure, with highest levels seen in the fat, liver, and kidneys. Distribution to the fat occurs over a long time period, while peak concentrations in liver and kidneys generally occur more rapidly. When male Sprague-Dawley rats were given single gavage doses of 1 or 500 mg/kg 14C-labelled tetrachloroethylene, radioactivity was found in the fat, kidney, liver, lung, and heart, but not the brain (Pegg et al. 1979). At the higher dose of 500 mg/kg, the concentrations were 0.272, 0.137, 0.097, 0.092, and 0.051 μmol eq/g in kidney, liver, fat, lung, and heart, respectively, at sacrifice 72 hours after exposure (Pegg et al. 1979). Following oral exposure of Sprague-Dawley rats to a single dose of tetrachloroethylene (10 mg/kg), the highest concentrations were found in the fat, liver, kidney, and brain (peak concentrations were 36, 12.3, 4.4, and 5.1 μg/g tetrachloroethylene, respectively; Dallas et al. 1994). Peak concentrations in the liver, kidney, and brain were reached 10–15 minutes after dosing, while the peak concentration in fat occurred 360 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; peak concentrations were 42.8, 11.3, 6.3, and 4.9 μg/g, respectively (Dallas et al. 1994a). 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; the study authors suggested that true maximum concentrations may have actually occurred earlier.

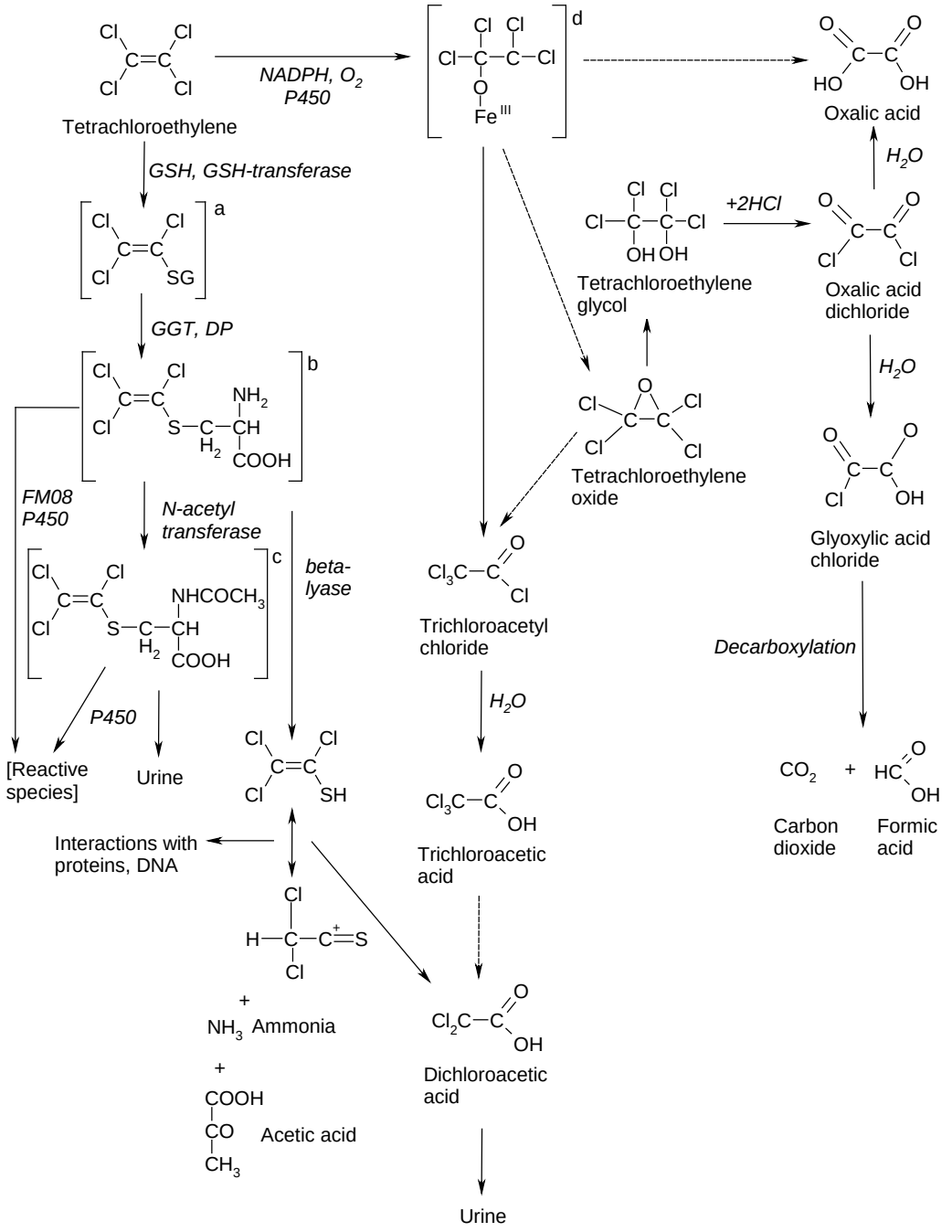
3.4.2.3 Dermal Exposure

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

3.4.3 Metabolism

The metabolism of tetrachloroethylene has been reviewed by Chiu and Ginsberg, (2011), Chiu et al. (2007), and Lash and Parker (2001); the proposed metabolic pathways for tetrachloroethylene is depicted in Figure 3-20. Tetrachloroethylene is metabolized through two irreversible pathways in humans, rats, and mice: oxidation by cytochrome P-450 isozymes and glutathione conjugation via glutathione-S-transferase. Qualitatively, the metabolism is similar in humans, rats, and mice; however, the extent of metabolism, as well as the predominant pathway, varies by species and exposure route, with evidence for dose-dependency as well.

Figure 3-20. Proposed Pathways for the Metabolism of Tetrachloroethylene



[a]*S*-(1,2,2-trichlorovinyl)glutathione
[b]*S*-(1,2,2-trichlorovinyl)cysteine
[c]*N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine
[d]tetrachloroethylene-Fe-O intermediate

DP = dipeptidase; FM08 = flavin mono-oxygenase-3; GGT= gamma-glutamyl transpeptidase
Dashed lines indicate hypothesized or quantitatively minor pathways.

Sources: Chiu and Ginsberg 2011; Dekant et al. 1986; Green et al. 1990; Pegg et al. 1979

Oxidative metabolism is postulated to occur in the liver, lung, and kidney (Chiu and Ginsberg 2011). The primary isozyme believed to be responsible for oxidation of tetrachloroethylene is CYP2E1, based on data for similar compounds, but other isozymes may also be involved (Lash and Parker 2001). Oxidation of tetrachloroethylene is believed to yield a Fe-O intermediate, which is converted to trichloroacetyl chloride and then hydrolyzed to trichloroacetic acid (Chiu and Ginsberg 2011). An epoxide intermediate, initially believed to be the progenitor to trichloroacetic acid, was shown to decompose to ethanedioyl dichloride and then to CO and CO_2 (Chiu and Ginsberg 2011); the epoxide pathway is believed to be minor. Oxalic acid has been observed to be a metabolite of tetrachloroethylene oxidation and may occur via either the epoxide or Fe-O intermediates. The urinary metabolites of tetrachloroethylene are trichloroacetic acid and dichloroacetic acid. These metabolites are considered to be the proximate toxicants responsible for the liver toxicity and carcinogenicity seen in tetrachloroethylene-exposed mice (Buben and O'Flaherty 1985; Chiu and Ginsberg 2011; Lash and Parker 2001).

Glutathione conjugation is proposed to occur primarily in the liver and kidney (Chiu and Ginsberg 2011). Glutathione conjugation of tetrachloroethylene produces trichlorovinyl glutathione and subsequently, S-trichlorovinyl-L-cysteine (TCVC) (Chiu and Ginsberg 2011; Lash and Parker 2001). TCVC may be bioactivated to reactive species via beta-lyase or flavin-containing monooxygenases (Anders et al. 1988; Krause et al. 2003). Dichloroacetic acid, which may also be formed via dechlorination of trichloroacetic acid, is postulated to occur primarily as an end product of beta-lyase activation after glutathione conjugation of tetrachloroethylene (Volkel et al. 1998). TCVC may also be N-acetylated to N-acetyl trichlorovinyl cysteine (NAcTCVC). NAcTCVC may be converted to reactive species via CYP3A sulfoxidation or excreted in the urine (Werner et al. 1996). Reactive metabolites in the kidneys produced via the glutathione conjugation pathway may play a role in the renal toxicity and carcinogenicity in tetrachloroethylene-exposed rats (Chiu and Ginsberg 2011; Lash and Parker 2001).

In humans, irrespective of the route of exposure, most (>80%) of the absorbed dose of tetrachloroethylene is exhaled unchanged (see Section 3.4.4). The major urinary metabolite in exposed humans is trichloroacetic acid; in three male and three female volunteers exposed to 10, 20, or 40 ppm tetrachloroethylene for 6 hours, cumulative excretion of trichloroacetic acid was 100-fold higher than cumulative excretion of the second major urinary metabolite, NacTCVC (Volkel et al. 1998). No dichloroacetic acid was detected in human urine. In this study, the elimination half-life in humans was 45.6 hours for trichloroacetic acid and 14.1 hours for NAcTCVC; the authors noted that the NAcTCVC was eliminated within 24 hours after exposure in all subjects.

Small amounts of *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine were detected in the urine of four workers occupationally exposed to tetrachloroethylene at 50 ppm for 4 or 8 hours/day, 5 days/week (Birner et al. 1996). The concentrations of *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine were 2.2–14.6 pmol/mg creatinine 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. Voelkel et al. (1999) also detected *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine in the urine of exposed humans.

Trichloroethanol has been reported to occur in the urine of workers exposed to tetrachloroethylene (Birner et al. 1996; Monster 1986); however, in studies of controlled exposure to pure tetrachloroethylene in humans or animals, trichloroethanol has not been detected in the urine (Buben and O'Flaherty 1985; Hake and Stewart 1977; Monster et al. 1979; Volkel et al. 1998).

The metabolism of tetrachloroethylene appears to be saturable in humans at high concentrations (>100 ppm), although the data are limited. 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 >100 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 <112 ppm (Seiji et al. 1989). Volkel et al. (1998) also observed a linear relationship between urinary excretion of trichloroacetic acid and NAcTCVC in humans exposed to 10, 20, or 40 ppm tetrachloroethylene for 6 hours, indicating that metabolic saturation did not occur at these low concentrations.

Biological monitoring data in occupationally exposed groups have indicated that the amount of tetrachloroethylene metabolized varies among different ethnic human populations; this finding is supported by a limited volunteer study. 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 trichloroacetic acid/L per ppm tetrachloroethylene in Chinese workers, while the value was 0.7 mg trichloroacetic acid/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/L in blood and 2.9 mg trichloroacetic acid/L in urine compared to the American Conference of Governmental Industrial Hygienists (ACGIH) values of 1 mg tetrachloroethylene/L in blood and 7 mg trichloroacetic acid/L in urine for exposure to 50 ppm (ACGIH 1991). In a controlled

exposure experiment evaluating ethnic differences, a 35% higher peak urinary trichloroacetic acid concentration and significantly ($p<0.05$) higher area under the urinary trichloroacetic acid concentration-time curve were observed in three Caucasian volunteers compared with three Asian volunteers exposed to 50 ppm tetrachloroethylene for 6 hours (Jang et al. 1997). Blood concentrations of parent compound measured at the end of exposure did not differ between the two groups.

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, as shown in Table 3-9.

Species variability in metabolic rates is evident from the V_{max} values for humans, rats, and mice (Table 3-9), which show that rats metabolize tetrachloroethylene at a greater rate than humans, and mice metabolize tetrachloroethylene at a much greater rate than rats. In a study comparing metabolism of tetrachloroethylene in humans and rats exposed to the same concentrations (10, 20, and 40 ppm) for 6 hours, the blood levels of trichloroacetic acid were much higher (20- and 10-fold higher immediately after exposure to 10 and 40 ppm, respectively) in rats than in humans. In addition, elimination half-lives of trichloroacetic acid and NAcTCVC in urine were much lower (11 and 7.5 hours, respectively) in rats than in humans (45.6 and 14.1 hours, respectively) (Volkel et al. 1998). Unlike humans, rats also excreted detectable levels of dichloroacetic aid in the urine, with an elimination half-life similar to that for trichloroacetic acid (11 hours).

3.4.3.1 Inhalation Exposure

Levels of an *N*-acetylcysteine glutathione conjugate detected in the urine of Wistar rats and NMRI and B6C3F1 mice and in the bile of F344 rats exposed to tetrachloroethylene were higher in rat urine than in mouse urine, and higher after gavage dosing than after inhalation exposure (Dekant et al. 1986; Green et al. 1990). 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). Green et al. (1990) compared the activities of the glutathione S-transferase and β-lyase enzymes in humans, B6C3F1 mice, and F344 rats (Table 3-9). 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.

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).

Table 3-9. Metabolism of Tetrachloroethylene in Mice, Rats, and Humans

Parameters	Human	Mouse	Rat
Total tetrachloroethylene metabolism[a]			
V_{max}/body weight (nmol/(minute/kg))	5.0–61 [13 (2.0)]	210–1860 [710 (2.04)]	27.2–400 [144 (2.97)]
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/(minute/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 metabolism of tetrachloroethylene[c]			
Rate (pmol/minute/mg protein)	2.08±2.57	19.26±1.33	3.87±2.12
In vitro liver cytosolic GSH conjugation of tetrachloroethylene			
Rate (pmol/minute/mg protein)[d]	Not detected	3.4	18.2
In vitro liver cytosolic GSH conjugation of tetrachloroethylene to *S*-(1,2,2-trichlorovinyl)glutathione			
V_{max} (pmol/minute/mg protein)[e], male	Not detected	27.9±6	84.5±12
V_{max} (pmol/minute/mg protein)[e], female	Not detected	26.0±4	19.5±8
In vitro kidney cytosolic GSH conjugation of tetrachloroethylene to *S*-(1,2,2-trichlorovinyl)glutathione			
V_{max} (pmol/minute/mg protein)[e], male	Not detected	11.6±6	Not detected
V_{max} (pmol/minute/mg protein) [e], female	Not detected	12.2±4	Not detected
In vitro kidney cytosolic metabolism of *S*-(1,2,2-trichlorovinyl)-L-cysteine (β-lyase activity)[d]			
K_m (mM), male	2.53±0.09	5.69±2.22	0.68±0.06
K_m (mM), female	2.67±2.11	4.43±1.42	1.26±0.21
V_{max} (nmol/minute/mg protein), male	0.49±0.07	1.15±0.31	4.00±0.11
V_{max} (nmol/minute/mg protein), female	0.64±0.54	1.66±0.27	3.64±0.41
V_{max}/K_m, male	0.21	0.20	5.88
V_{max}/K_m, female	0.24	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 Reitz et al. 1996; values are means±standard deviations.
[d]From Green et al. 1990; values are means or means±standard deviations.
[e]From Dekant et al. 1998; values are means or means±standard error of the mean.

GSH = glutathione

Studies quantifying metabolites in urine after inhalation exposure of laboratory rodents also show dose-dependency. Following a 6-hour inhalation exposure, the amount of tetrachloroethylene excreted as metabolites decreased with increasing exposure concentration in both F344 rats and B6C3F1 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, respectively.

3.4.3.2 Oral Exposure

Limited data on metabolism after oral exposure are available. 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 (Buben and O'Flaherty 1985). The amount of total metabolites found in the urine increased logarithmically with dose and approached a plateau with doses of tetrachloroethylene >1,000 mg/kg/day (Buben and O'Flaherty 1985).

3.4.3.3 Dermal Exposure

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

3.4.4 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. The relative importance of excretory routes in animals depends on the concentration in air, the species, and the sex of animal. Mice excrete more tetrachloroethylene as urinary metabolites, and much less as unmetabolized parent compound in exhaled breath, than either rats or humans. Tetrachloroethylene has 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.

3.4.4.1 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 of male

volunteers, 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 (Monster et al. 1979). Chiu et al. (2007) exposed six male volunteers to 1 ppm tetrachloroethylene for 6 hours, and reported average recovery of tetrachloroethylene in exhaled air to be 82%. 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 1–60 seconds (Opdam and Smolders 1986). Measurements made in the postexposure period showed that 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 trichloroacetic acid represented <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) or to 1 ppm for 6 hours (Chiu et al. 2007).

Volkel et al. (1998) observed dose-dependent increases in the excretion of trichloroacetic acid and N-acetyl-S(trichlorovinyl)-L-cysteine in volunteers (three males and three females) exposed for 6 hours to concentrations of 10, 20, and 40 ppm. Mean estimates of the cumulative urinary excretion of trichloroacetic acid (adjusted for body weight) were 0.07, 0.18, and 0.29 μmol/kg body weight up to 78 hours after exposure to 10, 20, and 40 ppm, respectively; estimates of cumulative excretion of N-acetyl-S(trichlorovinyl)-L-cysteine were 0.65, 2.02, and 3.01 nmol/kg body weight, respectively, up to 35 hours after exposure (Volkel et al. 1998). It has been reported that the urinary excretion of trichloroacetic acid 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 trichloroacetic acid 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 Mallol 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).

At the same tetrachloroethylene exposure concentrations, rats excrete greater quantities of the metabolites trichloroacetic acid and NAcTCVC than humans. Volkel et al. (1998) compared the excretion of trichloroacetic acid and NAcTCVC in rats exposed to 10, 20, or 40 ppm tetrachloroethylene for 6 hours with results observed in humans (see above). Greater cumulative excretion of both metabolites was seen in rats compared with humans; cumulative 72-hour excretion of trichloroacetic acid in exposed male and female rats was 1.92, 3.44, and 6.55 μmol/kg body weight at 10, 20, and 40 ppm, respectively, while corresponding cumulative 60-hour excretion of NAcTCVC was 3.48, 7.14, and 22.98 nmol/kg body weight (Volkel et al. 1998).

Mice excrete much higher quantities of urinary tetrachloroethylene metabolites when compared with rats exposed to the same concentration and duration. In two studies, both using a 6-hour inhalation exposure to 10 ppm radiolabeled tetrachloro[1,2-14C]ethylene, male Sprague-Dawley rats exhaled 68% of the absorbed radioactivity as unmetabolized parent compound (Pegg et al. 1979), while male B6C3F1 mice excreted only 12% through this route (Schumann et al. 1980). Exhalation of radiolabeled carbon dioxide represented 3.6% of the dose in rats, (Pegg et al. 1979) and 7.9% in mice (Schumann et al. 1980). Finally, urinary excretion of nonvolatile metabolites represented 18.7% of the absorbed radioactivity in rats and 62.5% in mice (Pegg et al. 1979; Schumann et al. 1980). In a study by Yllner (1961), female mice (unspecified strain) exposed for 2 hours to 14C-tetrachloroethylene vapors at a concentration reported to yield a dose of 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 <0.5% in the feces. Trichloroacetic acid 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 suggests that as the body burden of tetrachloroethylene increases, the percentage of unchanged parent compound excreted increases (Green 1990).

The study in rats by Pegg et al. (1979) showed dose-dependent changes in excretion pathways; at a higher exposure concentration, a larger fraction of the absorbed dose was exhaled as unmetabolized parent compound. In rats exposed to 10 ppm tetrachloroethylene, 68% of the absorbed radioactivity was exhaled

as unmetabolized parent compound and 3.6% was exhaled as CO_2, while in rats exposed to 600 ppm, the proportions exhaled as unmetabolized tetrachloroethylene and CO_2 were 88 and 0.7%, respectively. The rats' 72- hour urinary excretion of nonvolatile metabolites represented 18.7% of the absorbed dose at 10 ppm and 6.0% at 600 ppm (Pegg et al. 1979).

Volkel et al. (1998) showed markedly (>3-fold) higher excretion of glutathione-dependent metabolites in male Wistar rats compared with females when both were exposed for 6 hours to a high concentration (400 ppm) of tetrachloroethylene. Cumulative excretion of NAcTCVC was 414.8 nmol/kg body weight in males, compared with 125.8 nmol/kg body weight in females. Higher levels (1.6–2-fold) of the oxidative metabolites, trichloroacetic acid and dichloroacetic acid, were also excreted by males than by females (Volkel et al. 1998).

The half-lives for elimination of trichloroacetic acid and NAcTCVC in urine have been estimated to be 45.6 and 14.1 hours, respectively, in humans and 11.0 and 7.5 hours, respectively, in rats after inhalation exposure for 6 hours to 10, 20, or 40 ppm tetrachloroethylene (Volkel et al. 1998).

3.4.4.2 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, trichloroacetic acid, 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.

Male F344 rats given a daily oral dose of 1,500 mg/kg tetrachloroethylene for 42 days had evidence of kidney damage. In addition, radiolabeled material included with the doses given on days 1, 17, and 42 was detected in bile and urine (Green et al. 1990).

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 B6C3F1 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).

Tetrachloroethylene may also be eliminated via secretion into breast milk. Tetrachloroethylene was detected in goat's milk as early as 30 minutes after intraruminal administration of a mixture containing tetrachloroethylene and two other solvents (Hamada and Tanaka 1995). Increasing concentrations were seen up to 6.5 hours after dosing, and tetrachloroethylene remained at a detectable concentration in milk 24 hours after exposure (Hamada and Tanaka 1995).

3.4.4.3 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.

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

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

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

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific

physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

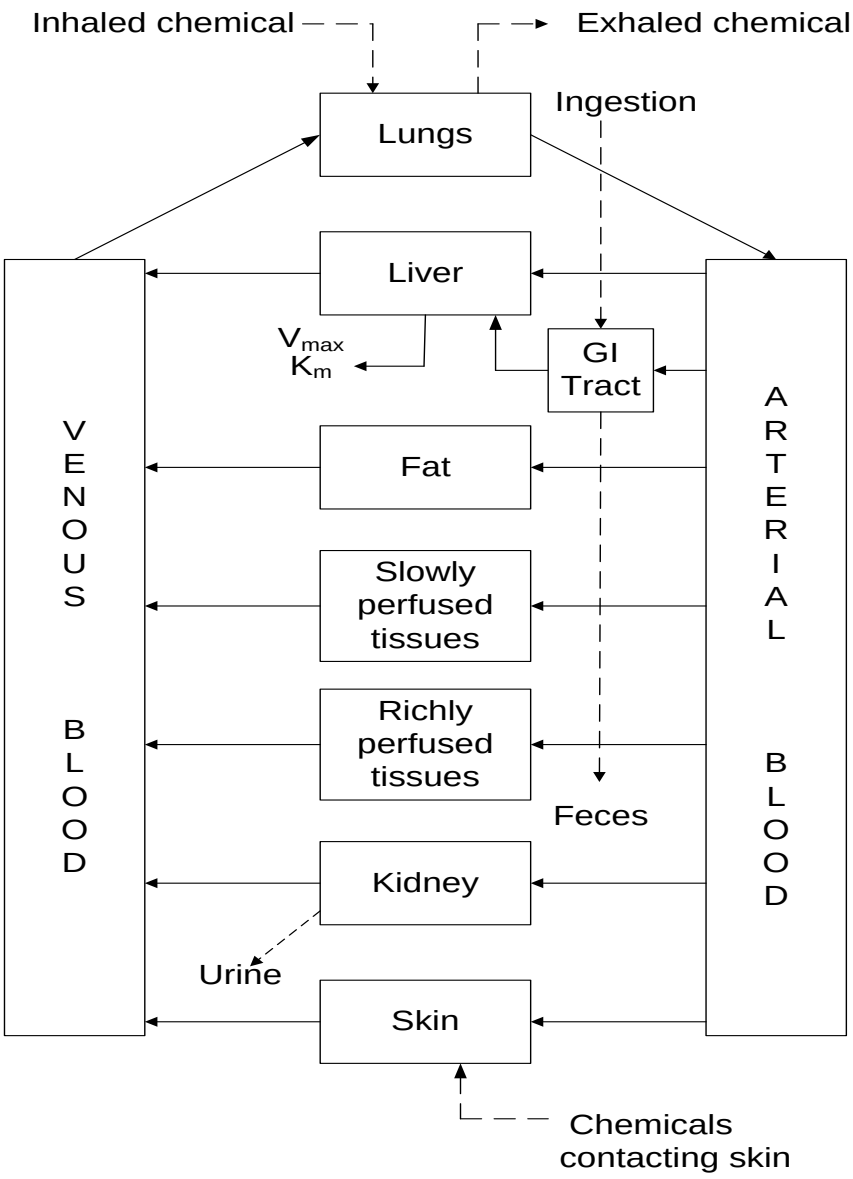
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. However, if the uptake and disposition of the chemical substance(s) are adequately described, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-21 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.

A number of PBPK models have been developed over the past 25 years to predict blood or target tissue doses of tetrachloroethylene or its metabolites after inhalation, oral, or dermal exposure in animals (Bois et al. 1990; Dallas et al. 1994, 1995; Fisher et al. 1997; Hattis et al. 1990, 1993; Loizou 2001; Poet et al. 2002; Rao and Brown 1993; Reitz et al. 1996). In addition, several PBPK models have been developed and/or applied for the purpose of evaluating ethnic differences in toxicokinetics (Jang and Droz 1997), age-related differences (Clewell et al. 2004; Rodriguez et al. 2007; Sarangapani et al. 2003; Yokley and Evans 2008), or gender-related differences (Clewell et al. 2004; Sarangapani et al. 2003) in tetrachloroethylene toxicokinetics. ATSDR has developed a VOC PBPK model toolkit, which includes a parameter for modeling tetrachloroethylene in humans (Mumtaz et al. 2012a, 2012b; Ruiz et al. 2011). NRC (2010), in its review of an earlier draft EPA Toxicological Review of Tetrachloroethylene, expressed concerns regarding the inadequate validation of model predictions after oral dosing and recommended that a harmonized PBPK modeling approach be used to synthesize the various models into a single structure,

Figure 3-21. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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.

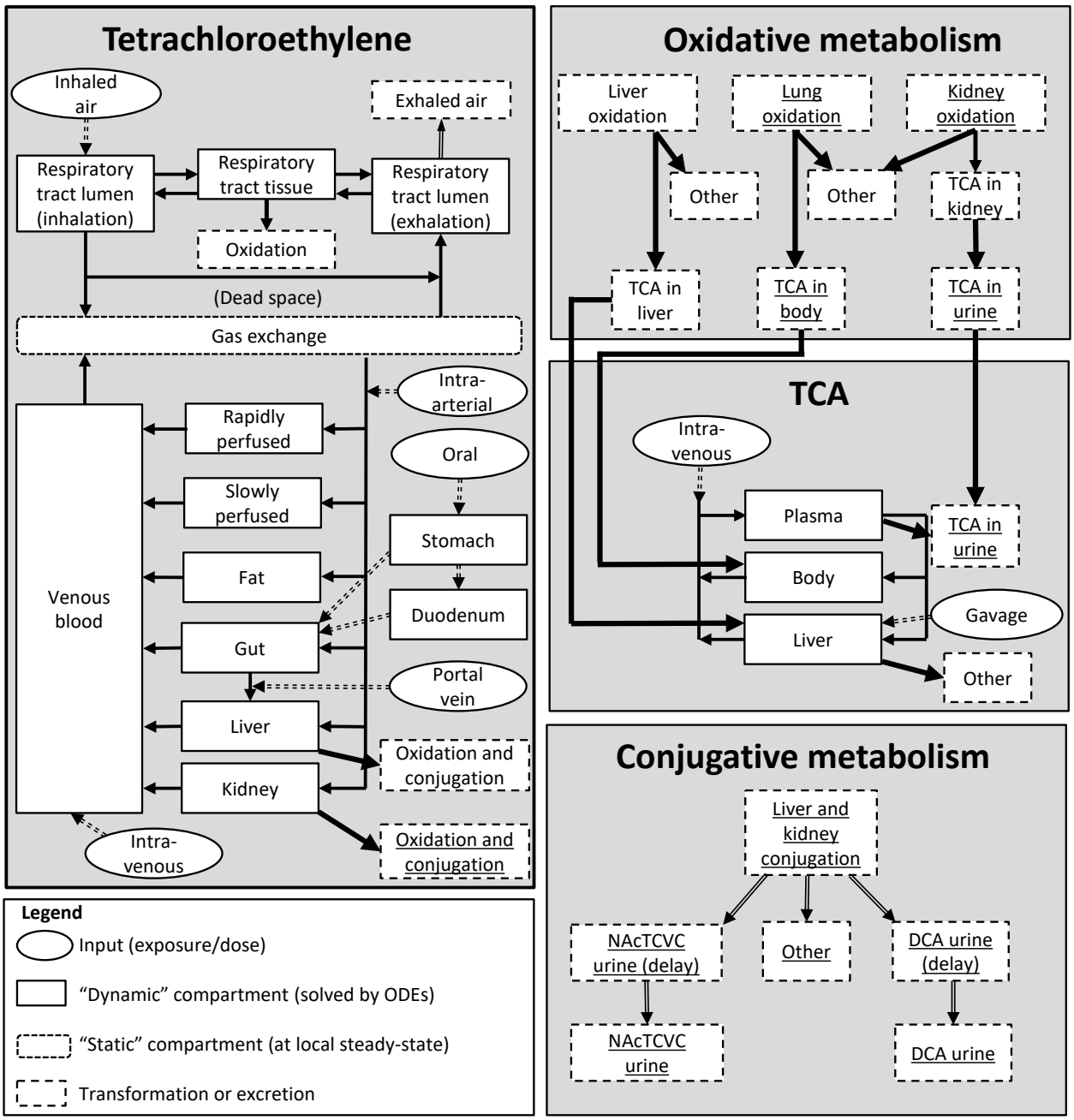
Source: adapted from Krishnan and Andersen 1994

particularly for the purpose of route-to-route extrapolation. In response to these concerns and recommendations, Chiu and Ginsberg (2011) developed a harmonized PBPK model for oral and inhalation exposure to tetrachloroethylene in mice, rats, and humans. The model was based on the authors' previously developed model for trichloroethylene (Chiu et al. 2009), and its structure and development included several important advances in PBPK modeling of tetrachloroethylene. One of the major controversies in tetrachloroethylene dosimetry extrapolation has been establishing the relative contribution of metabolism to total elimination of tetrachloroethylene in humans and other animal species. Chiu and Ginsberg (2011) addressed this problem in several novel ways. Unlike previous tetrachloroethylene models, it includes independent pathways for oxidation and glutathione conjugation, allowing each to vary independently in parameter-estimating procedures. Metabolism parameters were estimated using a larger set of data than had been applied to optimization of earlier tetrachloroethylene models. Data were separated into "calibration" and "evaluation" data sets, which allowed independent verification of the calibrated model. A Bayesian Markov Chain-Monte Carlo (MCMC) approach was used to estimate values for metabolism parameters and other highly influential parameters (e.g., alveolar ventilation). Baseline (Bayesian "prior") estimates for parameter values were informed by data from *in vitro* studies, with *in vitro* metabolism parameters (e.g., K_m, V_{max}) converted to corresponding estimates of tissue parameters. The MCMC provided improved empirically-based ("posterior") estimates of metabolism parameters and, as a result, more realistic simulation of inter-species and intra-species variability in tetrachloroethylene metabolism and attending uncertainties related to metabolism parameter estimation. One of the outcomes of the Chiu and Ginsberg (2011) analysis is that it establishes the importance of large variability and uncertainty in the glutathione conjugation pathway in estimations of total metabolic clearance of tetrachloroethylene. The Chiu and Ginsberg (2011) model was applied to the derivation of ATSDR MRLs (see Section 2.3) for tetrachloroethylene, and the EPA chronic inhalation reference concentration and oral reference dose (EPA 2012a). This model is discussed in further detail below.

Chiu and Ginsberg (2011) Model

Description of the Model. The structure of the Chiu and Ginsberg (2011) model is shown in Figure 3-22 and parameters and values for rats, mice, and humans are listed in Table 3-10. This model includes eight tissue compartments: respiratory tract, gastrointestinal tract, kidney, liver, fat, rapidly perfused and slowly perfused tissues, and venous blood. Metabolism is assumed to occur in the respiratory tract, kidney, and liver. Metabolism occurring in the respiratory tract consists of tetrachloroethylene oxidation, with a fraction of oxidative flux undergoing instantaneous elimination within the respiratory tract or translocation to the body. In both liver and kidney, a fraction of the tetrachloro

Figure 3-22. Overall Structure of PBPK Model for Tetrachloroethylene and Metabolites



Boxes with underlined labels are additions or modifications of the Chiu et al. (2009) model.

DCA = dichloroacetic acid; NAcTCVC = N-acetyl trichlorovinyl cysteine; ODE = ordinary differential equation; TCA = trichloroacetic acid

Source: Chiu and Ginsberg 2011

Table 3-10. Baseline and Posterior Values of PBPK Model Parameters Selected for Optimization using MCMC

Parameter description	PBPK parameter	Baseline	Posterior mode	GSD of posterior mode across chains	Range of posterior modes across chains
Human					
Alveolar ventilation (L/hour)	QP	372	476	1.1	450–640
Hepatic oxidation (linear) (L/hour)	VMax/KM	0.353	0.454	1.08	0.346–0.468
Renal oxidation (linear) (L/hour)	VMaxKid/KMKid	0.00076	0.0947	1.09	0.0702–0.105
Hepatic GSH conjugation (linear)	VmaxTCVG/KMTCVG	0.0196	5.26	17.1	0.00194–5.48
Rate constant for urinary excretion of NAcTCVC (/hour)	kNAT	–	0.28	1.07	0.228–0.293
Fraction of GSH conjugation to urinary NAcTCVC	FracNATUrn	–	0.000482	15.8	0.000472–1
Fraction of GSH conjugation to urinary DCA	FracDCAUrn	–	0.00022	18.5	0.0000112–0.442
Rat					
Alveolar ventilation (L/hour)	QP	10.2	6.31	1.02	6.28–6.68
V_{MAX} for saturable hepatic oxidation (mg/hour)	V_{MAX}	0.256	0.87	1.37	0.415–1.93
K_M for saturable hepatic oxidation (mg/L)	K_M	69.7	31.1	1.39	14.8–71.9
Hepatic GSH conjugation (linear)	VmaxTCVG/KMTCVG	2.22	0.00204	1.27	0.00131–0.00355
Rate constant for urinary excretion DCA (/hour)	kDCA	–	0.129	1.65	0.0758–0.451
Fraction of GSH conjugation to urinary NAcTCVC	FracNATUrn	–	0.0143	1.29	0.00919–0.0253
Fraction of GSH conjugation to urinary DCA	FracDCAUrn	–	0.702	1.26	0.43–0.98
Mouse					
Alveolar ventilation (L/hour)	QP	2.09	2.89	1.03	2.86–3.22
V_{MAX} for saturable oxidation (mg/hour)	V_{MAX}	0.23	0.026	1.16	0.022–0.0369
K_M for saturable oxidation (mg/L)	K_M	88.6	0.417	1.28	0.338–0.892
Linear oxidation pathway	Vmax2/KM2	–	0.0188	1.05	0.0165–0.0207
Linear conjugation pathway	VmaxTCVG/KMTCVG	0.656	0.0000683	3.83	0.0000305–0.00179

Table 3-10. Baseline and Posterior Values of PBPK Model Parameters Selected for Optimization using MCMC

Parameter description	PBPK parameter	Baseline	Posterior mode	GSD of posterior mode across chains	Range of posterior modes across chains
Rate constant for TCA plasma→urine (/hour)	kUrnTCA	1.48	0.638	1.05	0.56–0.695
Rate constant for hepatic TCA→other (/hour)	kMetTCA	2.93	1.26	1.05	1.11–1.38

DCA = dichloroacetic acid; GSD = geometric standard deviation; GSH = glutathione; MCMC = Markov Chain Monte Carlo; NAcTCVC = N-acetyl trichlorovinyl cysteine; PBPK = physiologically based pharmacokinetic; TCA = trichloroacetic acid; TCVG = *S*-(1,2,2-trichlorovinyl)glutathione

Source: Chiu and Ginsberg 2011

ethylene is converted to the glutathione conjugate, *S*-(1,2,2-trichlorovinyl)glutathione; disposition of this metabolite is simulated with a simplified structure allowing for urinary excretion of the downstream metabolites NAcTCVC or dichloroacetic acid or an alternative fate that encompasses all other possible fates, such as activation by beta-lyase to products other than dichloroacetic acid or activation to reactive products by flavin-containing monooxygenases or sulfoxidation. Urinary excretion of NAcTCVC and dichloroacetic acid is modeled using a fitted delay parameter to better simulate available time-course data. The total rate of oxidation of tetrachloroethylene in liver, kidney, and lung is split into fractions leading to trichloroacetic acid and to other oxidative pathways. A second, saturable oxidative pathway was added to the liver to account for evidence of tetrachloroethylene metabolism by cytochrome P-450s other than CYP2E1. A fraction of the trichloroacetic acid formed in the kidney is assumed to be excreted in the urine, with the remainder translocated to the body compartment.

Oxidative metabolism in the liver and kidney of humans is modeled as a linear process due to a lack of data on the degree of saturation. Oxidative metabolism in the rat and mouse is modeled as a saturable process, with an additional linear process in the mouse to provide better fit than seen with a single saturable process. Glutathione conjugation is modeled as a linear process in all three species.

Baseline Parameter Values. The Chiu and Ginsberg (2011) model used baseline physiological values primarily obtained from standard references including the International Commission on Radiological Protection (ICRP 2002) and Brown et al. (1997). Partition coefficients were obtained by pooling available *in vitro* data from six studies (Gargas et al. 1989; Gearhart et al. 1993; Koizumi 1989; Mahle et al. 2007; Mattie et al. 1994; Reitz et al. 1996). In addition, *in vitro* metabolic parameters from the published literature were selected and converted to V_{max}, K_m, and/or V_{max}/K_m values using the microsomal and cytosolic protein content and tissue-specific cellularity for liver and kidney in mice, rats, and humans.

Parameter Optimization. Model predictions obtained with the selected baseline values were compared with *in vivo* inhalation data, and the results were used to select parameters for optimization. All of the tetrachloroethylene metabolism parameters were selected for optimization, while most physiological parameters (with the exception of alveolar ventilation rate) and partition coefficients were held at their baseline values. The selected parameters were optimized using a limited Bayesian approach with flat priors and inferences obtained by MCMC. Table 3-10 shows the baseline parameter values and posterior mode values obtained using MCMC.

Model Evaluation. Model predictions were compared with tissue, blood, and urinary levels of tetrachloroethylene and its metabolites from *in vivo* studies of mice, rats, and humans. Residual errors within a factor of 2–3 were observed for most of the data. The poorest predictions in mice were the fraction of tetrachloroethylene exhaled and the liver concentration of trichloroacetic acid; in rats, the concentration of tetrachloroethylene in fat had the highest residual error. The evaluation dataset for humans did not contain enough data to evaluate the uncertainty in the internal dose metrics.

Target Tissues. The model was used to predict a variety of dose metrics, including area under the tetrachloroethylene blood concentration-time curve (mg-hour/L/day), fraction of dose oxidized, fraction of dose conjugated, and systemic trichloroacetic acid dose (mg/kg/day). The metric with the lowest uncertainty across all three species was the blood concentration metric. The fraction conjugated was most uncertain, especially in humans, with a 3,000-fold range across chains in the human model.

Species Extrapolation. The model simulates toxicokinetics in mice, rats, and humans. Models for these species were developed by optimization of metabolic parameters using a limited Bayesian analysis. The scaled rat and human models have been evaluated against independent observations not used to estimate model parameter values (Chiu and Ginsberg 2011).

Mass balance inferences based on the estimates of various dose metrics in the Chiu and Ginsberg (2011) model confirm the species differences in metabolism. In mice exposed by inhalation, the model predicts that ~20% of the intake is metabolized, of which only ~1% is conjugated via glutathione and the balance is oxidized. In mice exposed orally, ~60% of the intake is metabolized, of which only ~2% is conjugated and the balance is oxidized. In rats exposed by inhalation, ~4% of the intake is metabolized, of which ≤0.3% is conjugated and the balance is oxidized. In rats exposed orally, ~10% of the intake is metabolized, of which ≤0.6% is conjugated and the balance is oxidized. In humans exposed by inhalation, ~10% of the intake is metabolized; after oral exposure, ~20% of the intake is metabolized. The fractions of metabolism attributable to the oxidative and conjugative pathways in humans were very uncertain, with glutathione conjugation estimates ranging from <0.003 to 10% after inhalation and from 0.006 to 19% after oral exposure (the high values assume that all metabolism occurred via this pathway).

Interroute Extrapolation. The tetrachloroethylene model (Chiu and Ginsberg 2011) simulates tetrachloroethylene kinetics associated with inhalation, oral, and intravenous dosing. The model predicted very similar blood concentration-time AUC estimates for oral and inhalation exposures in humans (~2 mg hour/L/day per mg/kg/day oral dose or ppm air across a wide range of doses and exposure

concentrations). Model predictions of AUC in rats were about 2-fold higher after inhalation exposure than after oral exposure, presumably due to higher hepatic metabolism after oral exposure. In mice, the route differences were marked; oral exposure resulted in AUC estimates about 5% of the AUC estimates after inhalation exposures, again due to the higher hepatic metabolism.

Risk Assessment. EPA (2012a) used the human model to extrapolate from an inhalation reference concentration to an oral reference dose. The basis of the inhalation reference concentration was epidemiological evidence of neurotoxicity (neurobehavioral impairments and decrements in color vision) in humans exposed to tetrachloroethylene. The interroute extrapolation was based on the AUC of blood tetrachloroethylene as the internal dose metric; this metric was presumed to be a step in the neurotoxicity pathway. Simulations by Chiu and Ginsberg (2011) indicated that route-to-route dose conversions are not very sensitive to the choice of dose metric; other metrics yielded route-to-route conversions within 1.4-fold of the conversion resulting from blood AUC.

EPA (2012a) also used the Chiu and Ginsberg (2011) model for interspecies extrapolations in the cancer risk assessment. For extrapolation from mice to humans in the assessment of liver tumors, the total rate of oxidative metabolism was used as the dose metric; AUC for trichloroacetic acid in the liver was also evaluated for comparison purposes. For mononuclear cell leukemia in rats, the AUC of the parent compound in blood was used as a dose metric, as the proximate toxicant for this neoplasm is not known. Parent compound AUC in blood was also selected as the internal dose metric for renal tumors in rats; this metric was chosen in light of the substantial uncertainty in model predictions for glutathione conjugation in humans.

3.5 MECHANISMS OF ACTION

3.5.1 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). The lipophilicity of this compound may also lead to diminished absorption of tetrachloroethylene administered orally in an oil vehicle compared with water-soluble vehicles.

Effect of Dose and Duration of Exposure on Toxicity. Available data show saturation of the oxidative metabolic pathways for tetrachloroethylene in rats and mice (Pegg et al. 1979; Reitz et al. 1996), with limited evidence for saturation in humans exposed to high airborne concentrations (Ohtsuki et al. 1983; Seiji et al. 1989). In contrast, there is no evidence for saturation of metabolism via glutathione conjugation, which represents a relatively small fraction of the metabolic fate of tetrachloroethylene administered either orally or via inhalation, in the available data. However, there is a great deal of uncertainty in the degree of glutathione conjugation versus oxidative metabolism of tetrachloroethylene in humans (Chiu and Ginsberg 2011), and it is possible that high exposures may lead to nonlinearities in the production and elimination of downstream metabolites of this pathway.

Route Dependent Toxicity. In humans, exposure route has only a small impact on the pharmacokinetic fate of tetrachloroethylene. PBPK simulations have suggested that the total metabolism of tetrachloroethylene is about twice as high after oral exposure of humans compared with inhalation exposure (Chiu and Ginsberg 2011); regardless of route, ≥80% of tetrachloroethylene is not metabolized. In rats, the route differences in metabolism are similar to those in humans (Chiu and Ginsberg 2011). In mice, however, oral exposure results in oxidative metabolism of about 60% of the administered dose, while only 20% is metabolized after inhalation (Chiu and Ginsberg 2011). The differences in total, oxidative, and conjugative metabolism are important predictors of target organ and toxicity because the parent compound, oxidative metabolites, and glutathione metabolites are believed to be (or be converted to) the proximate toxicants associated with neurotoxicity, hepatotoxicity and liver tumors, and renal toxicity and tumors, respectively (Bale et al. 2005; Benane 1996; Briving et al. 1986; Green 1990; Kyrklund et al. 1984, 1990; Lash and Parker 2001; Lash et al. 1998, 2002, 2007; Shafer et al. 2005), as discussed below.

3.5.2 Mechanisms of Toxicity

Based on effects reported in humans and in animal studies, the primary targets for tetrachloroethylene toxicity are the nervous system, kidney, and liver; the immune system may also be affected, although data on this end point are limited. It is not certain whether the neurological effects of tetrachloroethylene result from the parent compound or one or more of its metabolites.

Neurological Effects. 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, 1987,

1988, 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 and that cytoskeletal elements are more sensitive than cytosolic proteins.

Other studies have shown that tetrachloroethylene can interfere with voltage-gated channels and neuronal receptors. Shafer et al. (2005) demonstrated that tetrachloroethylene perturbs whole-cell calcium currents in nerve growth factor-differentiated pheochromocytoma (P12) cells. An *in vitro* study found that Xenopus oocytes exposed to tetrachloroethylene at 0.065 mM showed marked inhibition (40–62%) of human and rat neuronal nicotinic acetylcholine receptors (Bale et al. 2005). Related compounds, including trichloroethylene, exhibit effects on a wide range of inhibitory and excitatory receptors and ion channels (reviewed by Bale et al. 2011). Additional data regarding the mechanisms by which tetrachloroethylene produces changes in the central nervous system are needed.

Hepatic Effects. In contrast to nervous system effects, which are thought to be a result of tetrachloroethylene itself, effects on the liver, including cancer in mice, are thought to be a result of metabolism to oxidative metabolites, including trichloroacetic acid and dichloroacetic acid (Benane et al. 1996). Rodents, especially mice, produce more trichloroacetic acid than humans (Hattis et al. 1990). In addition, the trichloroacetic acid appears to be preferentially localized in the liver after oral exposure. Green et al. (2001) showed that gavage administration of tetrachloroethylene in mice resulted in the formation of trichloroacylated protein adducts in the liver, primarily in the centrilobular zones, and not in other organs.

Hepatic peroxisome proliferation induced in mice by trichloroacetic acid may play a role in the liver carcinogenicity of tetrachloroethylene in this species. A study by Maloney and Waxman (1999) showed that trichloroacetic acid and dichloroacetic acid, but not the parent tetrachloroethylene compound, activated mouse and human peroxisome proliferator-activated receptor (PPAR) receptor α (highly expressed in the liver of rodents; less highly expressed in the human liver) expressed in COS-1 cells. The role of peroxisome proliferation in hepatocarcinogenicity may involve induction of peroxisomal enzymes that produce hydrogen peroxide as a byproduct without inducing catalase. 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).

Some data indicate that exposure to tetrachloroethylene itself (at concentrations approximating the blood levels attained by exposed human subjects, 1.5 μg/mL) induces toxicity (measured as the release of AST and LDH and the decrease of mitochondrial-reducing activity) and lipid peroxidation (measured as thiobarbituric acid reactive substances production) in rat hepatocytes exposed *in vitro* (Costa et al. 2004). Increased cytotoxicity (MTT assay) was also observed in isolated rat hepatocytes treated with tetrachloroethylene in the range of 3–49 mM (Zapór et al. 2002). The increased production of hydrogen peroxide may increase DNA damage.

An *in vitro* study 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 (Kukongviriyapan et al. 1990). 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. Another *in vitro* study (Benane et al. 1996) showed that tetrachloroethylene and its metabolites, trichloroacetic acid and dichloroacetic acid, effectively inhibited gap junction intercellular communication in rat hepatocytes; this reduction in intercellular communication is thought to play an important role in tumor promotion.

Although P-450 metabolism is critical for tetrachloroethylene-induced liver toxicity, the relative contribution of glutathione conjugation to effects in this target organ has not been fully elucidated. In a study conducted using isolated rat liver cells, Lash et al. (2007) showed that cytotoxicity was not dependent on P-450 metabolism alone, since significant toxicity was observed despite perturbations to the P-450 pathway. Although *S*-(1,2,2-trichlorovinyl)glutathione generated in the liver is thought to be transported to the kidneys, alterations in the glutathione status of liver cells influence toxicity induced by tetrachloroethylene. Decreased cellular glutathione enhanced, while increased cellular glutathione diminished, tetrachloroethylene-induced cytotoxicity in hepatocytes (Lash et al. 2007), suggesting that interactions between these metabolic pathways likely contribute to liver toxicity.

A study in B6C3F1 mice exposed to oral tetrachloroethylene reported a dose-related increase in the number of transcriptomes (sum of messenger RNA molecule) in the liver (Zhou et al. 2017). Results indicate that epigenetic mechanisms may be involved in the development of tetrachloroethylene-induced toxicity.

Several mechanisms may contribute to hepatic carcinogenicity of tetrachloroethylene, including genotoxicity, changes in mitochondrial transcription, effects on transporter pathways, oxidative stress, and PPARα activation. Evidence for possible involvement of DNA hypomethylation in hepatic carcinogenesis comes from observations made in mice administered trichloroacetic acid or dichloroacetic acid (EPA 2012a; Guyton et al. 2014; IARC 2014, NRC 2010). Evidence for possible involvement of oxidative stress comes from studies conducted in mice in which antioxidants were shown to protect against hepatotoxicity of tetrachloroethylene and *in vitro* studies of showing altered expression of genes that are activated by reactive oxygen species (EPA 2012a).

Renal Effects. A low incidence of kidney cancer has been observed in male rats following inhalation exposure to tetrachloroethylene (NTP 1986). Several mechanisms may contribute to the renal carcinogenicity of tetrachloroethylene, including genotoxicity or cytotoxicity related to or unrelated to α-2u-globulin accumulation in the proximal tubule epithelium. Peroxisome proliferation may also be a contributing factor (EPA 2012a; Guyton et al. 2014; IARC 2014, NRC 2010). Kidney cancer may in part be a result of the formation of the genotoxic metabolites from *S*-(1,2,2-trichlorovinyl)glutathione catalyzed by β-lyase, CYP3A, or flavin-containing oxygenases, or from cellular damage and regeneration associated with lipid peroxidation from glutathione depletion. In agreement, the increased susceptibility of male rats to renal tumors correlates with increased *S*-(1,2,2-trichlorovinyl)glutathione formation in male rats relative to female rats (Lash et al. 1998). Treatment of renal cells with tetrachloroethylene or *S*-(1,2,2-trichlorovinyl)glutathione *in vitro* at up to 10 mM induced cytotoxicity, as measured by increased leakage of LDH from cells and/or compromised respiratory function of mitochondria (inhibition of state 3 respiration) (Lash et al. 2002, 2007). In addition, NAcTCVC and N-acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine sulfoxide (at 0.1 mM) were shown to be cytotoxic to rat renal epithelial cells, with the sulfoxide conjugate being more toxic than its mercapturic acid (Werner et al. 1996). Taken together, these data suggest that glutathione conjugation of tetrachloroethylene likely plays a significant role in tetrachloroethylene-induced renal toxicity. In contrast, modulation of P-450 activity (using specific or nonselective inhibitors or inducers) had no significant effect on tetrachloroethylene-induced kidney toxicity (Lash et al. 2007).

Tetrachloroethylene has also been shown to selectively affect the tubular S2 segment in the kidney of male rats through the accumulation of α-2u-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-2u-globulin or proteins in the same family (lipocalin) in large quantities as observed in male rats (Swenberg et al. 1989). However, the histopathology findings in male rats in the two inhalation bioassays of tetrachloroethylene (JISA 1993; NTP 1986) were not consistent with α-2u-globulin nephropathy (NRC 2010). In addition, similar renal effects were observed in female rats and both sexes of mice (JISA 1993; NRC 1986), providing additional evidence against α-2u-globulin-mediated effects. Taken in conjunction with evidence for injury associated with glutathione metabolites of tetrachloroethylene, the available information indicates that accumulation of α-2u-globulin is not the primary mechanism of renal toxicity and carcinogenicity associated with tetrachloroethylene exposure.

A study in B6C3F1 mice exposed to oral tetrachloroethylene reported a dose-related increase in the number of transcriptomes (sum of messenger RNA molecule) in the liver (Zhou et al. 2017). Results indicate that epigenetic mechanisms may be involved in the development of tetrachloroethylene-induced toxicity.

Immune Effects. Data from Seo et al. (2008b) showed that exposure to tetrachloroethylene (at 0.1–1 mg/L) increased histamine release in rat peritoneal mast (NPMC) and basophilic leukemia (RBL-2H3) cells. Treatment with tetrachloroethylene also increased mRNA expression of IL-4 ($p<0.05$) and TNF-α ($p>0.05$) as well as the production of these mediators ($p<0.05$ for both) in RBL-2H3 cells. A dose-dependent increase in antigen-induced histamine release from mouse bone marrow cells treated with tetrachloroethylene was reported in another study from this laboratory (Seo et al. 2012). These data suggest possible mechanisms for tetrachloroethylene-induced perturbation of the immune response to allergens, and exacerbation of inflammation. An *in vitro* study by Kido et al. (2013) also showed effects on pro-inflammatory cytokine gene expression. Significant ($p<0.05$) increases in the expression of IL-6 and IL-10 mRNA were observed in murine macrophage cells exposed to 800 μg/mL tetrachloroethylene. However, cell viability was significantly diminished at this concentration, and exposure to a higher concentration (1,000 μg/mL) yielded mRNA levels comparable to controls, so a clear dose-response relationship was not demonstrated. Wang et al. (2017) suggested that lipid-derived aldehydes (e.g., malondialdehyde [MDA]) may be involved in the development of tetrachloroethylene-induced autoimmunity. Following exposure of mice to drinking water containing 0.5 mg/mL tetrachloroethylene for 12–24 weeks, isolated splenocytes stimulated with MDA-mouse serum protein adducts showed an increase in Th17 cell (an effector T-cell type) proliferation and increase of IL-17 into culture media.

Genotoxic Effects. Genotoxic effects produced by tetrachloroethylene are thought to be the result of reactive metabolic intermediates of metabolism of tetrachloroethylene (Cichoki et al. 2016; EPA 2012a; IARC 2014; NRC 2010). Evidence for genotoxicity of tetrachloroethylene metabolites comes from numerous *in vitro* studies that have found that metabolic activation (e.g., S9 fraction) is required or greatly enhances genotoxicity. Studies of the genotoxicity of tetrachloroethylene metabolites suggest that genotoxicity may involve tetrachloroethylene epoxide, trichloroacetyl chloride, and metabolites formed in the glutathione conjugation pathway.

3.5.3 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 more sensitive to the liver effects of tetrachloroethylene than rats, produce more trichloroacetic acid. Production of trichloroacetic acid in mice may result in 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.

Although rats produce lower amounts of the intermediate *S*-(1,2,2-trichlorovinyl)glutathione in either kidney or liver cytosol or microsomes tested *in vitro* (Lash and Parker 2001), this species appears to have greater potential than mice for producing reactive intermediates in the kidney from the glutathione conjugate of tetrachloroethylene through the activity of kidney β-lyase (Green et al. 1990). The increased production of reactive metabolites may explain the higher sensitivity of rats to renal effects when compared with mice. Male rats also develop α-2u-globulin nephropathy following exposure to tetrachloroethylene. Due to the potential contribution of α-2u-globulin nephropathy in the observed kidney effects, the male rat is a relatively poor model for humans.

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 trichloroacetic acid may serve to reduce nervous system toxicity. Therefore, rats, which metabolize less tetrachloroethylene to trichloroacetic acid than mice (Hattis et al. 1990), may serve as a better model of nervous system effects in humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

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

No studies were located regarding endocrine disruption in humans or animals after exposure to tetrachloroethylene.

No *in vitro* studies were located regarding endocrine disruption of tetrachloroethylene.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when most biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

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

Children sometimes differ from adults in their susceptibility to adverse health effects from exposure to hazardous chemicals, but whether there is a difference depends on the chemical(s) (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to exposure-related health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life that are most sensitive to disruption from exposure to hazardous substances. Damage from exposure in one stage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). Past literature has often described the fetus/infant as having an immature (developing) blood-brain barrier that is leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the brain, there are differences between fetuses/infants and adults that are toxicologically important. These differences mainly involve variations in physiological transport

systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; whether these mechanisms provide protection for the developing brain or render it more vulnerable to toxic injury is an important toxicological question. Chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns given their low glomerular filtration rate and not having developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

Studies in mice suggest that tetrachloroethylene can cross the placenta and that trichloroacetic acid 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). Intake from tetrachloroethylene-contaminated water is expected to be greater in children than adults because children tend to drink more water on a per-kg body weight basis than adults, but this has not been experimentally determined. Absorption of tetrachloroethylene following exposure appears to be similar in adults and children, as *in vitro* blood:gas partition coefficients obtained by Mahle et al. (2004) suggest no age-related difference in partitioning between pediatric and adult blood. In support, PBPK modeling does not predict age-dependent variations in steady-state blood concentrations (Sarangapani et al. 2003). However, PBPK modeling predicts that metabolite blood concentration increases with age, associated with a concomitant increase in hepatic enzyme activity with age, indicating lower ability to metabolize tetrachloroethylene during early life stages (Clewell et al. 2004; Sarangapani et al. 2003). As the parent compound may mediate neurotoxic effects of exposure (see Section 3.5.2. Mechanisms of Toxicity), this decrease in metabolic capacity may confer increased risk to the developing nervous system. However, *in vitro* organ:air partition coefficients indicate lower fat:air, muscle:air, and brain:air coefficients in pups compared with adult rats, suggesting decreased distribution of tetrachloroethylene in the young (Mahle et al. 2004).

The data available for assessing the potential susceptibility of infants and children to the toxic effects of tetrachloroethylene are very limited. Results of some epidemiological studies indicate that exposure to tetrachloroethylene in the drinking water, ambient air, or workplace environments *in utero* or during early childhood may be associated with developmental effects such as increased rates of spontaneous abortion (Ahlborg 1990; Bosco et al. 1986; Doyle et al. 1997; Hemminki et al. 1980; Kyyrönen et al. 1989; Lindbohm et al. 1990; Windham 1991), ocular and auditory defects and other central nervous system abnormalities (Lagakos et al. 1986), oral cleft defects (Aschengrau et al. 2009; Bove et al. 1995), neural tube defects (Aschengrau et al. 2009), impaired immunity (Lagakos et al. 1986), and increased risk of mental illness as adults (Aschengrau et al. 2012; Perrin et al. 2007). However, the data supporting a cause-and-effect relationship for these effects are inadequate. Results of some animal studies indicate that tetrachloroethylene can cause reduced fetal weight and increased skeletal and soft-tissue anomalies (Carney et al. 2006; Schwetz et al. 1975; Szakmáry et al. 1997), decreased litter size (Narotsky and Kavlock 1995), neurobehavioral changes (Nelson et al. 1980; Fredriksson et al. 1993), neurochemical changes (Nelson et al. 1980), and brain composition alterations (Kyrklund and Haglid 1991).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of a generalizable sample of the exposure of the U.S. population to environmental chemicals using biomonitoring. This report is available at http://www.cdc.gov/exposurereport/. The biomonitoring data for tetrachloroethylene from this report is discussed in Section 6.5. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to tetrachloroethylene are discussed in Section 3.8.1.

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

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Tetrachloroethylene

Biological monitoring for exposure to tetrachloroethylene is possible by measuring levels of the parent compound in the blood, urine, or exhaled air or trichloroacetic acid in the blood or urine. Biological monitoring for tetrachloroethylene exposure has been performed to measure both the 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 (Dias et al. 2017; 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 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 tetrachloroethylene 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 tetrachloroethylene level of 7.8 μg/m^3, whereas people living on the second floor and above had a mean tetrachloroethylene 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 the 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, trichloroacetic acid, in blood and urine. However, trichloroacetic acid is not specific for tetrachloroethylene because it is also produced from the metabolism of trichloroethylene and 1,1,1-trichloroethane (Monster 1988). In a study of occupationally exposed individuals, measurements of tetrachloroethylene and trichloroacetic acid 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 trichloroacetic acid 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 associated with a TWA concentration of 25 ppm tetrachloroethylene is 0.5 mg tetrachloroethylene/L in blood and 3 ppm in end-exhaled air (ACGIH 2012). Jang et al. (1997) observed differences in tetrachloroethylene metabolism between persons of Caucasian and Asian descent in a controlled human exposure study, with higher levels of tetrachloroethylene measured in exhaled breath of Caucasians.

3.8.2 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 LDH. 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 tetrachloroethylene-exposed workers with no other evidence of liver effects (SGOT, SGPT, serum alkaline phosphatase, LDH, 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 BUN 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). Voss et al. (2005) evaluated the available data supporting a variety of potential biomarkers for early detection of renal damage from solvents. Data were sufficient for evaluation of only three: urinary albumin, β2-microglobulin, and NAG. The authors concluded that, because increased albumin excretion was frequently seen in exposed workers, this parameter might be suitable for biomonitoring for renal effects. However, the authors noted the uncertainties stemming from their simplistic analysis, which did not take into account variations in exposure intensity and duration. In addition, the authors cautioned that factors associated with albuminuria, including strenuous exercise prior to sampling, as well as diabetic nephropathy and hypertension, need to be considered in the interpretation of urinary albumin levels (Voss et al. 2005).

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 evaluation of symptoms,

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.

3.9 INTERACTIONS WITH OTHER CHEMICALS

The potential interactions between tetrachloroethylene and other chlorinated solvents are discussed in detail by ATSDR (2004). As concluded by ATSDR (2004), there are no studies available that directly characterize health hazards and dose-response relationships for exposures to mixtures of chlorinated solvents with tetrachloroethylene. The limited available data indicate no evidence for greater-than-additive joint toxic actions on the liver and kidney; there is some evidence that tetrachloroethylene may inhibit the effect of trichloroethylene on the liver and kidney (Goldsworthy and Popp 1987; Seiji et al. 1989). Potential interactions between tetrachloroethylene and other common indoor air contaminants (carbon monoxide, formaldehyde, methylene chloride, and nitrogen dioxide) are discussed by ATSDR (2007b). While several of these compounds exert toxic effects on the same target sites, there are no data to evaluate potential interactions among them.

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).

In many instances, exposure to tetrachloroethylene in air or water occurs in conjunction with several other compounds (co-contaminants). For example, drinking water at the Camp Lejeune was contaminated with tetrachloroethylene, trichloroethylene, benzene, vinyl chloride, and trans-1,2-dichloroethylene (Cohn et al. 1994; Ruckert et al. 2013) and drinking water in the Vartiainen et al. (1993) study of a Finish population was contaminated with both trichloroethylene and tetrachloroethylene. Co-contaminant exposure may result in effects that are different from those of tetrachloroethylene, or produce effects that are similar to tetrachloroethylene, potentially causing additive effects. For example, metabolic pathways

for tetrachloroethylene and trichloroethylene are qualitatively similar, although quantitative metabolic differences exist between the two compounds (Cichocki et al. 2016). However, metabolism of both compounds produces the common active metabolite. Indeed, a review by Cichocki et al. (2016) recommends that research be conducted on the effects of tetrachloroethylene and trichloroethylene coexposure so that differences in toxicokinetics and biomolecular markers may be ascertained.

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 tetrachloroethylene on the hepatic toxicity in rats. Rats were exposed to 15% ethanol in the drinking water and/or to tetrachloroethylene aerosol for 10 minutes/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 10-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, trichloro-ethanol, was greatest, with little effect on trichloroacetic acid, a metabolite of both trichloroethylene and tetrachloroethylene. The study authors indicated that because of the smaller amount of tetrachloro-ethylene 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 tetrachloroethylene alone (Ebrahim et al. 1996). 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. A follow-up study by this group further examined the potential protective properties of 2-deoxy-D-glucose (2DG) and vitamin E, as well as taurine, against tetrachloroethylene-induced membrane damage (Ebrahim et al. 2001). All three treatments reduced the membrane damage caused by 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 three: tetrachloroethylene, dieldrin, arsenic trioxide, and lead tetraacetate) were tested, interactions were also not observed.

3.10 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. Factors that may increase susceptibility include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of 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 6.7, Populations with Potentially High Exposures.

The elderly with declining organ function and the youngest of the population with immature and developing organs (i.e., premature and newborn infants) will be more vulnerable to toxic substances in general than healthy adults. As discussed in Section 3.7 (Children's Susceptibility), the developing fetus, children, and especially the developing nervous system may be particularly susceptible to the toxic effects of tetrachloroethylene, potentially due to age-related pharmacokinetic differences. Studies in mice suggest that tetrachloroethylene can cross the placenta and that trichloroacetic acid 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). As tetrachloroethylene is lipophilic, it is capable of accumulating in the body over time, which may account for the observed increase in dose metrics predicted by PBPK models for later life stages (Clewell et al. 2004). The lipophilicity of tetrachloroethylene may also result in higher accumulations of the compound in exposed persons with higher body fat content; conversely, lower body fat may result in higher blood levels of tetrachloroethylene. There are no data on the potential effects of obesity or underweight on tetrachloroethylene pharmacokinetics. Studies in rats indicate that blood:air and organ:air partition coefficients are elevated in aged male rats compared with adult male or postnatal day 10 male rats, suggesting greater absorption and distribution of tetrachloroethylene among older animals (Mahle et al. 2004); there are no data on tetrachloroethylene partitioning in aged human blood.

Underlying liver disease may increase susceptibility to tetrachloroethylene-induced liver toxicity. Studies conducted by Cichocki et al. (2017a, 2017b) in mice indicate that nonalcoholic fatty liver disease in mice may alter the toxicokinetics and hepatic effects of tetrachloroethylene. In mice with experimental nonalcoholic fatty liver disease, tetrachloroethylene levels in the liver increased up 7.6-fold. As a result, hepatic inflammation was increased.

Certain ethnic populations may also have increased susceptibility to toxicity based on pharmacokinetics of tetrachloroethylene, as 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 trichloroacetic acid/L per ppm tetrachloroethylene in Chinese workers, while the value was 0.7 mg trichloroacetic acid/L per ppm tetrachloroethylene in Japanese workers. Jang et al. (1997) observed differences in tetrachloro-ethylene metabolism among different ethnic populations between persons of Caucasian and Asian descent

in a controlled human exposure study, with higher levels of tetrachloroethylene measured in exhaled breath of Caucasians compared with those of Asian descent. Data on differences in the pharmacokinetic behavior of tetrachloroethylene in people of other ethnicities were not located in the available literature.

Patients who had detectable blood levels of VOCs (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 to catecholamines) (Gummin 2015; Shusterman 2018). 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.

Genotoxic effects of tetrachloroethylene appear to be mediated through reactive metabolic intermediates (see discussion in Section 3.5.2, Mechanisms of Toxicity, Genotoxic Effects). Therefore, polymorphisms of enzymes that produce these reactive intermediates (cytochrome P-450 isozymes, glutathione transferase isozymes, N-acetyl transferase) could increase susceptibility to tetrachloroethylene (Chiu and Ginsberg 2011; EPA 2012a; Spearow et al. 2017).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to tetrachloroethylene. 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, board certified medical toxicologists, board-certified occupational medicine physicians, and/or other medical specialists with expertise and experience treating patients overexposed to tetrachloroethylene can be consulted for medical advice. The following texts provide specific information about treatment following exposures to tetrachloroethylene:

ATSDR. 2014. Medical Management Guidelines (MMGs). Tetrachloroethylene. Atlanta, GA: Agency for Toxic Substances and Disease Registry.
https://www.atsdr.cdc.gov/mmg/mmg.asp?id=261&tid=48.pdf. September 3, 2018.

ATSDR. 2018. Agency for Toxic Substances and Disease Registry case studies in environmental medicine. Tetrachloroethylene toxicity. Atlanta, GA: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/csem/csem.asp?csem=36&po=0.pdf. September 3, 2018.

Gummin DD. 2015. Hydrocarbons. In: Hoffman RS, Lewin NA, Goldfrank LR, et al., eds. Goldfrank's toxicologic emergencies. 10th ed. New York, NY: McGraw-Hill Education, 309-310, 1334.

Shusterman D. 2018. Trichloroethane, trichloroethylene, and tetrachloroethylene. In: Olson KR, Anderson IB, Benowitz NL, et al., eds. Poisoning and drug overdose. 7th ed. McGraw-Hill Education.

The front of the profile contains the QUICK REFERENCE FOR HEALTH CARE PROVIDERS that provides additional relevant information.

3.11.1 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 (ATSDR 2018). Anesthetic overexposure may require respiratory assistance and the treatment of cardiac arrhythmias. General recommendations for reducing absorption following acute oral exposure is administration of a charcoal slurry (ATSDR 2014; Gummin 2015; HSDB 2013). Induction of emesis is not recommended (ATSDR 2014; Gummin 2015). In the case of eye exposure, irrigation with copious amounts of water or saline has been recommended (ATSDR 2014; HSDB 2013). For dermal exposure, the removal of contaminated clothing and a thorough washing of any exposed areas with mild soap and water have been recommended (ATSDR 2018; Gummin 2015; HSDB 2013).

3.11.2 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 3.4.4). 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. 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 g of tetrachloroethylene (Koppel et al. 1985). It is emphasized that no clinical treatments, other than supportive measures, are currently available to enhance elimination (ATSDR 2014, 2018; Gummin 2015).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No clear approaches to interfering with the mechanisms of tetrachloroethylene toxicity have emerged from the available literature. Efforts to do so may be stymied by the limited data and variety of mechanisms postulated for the known target organs (central nervous system, kidney, and liver), as well as the role of pharmacokinetics in the effects on each organ.

3.12 ADEQUACY OF THE DATABASE

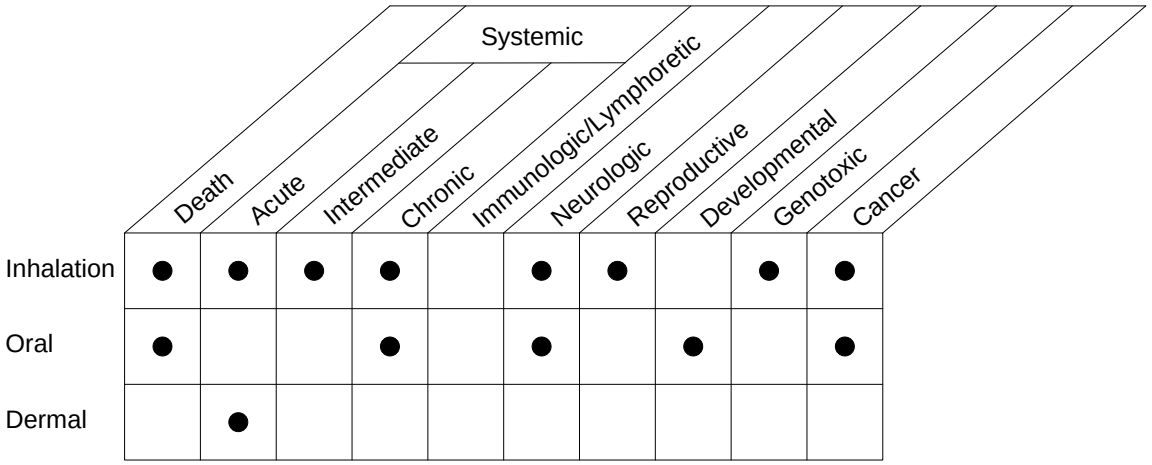
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of tetrachloroethylene is available. Where adequate information 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 adverse 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 risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

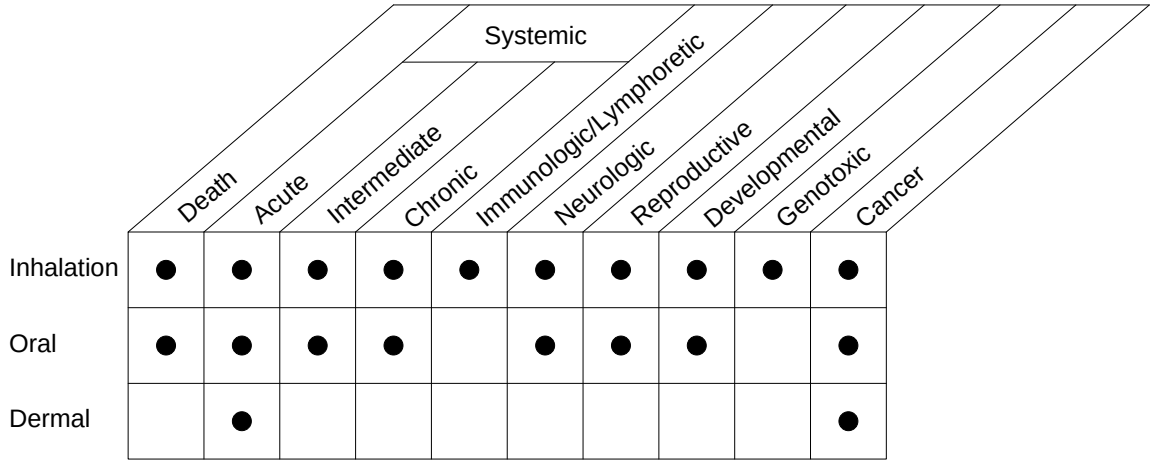
3.12.1 Existing Information on Health Effects of Tetrachloroethylene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to tetrachloroethylene are summarized in Figure 3-23. 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.

Figure 3-23. Existing Information on Health Effects of Tetrachloroethylene



Human



Animal

● Existing Studies

Most of the literature regarding health effects in humans comes from studies of workers exposed to tetrachloroethylene during occupational uses. Limited data are available from residential exposure to tetrachloroethylene from close proximity to dry cleaning establishments and from contaminated drinking water. 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 from acute exposure observed in the humans reported in these occupational and case studies are the result of central nervous system depression or skin injury. According to one case report, direct dermal exposure to tetrachloroethylene reportedly resulted in erythema and blistering of the skin. Transient kidney and liver injury are observed when acute and prolonged exposure to higher vapor concentrations occurs. Acute exposure to high vapor concentrations has also resulted in death, from either profound respiratory center depression or cardiac arrhythmia. Additional effects potentially associated with chronic exposure include loss of color vision, liver and kidney effects, immunological effects, reproductive effects, and cancer. Most of these studies are limited by the inadequate characterization of exposure levels and associated health effects and the lack of control for other chemical exposures, socioeconomic status, alcohol consumption, and tobacco consumption. 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 tetrachloroethylene. 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. Evidence suggests that tetrachloroethylene exposure during gestation affects growth and development, but is not overtly teratogenic. 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.

3.12.2 Identification of Data Needs

While the database of toxicity information on tetrachloroethylene is adequate for some end points, significant data gaps exist for several end points, including developmental and neurodevelopmental toxicity, and immunotoxicity (in both developmental and in adult populations). Data needs by exposure

duration and end point are discussed in further detail below; specific research recommendations include the following:

- Studies of immunotoxicity and immune function in developing and adult animals and/or in human populations exposed to tetrachloroethylene via oral or inhalation routes, for both intermediate and chronic durations;
- Additional studies of developmental and neurodevelopmental end points in humans or animals exposed to tetrachloroethylene via oral or inhalation routes;
- Additional oral bioassays evaluating chronic effects and cancer in animals; and
- Studies of tetrachloroethylene effects in humans or animals exposed dermally.

Additional empirical data from *in vivo* or *in vitro* studies on interactions between tetrachloroethylene and other constituents of commonly-encountered chemical mixtures are needed. Tetrachloroethylene frequently occurs in conjunction with other chlorinated solvents in water from hazardous waste sites (ATSDR 2004) and in conjunction with other indoor air contaminants (ATSDR 2007b); however, few data are available on the toxicity of these mixtures. Finally, research on the potential vulnerability of minority and low-income populations, which may be exposed to multiple health stressors in addition to chemical exposure, would be beneficial.

Acute-Duration Exposure. There are reports on acute tetrachloroethylene exposure of humans and 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; Haerer and Udelman 1964; Hake and Stewart 1977; 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 liver (Berman et al. 1995; Goldsworthy and Popp 1987; Hake and Stewart 1977; Hanioka et al. 1995; Kylin et al. 1963; Levine et al. 1981; NTP 1986; Odum et al. 1988; Saland 1967; Schumann et al. 1980; Stewart 1969).

The majority of the human studies are cases involving accidental exposure (Garnier et al. 1996; Koppel et al. 1985; Saland 1967), occupational exposure (Levine et al. 1981; Lukaszewski 1979; Morgan 1969; Patel et al. 1973), exposure from the use of tetrachloroethylene as an anthelminthic (Kendrick 1929; Wright et al. 1937), and exposure from contaminated drinking water (Aschengrau et al. 2012; Getz et al. 2012; Janulewicz et al. 2008, 2012). 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 could be obtained based on the NOAEL of 2 ppm for human central nervous system effects (Altmann et al. 1992); however, PBPK simulations indicate that an MRL obtained from this study would not be adequately protective for exposures up to 2 weeks. Furthermore, since the chronic-duration LOAEL of 2 ppm used to obtain the chronic-duration inhalation MRL is the same value, the chronic value was adopted for the acute-duration inhalation MRL. 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), as well as neurotoxic effects in rats (Albee et al. 1991; Boyes et al. 2009; Goldberg et al. 1964; Mattson et al. 1998; 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 (Philip et al. 2007; 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; Potter et al. 1996), decreased body weight gain in rats (Schumann et al. 1980), neurological effects in rats (Moser et al. 1995; Warren et al. 1996), and liver hypertrophy (Schumann et al. 1980) in mice. Interpretation of some of these data is difficult because of limitations in the design and methodology of the studies (e.g., decreased survival, poor study methodology).

Oral exposure of young mice to tetrachloroethylene resulted in hyperactivity when the mice were tested as adults (Fredriksson et al. 1993); however, metabolic differences between mice and humans exposed orally suggest that mice would be a poor model for neurotoxicity in humans. The chronic-duration oral MRL of 0.008 mg/kg/day has been adopted as the acute-duration oral MRL based on PBPK modeling results that predict that neurological effects would occur at the same concentration after acute and chronic exposures. Acute dermal exposure data in animals were not identified. Additional data on dermal exposure of animals would be useful to provide threshold levels. 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

experience acute-duration exposures to tetrachloroethylene via inhalation, oral, or dermal routes as a result of accidental releases.

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) and cardiac sensitization (Abedin et al. 1980). However, exposure concentrations are not well defined in these studies. As with the acute-duration inhalation MRL, the intermediate-duration inhalation MRL was set equal to the chronic-duration inhalation MRL (using human data) based on PBPK simulations. No human data were located regarding oral or dermal intermediate-duration exposure to tetrachloroethylene. The target organs identified in animal studies of intermediate-duration oral or inhalation exposure to tetrachloroethylene include the nervous system (Carpenter 1937; Karlsson et al. 1987; Kyrklund et al. 1988; Mattsson et al. 1992, 1998; Rosengren et al. 1986), liver (Boverhof et al. 2013; Buben and O'Flaherty 1985; Carpenter 1937; Hayes et al. 1986; Jonker et al. 1996; Kjellstrand et al. 1984; Kylin et al. 1965; Kyrklund et al. 1988; NTP 1986; Odum et al. 1988; Philip et al. 2007; Rajamanikandan et al. 2012; Rowe et al. 1985; Story et al. 1986), kidney (Carpenter 1937; Ebrahim et al. 1996; Green et al. 1990; Hayes et al. 1986; Jonker et al. 1996; NTP 1986; Rowe et al. 1985), and immune system (Seo et al. 2008a, 2012). These studies were conducted in a variety of animal species including mice, rats, guinea pigs, and gerbils. No intermediate-duration dermal studies in animals were located.

The chronic-duration oral MRL of 0.008 mg/kg/day has been adopted as the intermediate-duration oral MRL based on PBPK modeling results indicating that neurological effects occur at the same concentration after acute, intermediate, and chronic exposures. The lowest animal LOAEL was for neurological effects in rats (Chen et al. 2002). After conversion to a human equivalent dose, the LOAEL (1.8 mg/kg/day) from Chen et al. (2002) is equivalent to the LOAEL (2.3 mg/kg/day) for chronic human exposure used to obtain the chronic oral MRL; thus, because the chronic value was derived from human data, the chronic-duration oral MRL was adopted as the intermediate-duration oral MRL. 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.

Two oral exposure studies in rats and mice (Seo et al. 2008a, 2012) have suggested that very low levels of tetrachloroethylene in the drinking water of rodents may enhance the immune response to allergens and exacerbate inflammation. The toxicological importance of these findings and their relevance to humans are uncertain, and available human data on immune system end points are inadequate to inform these

questions. Additional human epidemiological studies, animal studies, and *in vitro* investigations of potential immune system perturbations are needed to confirm the findings of Seo et al. (2008a, 2012) and/or to further evaluate functional immune system effects of tetrachloroethylene exposure.

Chronic-Duration Exposure and Cancer. Kidney toxicity (Bundschuh et al. 1993; Franchini et al. 1983; Mutti et al. 1992; Price et al. 1995; Vyskocil et al. 1990), liver toxicity (Brodkin et al. 1995; Coler and Rossmiller 1953), immunotoxicity (Andrys et al. 1997; Emara et al. 2010), 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 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 evaluation of the Cavalleri et al. (1994) cohort revealed that workers whose exposure to tetrachloroethylene had increased demonstrated further decrements in color vision, after controlling for age, while those whose exposure had decreased had no changes in color vision (Gobba et al. 1998). Other studies indicate that color vision may be impaired in workers or offspring following occupational tetrachloroethylene exposure (Sharanjeet-Kaur et al. 2004; Till et al. 2003), but these studies did not quantify exposure levels. Further studies to evaluate the dose-response relationship between exposure to tetrachloroethylene and 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.

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. Deficits in visual contrast sensitivity, but not in color discrimination, were observed in children or adults living in residential buildings that also housed dry cleaning facilities (Schreiber et al. 2002; Storm et al. 2011). Studies in residential populations suggested effects at lower concentrations than studies in occupational populations, but were not considered adequate for MRL derivation. Thus, further studies of larger residential populations exposed to very low levels of

tetrachloroethylene would be useful. In addition, studies of tetrachloroethylene effects in potentially susceptible populations, including minority and low-income populations who may be exposed to multiple health stressors in addition to chemical exposure, may serve to inform or refine the MRL. As there are few studies of health effects in human populations exposed to tetrachloroethylene orally, additional investigation of such populations would serve to fill this data gap.

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). 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; Boice et al. 1999; Brown and Kaplan 1987; Chapman et al. 1981; Chang et al. 2003; Duh and Asal 1984; Katz and Jowett 1981; Lipworth et al. 2011; Lynge and Thygesen 1990; Lynge et al. 2006; Ma et al. 2009; Ruder et al. 1994, 2001; Spirtas et al. 1991). The cancer types most consistently showing an increase were bladder cancer, multiple myeloma, and non-Hodgkin's lymphoma (reviewed by NRC 2010; EPA 2012a). In general, studies examining other cancer types 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 (Aschengrau et al. 1998, 2003; Cohn et al. 1994; Gallagher et al. 2011; Lagakos et al. 1986; Paulu et al. 1999; Vieira et al. 2005). 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. Nested case-control studies within a cohort exposed to tetrachloroethylene in drinking water suggested a potential association between tetrachloroethylene exposure and breast cancer (Aschengrau et al. 1998, 2003; Gallagher et al. 2011; Vieira et al. 2005), but not other types of cancers (Paulu et al. 1999). No chronic dermal exposure data are available for humans.

Inhalation and oral bioassays using rats and mice have been conducted (JISA 1993; 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 mechanistic data to aid interpretation of the mouse liver tumors and rat mononuclear cell leukemias and their relevance to humans would be useful. In addition, research investigating the potential contribution of inflammation to adverse effects of chronic tetrachloroethylene exposure (including cancers as well as liver, kidney, and neurological effects) would be beneficial in light of the data from Seo et al. (2008a) suggesting enhancement of inflammation in rats exposed to this compound.

Genotoxicity. *In vivo* genotoxicity studies examining human lymphocytes (Ikeda et al. 1980; Seiji et al. 1990) or leukocytes (Toraason et al. 2003) from persons occupationally exposed to tetrachloroethylene (Ikeda et al. 1980; Seiji et al. 1990) were negative for sister chromatid exchange; however, one study reported an increase in transient DNA damage (acentric DNA fragments) that correlated with the TWA blood levels of tetrachloroethylene in dry cleaners (Tucker et al. 2011). The majority of *in vivo* animal assays (Cedaerburg et al. 2010; Murakami and Horikawa 1995; Toraason et al. 1999) and *in vitro* genotoxicity tests using prokaryotic cells (Bartsch et al. 1979; Emmert et al. 2006; Haworth et al. 1983; NTP 1986; Shimada et al. 1983; Watanabe et al. 1998), eukaryotic cells (Bronzetti et al. 1983; Callen et al. 1980; Koch et al. 1988), or mammalian cells (Costa and Ivanetich 1980; Hartman and Speit 1995; Matsushima et al. 1999; Mazzullo et al. 1987; NIOSH 1980; NTP 1986; Shimada et al. 1983; Tu et al. 1985; Walles 1986) showed negative or marginal results for gene mutation, recombination, DNA damage, micronuclei, and sister chromatid exchange. 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 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.

Reproductive Toxicity. Reproductive data are available on women occupationally exposed to tetrachloroethylene in dry cleaning operations. Some studies suggest an increase in spontaneous abortion (Ahlborg 1990; Bosco et al. 1986; Doyle et al. 1997; Hemminki et al. 1980; Kyyrönen et al. 1989; Lindbohm et al. 1990; Windham et al. 1991), but other studies reported no increase (McDonald et al. 1986, 1987; Olsen et al. 1990). Limited evidence also suggests that time-to-pregnancy may be increased among women occupationally exposed to tetrachloroethylene (Sallmén 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). Similarly, paternal occupational exposure to tetrachloroethylene was associated with decreased fecundability, but not increased rates of spontaneous abortion (Sallmén et al. 1998; Taskinen et al. 1989). These studies suggest that tetrachloroethylene may affect the ability of men to reproduce. Collectively, these occupational studies are limited by inadequate information on exposure levels, limited controls for lifestyle factors, the difficulty in identifying appropriate controls, and the problems in controlling for concomitant exposures to other chemicals. No studies were located regarding reproductive effects in humans after oral or dermal exposure to tetrachloroethylene.

Evidence from a limited number of well-conducted reproductive studies in laboratory animals, including a multigenerational study, suggests that tetrachloroethylene is a potential female reproductive toxicant following inhalation exposure. Exposure to concentrations ≥664 ppm resulted in decreased numbers of liveborn pups, increased pre- and postimplantation losses, and increased resorptions (Szakmáry et al. 1997; Tinston 1995). These exposure levels also resulted in maternal toxicity (e.g., frank neurological toxicity, reduced maternal weight gain). 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). These studies suggest that reproductive effects following inhalation or oral exposure are unlikely to occur at exposure levels below those that result in maternal toxicity. No studies were located regarding reproductive effects in animals following dermal exposure.

There is also limited evidence that tetrachloroethylene can damage both male and female gametes. Spermhead abnormalities were observed in mice, but not rats, 4 and 10 weeks following a 5-day exposure to 500 ppm tetrachloroethylene (NIOSH 1980), and decreased oocyte quality was reported in rats exposed to 1,700 ppm tetrachloroethylene for 2 weeks (Berger and Homer 2003). However, 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).

There is a need to further assess relationships between exposure to tetrachloroethylene and reproductive outcomes among humans following occupational exposure, and studies should be conducted to assess if there is a reproductive risk associated with consuming contaminated drinking water. 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. A human epidemiological study examined birth outcomes associated with maternal residence in Endicott, New York, an area where soil was contaminated with VOCs (Forand et al. 2012). In a region primarily contaminated with tetrachloroethylene, there was no association with elevated risk for cardiac defects, low-birth weight, preterm birth, fetal growth restriction, or other birth defects, compared with state-wide incidence (excluding New York City). This study is limited by the ecological design that precludes assignment of actual exposures to individual subjects, small number of births in the study area, lack of control for potential occupational exposure to tetrachloroethylene (which was associated with elevated risk of adverse birth outcomes), lower socioeconomic status in the study area than the general comparison population, concurrent exposure to other VOCs, and other uncontrolled confounders such as alcohol, diet, and pre-existing maternal illness (Bukowski 2014).

A prospective population-based cohort study in Jerusalem suggests that parental exposure to tetrachloroethylene may lead to the development of neurological disorders in offspring, as the diagnosis of schizophrenia in children of dry cleaners almost tripled compared with the general population (Perrin et al. 2007). Limitations of this study include a small number of diagnosed cases (n=4), lack of exposure data, and lack of control for family history of mental illness, an important risk factor for developing schizophrenia. Studies examining the association between drinking water contamination and birth outcome (Aschengrau et al. 2008, 2009; Bove et al. 1995; Lagakos et al. 1986; Sonnenfeld et al. 2001) have suggested that tetrachloroethylene exposure may be associated with increased ocular and auditory defects, central nervous system abnormalities, oral cleft defects, neural tube defects, low birth weight, and small for gestational age. Additional negative outcomes in these studies include evidence for impaired immunity (Lagakos et al. 1986) and increased risk for mental illness in adulthood (Aschengrau et al. 2012) following exposure during early life stages. These studies are not conclusive because the water was contaminated with other solvents in addition to tetrachloroethylene.

Evidence from multiple studies in laboratory animals indicates that gestational exposure to tetrachloroethylene via inhalation affects growth and development, but that tetrachloroethylene is not teratogenic. Developmental effects have been reported in rats, mice, and rabbits at concentrations as low as 300 ppm, and include growth retardation and skeletal (e.g., delayed ossification) and soft tissue (e.g., kidney dysplasia) anomalies (Carney et al. 2006; Schwetz et al. 1975; Szakmáry et al. 1997). These effects often occur at concentrations that illicit maternal toxicity. Following oral exposure, 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).

Behavioral and neurochemical alterations were observed in rats after maternal exposure to 900 ppm tetrachloroethylene (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 days of age, but not at 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. 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 trichloroacetic acid 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. The available studies of immunological effects in humans exposed to tetrachloroethylene provide suggestive evidence for alterations in cytokine signaling related to hypersensitivity;

however, the data are limited. Egyptian dry cleaners exposed to <140 ppm tetrachloroethylene demonstrated increased serum and cellular IL-4 levels and serum IgE levels compared to age- and lifestyle-matched referent subjects (Emara et al. 2010). In a study examining a wide variety of VOCs, Lehmann et al. (2002) reported decreased percentages of IFN-γ-producing T cells in the umbilical cord blood of infants from homes with higher levels of tetrachloroethylene (>7.3 μg/m^3, the 75th percentile concentration) compared with infants from homes with lower levels (Lehmann et al. 2002). The limited available epidemiological studies investigating allergic sensitization and asthma have not observed a clear role for tetrachloroethylene exposure in the development of these conditions (Delfino et al. 2003; Lehmann et al. 2001), but a case report of hypersensitivity pneumonitis in a female dry cleaner provides some support (Tanios et al. 2004).

A very small cohort study reported statistically significant alterations in a number of blood immunological parameters when dry cleaning workers with high tetrachloroethylene exposure were compared with measurements from a referent group of "administrators" or when compared with laboratory reference values (Andrys et al. 1997). However, the small number of subjects limits the interpretation of these findings. 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.

Findings of immunological effects following tetrachloroethylene exposure in animals are inconsistent. No evidence of immunotoxicity was reported following inhalation exposure in rats (Boverhof et al. 2013). Increased susceptibility to bacterial infection was observed in mice exposed to 50 ppm tetrachloroethylene for 3 hours (Aranyi et al. 1986). 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. Atrophy of the spleen and thymus was reported in rats following exposure to 2,000 mg tetrachloroethylene/kg for 5 days (Hanioka et al. 1995). 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 humoral 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). Seo et al. (2008a, 2012)

observed enhanced immune response to allergens in rats and mice exposed orally to very low doses of tetrachloroethylene; Seo et al. (2008a) also observed exacerbation of inflammation in skin lesions, as well as enhanced expression of the pro-inflammatory cytokine IL-4, when rats were exposed to tetrachloroethylene for 2 and 4 weeks (respectively). There are no dermal studies regarding the immunotoxic effects of tetrachloroethylene.

Further study of the immune system effects of tetrachloroethylene is needed, given: (1) the effects suggested by the studies of Seo et al. (2008a, 2012); (2) the observation in human epidemiological studies of potential associations between tetrachloroethylene and immune system cancers (multiple myeloma and lymphoma); (3) the potential role of enhanced inflammation in the observed effects of tetrachloroethylene on other systems including the liver, kidney, and neurological system; and (4) evidence that the related compound trichloroethylene exerts immunotoxic effects. A comprehensive immunotoxicity evaluation, including a range of functional tests, is warranted.

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, 1981) 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 indicate that chronic occupational exposure to tetrachloroethylene can produce more serious effects, including memory deficits (Cai et al. 1991; Echeverria et al. 1995; Gregersen 1988; Seeber 1989), disorientation (Coler and Rossmiller 1953), and loss of color vision (Cavalleri et al. 1994 Gobba et al. 1998; Sharanjeet-Kaur et al. 2004; Till et al. 2003). Suggestive evidence for an association with schizophrenia (Perrin et al. 2007) has also been reported in small human epidemiological studies. 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. Deficits in visual contrast sensitivity, but not color discrimination, were observed in

children or adults living in residential buildings that also housed dry cleaning facilities (Schreiber et al. 2002; Storm et al. 2011). Further studies of larger residential populations exposed to very low levels of tetrachloroethylene would be useful to confirm or refute these findings. Effects observed in humans after acute oral exposure appear to parallel those observed after inhalation exposure (Haerer and Udelman 1964; Kendrick 1929; Koppel et al. 1985; Sandground 1941; Wright et al. 1937). Chronic exposure to tetrachloroethylene via contaminated drinking water during childhood has been associated with increased risk for mental illness and risky behavior later in life (Aschengrau et al. 2011) and impaired color vision (Getz et al. 2012); however, exposure did not affect the frequency of learning, behavior, or attention (Janulewicz et al. 2008, 2012). These studies are limited by small group sizes. 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; Boyes et al. 2009; Mattsson et al. 1992, 1998), ataxia in rats (Goldberg et al. 1964; NTP 1986), hypoactivity in rats (NTP 1986; Tinston 1995), hyperactivity in rats (Savolainen et al. 1977), and impaired attention in rats (Oshiro et al. 2008). Signs of central nervous system depression (Jonker et al. 1996), ataxia (Narotsky and Kavlock 1995), increased lacrimation, gait changes, and decreased activity (Moser et al. 1995), and impaired operant learning (Warren et al. 1996) have been reported in rats following acute oral exposure to tetrachloroethylene. Oral exposure for 8 weeks resulted in impairments in nociception, increased seizure threshold, and reduced locomotor activity in rats (Chen et al. 2002). 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. The epidemiological data for inhalation exposure to tetrachloroethylene derive predominantly from exposures in the workplace, where potential associations have been reported between tetrachloroethylene exposure and cancer (Anttila et al. 1995; Blair et al. 1979, 1990; Boice et al. 1999; Brown and Kaplan 1987; Chang et al. 2003; Chapman et al. 1981; Duh and Asal 1984; Katz and Jowett 1981; Lipworth et al. 2011; Lynge and Thygesen 1990; Lynge et al. 2006; Ruder et al. 1994, 2001), kidney effects (Bundschuh et al. 1993; Franchini et al. 1983; Mutti et al. 1992; Price et al. 2005; Vyskocil et al. 1990), liver effects (Brodkin et al. 1995; Coler and

Rossmiller 1953), cardiovascular effects (Abedin et al. 1980; Hake and Stewart 1977), neurological effects (Cavalleri et al. 1994; Echeverria et al. 1995; Ferroni et al. 1992; Gobba et al. 1998; Nakatsuka et al. 1992; Sharanjeet-Kaur et al. 2004; Till et al. 2003), immunological effects (Andrys et al. 1997; Emara et al. 2010), and reproductive effects (Ahlbor 1990; Bosco et al. 1986; Doyle et al. 1997; Eskenazi et al. 1991a, 1991b; Hemminki et al. 1980; Kyyronen et al. 1989; Lindbohm et al. 1990; Sallmén et al. 1995, 1998; Windham et al. 1991). There are a limited number of epidemiological studies suggesting potential associations between living in close proximity to dry cleaning establishments and cancer (Ma et al. 2009) and neurological effects (Altmann et al. 1995; Schreiber et al. 2002; Storm et al. 2011). Most studies do not include adequate characterization of exposure levels and associated health effects, and lack control for other chemical exposures, socioeconomic status, alcohol consumption, and tobacco consumption. Epidemiological data for oral exposure to tetrachloroethylene are available from studies of tetrachloroethylene in the drinking water, where tetrachloroethylene has been associated with breast cancer (Aschengrau et al. 1998, 2003; Gallagher et al. 2011; Vieira et al. 2005), neurological effects (Aschengrau et al. 2011, 2012; Getz et al. 2012; Perrin et al. 2007), immunological effects (Byers et al. 1998; Lagakos et al. 1986), and developmental effects (Aschengrau et al. 2008, 2009; Bove et al. 1995; Lagakos et al. 1986; Sonnenfeld et al. 2001). These studies are limited by a number of confounding factors (e.g., uncertain exposure duration, exposure to multiple organic compounds). 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; Storm et al. 2011).

Additional epidemiological studies are needed that focus on the effects of low levels of tetrachloroethylene in the air, water, or soil near hazardous waste sites. These studies should carefully consider possible confounding factors, including exposure to multiple chemicals, smoking and drinking habits, age, and gender. The end points that need to be carefully considered are kidney and liver effects, cardiovascular effects, developmental effects, neurological effects, immunological effects, and cancer.

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 or vapor intrusion 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 exposures, 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 exposure (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 decreases with increased exposure duration (Monster et al. 1979). Oral studies in animals that 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 Fernandez 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 Fernandez 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 (Birner 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 (Birner 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 tetrachloroethylene 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 tetrachloroethylene, or is produced from trichloroethylene (a contaminant of 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 (Koppel et al. 1985), one dermal (Stewart and Dodd 1964), and several inhalation (Ikeda et al. 1972; Monster et al. 1979; Ogata et al. 1971; Ohtsuki et al. 1983; Opdam and Smolders 1986) studies 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.

Uncertainty in the degree of glutathione-mediated metabolism of tetrachloroethylene in humans, and the interindividual variability in this pathway, represents a significant data gap.

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).

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 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 (Stewart and Dodd 1964) exposure 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 (Bentley 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, dermal, or ocular exposure are well established and have a proven efficacy (ATSDR 2014, 2018; Gummin 2015; HSDB 2013). 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 trichloroacetic acid, a metabolite of tetrachloroethylene (Odum et al. 1988). Shifting metabolism away from formation of trichloroacetic acid 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.

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

Additional human and animal studies are needed to assess whether infants and children are more susceptible than adults to tetrachloroethylene toxicity.

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

3.12.3 Ongoing Studies

Ongoing studies funded by the National Institutes of Health (NIH) pertaining to tetrachloroethylene are shown in Table 3-11.

Table 3-11. Ongoing Studies on Tetrachloroethylene

Principal Investigator	Study topic	Institution	Sponsor
Aschengrau, AA	Tetrachloroethylene in the drinking water and risk of birth defects in a population-based case-control study	Boston University Medical Campus, Boston, Massachusetts	National Institute of Environmental Health Sciences
Aschengrau, AA	Early life exposure to tetrachloroethylene and social stressors and substance abuse in adolescence and adulthood	Boston University Medical Campus, Boston, Massachusetts	National Institute of Environmental Health Sciences
Beck, KD	Effects of chronic drinking water exposure to tetrachloroethylene and trichloroethylene on Parkinson's disease neurotoxicity in rats	VA New Jersey Health Care System	Veterans Administration
Ozonoff, DM	Epidemiologic studies of neurodevelopment in a population exposed to tetrachloroethylene in the drinking water	Boston University Medical Campus, Boston, Massachusetts	National Institute of Environmental Health Sciences
DeRoos, AJ	Risk of multiple myeloma from exposure to occupational solvents, including tetrachloroethylene	Drexel University, Philadelphia, Pennsylvania	National Institute of Environmental Health Sciences

Source: RePORTER 2013, 2018