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 trichloroethylene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (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. 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 trichloroethylene are indicated in Tables 3-1 and 3-3 and Figures 3-1 and 3-17.

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

Humans have died from breathing high concentrations of trichloroethylene fumes. Most of the reported deaths have been associated with accidental breathing of unusually high levels of trichloroethylene vapors in the workplace during its use in cleaning, degreasing, dry cleaning, or construction operations (Bell 1951; Coopman et al. 2003; Ford et al. 1995; James 1963; Kleinfeld and Tabershaw 1954; McCarthy and Jones 1983; Pantucharoensri et al. 2004; Smith 1966; Thorburn et al. 2004). A number of the deaths occurred after the trichloroethylene exposure ended and involved physical exertion that may have contributed to the sudden deaths (Smith 1966; Troutman 1988). Deaths have also resulted from the early use of trichloroethylene as an anesthetic (DeFalque 1961) as well as the presumed intentional inhalation of concentrated fumes from trichloroethylene-containing substances (Clearfield 1970; Jones and Singer 2008; Takaki et al. 2008; Troutman 1988). Death associated with liver damage has also been reported in persons occupationally exposed to trichloroethylene for intermediate and chronic durations, followed by a high acute-duration exposure (Joron et al. 1955; Priest and Horn 1965). None of these cases provided adequate exposure level or duration data to define with accuracy the levels of inhalation exposure that cause human deaths.

In a cohort mortality study of 14,457 aircraft maintenance workers employed for at least 1 year between 1952 and 1956, a significant excess of death from asthma was found among 6,153 workers with reported occupational exposure to trichloroethylene; however, the workers were likely exposed to other chemicals as well (Blair et al. 1998).

Animal experimentation has revealed inhaled concentrations that result in death following acute, intermediate, and chronic exposures. An LC_{50} value for acute exposure in rats was reported as 12,500 ppm for a 4-hour exposure (Siegel et al. 1971). Two out of 10 mice died after a 4-hour exposure to 6,400 ppm trichloroethylene (Kylin et al. 1962). Death was often caused by the central nervous system depression that occurs with very high exposure levels. Data on the lethality of longer-term exposure to trichloroethylene have been provided by studies of intermediate and chronic duration. Laboratory animals (rats, guinea pigs, monkeys, rabbits, and dogs) survived intermittent exposure to 700 ppm for 6 weeks or continuous exposure to 35 ppm for 90 days (Prendergast et al. 1967). There was no decrease in survival for rats and hamsters exposed to 500 ppm for 18 months, although a significant decrease in survival was seen for mice exposed to 100 ppm for the same amount of time (Henschler et al. 1980).

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 values and all LOAEL values from each reliable study for each species, duration, and end point for systemic effects are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. A worker developed labored breathing and respiratory edema after welding stainless steel that had been washed in trichloroethylene (Sjogren et al. 1991). The effects were attributed to inhalation of the trichloroethylene decomposition products, phosgene and dichloroacetyl chloride, although a history of cigarette smoking may have predisposed the subject to these respiratory effects. In a cohort mortality study of 14,457 aircraft maintenance workers employed for at least 1 year between 1952 and 1956, a significant excess of death from asthma (standardized mortality ratio [SMR] 160; 95% confidence interval [CI] 102–251) was reported for a group of 6,153 workers with reported occupational exposure to trichloroethylene compared to a referent group of workers not exposed to any chemical (Blair et al. 1998). The follow-up period was 1952–1990 and the trichloroethylene-exposed workers were likely exposed to other chemicals as well. Asthma-related symptoms and lung function decrements were

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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 (Sprague-Dawley)	4 hr				12500 M (LC50)	Siegel et al. 1971	
2	Mouse (Albino)	4 hr				6400 (2/10 deaths)	Kylin et al. 1962	
Systemic								
3	Human	4 hr	Hemato	95 M			Konietzko and Reill 1980	
			Hepatic	95 M				
4	Human	5 d 7 hr/d	Hemato	200			Stewart et al. 1970	
			Hepatic	200				
			Ocular		200 (eye irritation)			
5	Human	2.5 hr	Cardio	200 M			Windemuller and Ettema 1978	
6	Rat (Fischer- 344)	6 hr	Renal		1000 M (increased urinary gamma-glutamyl transpeptidase, glucose, protein, serum urea nitrogen, decreased uptake of p-aminohippurate by renal cortical slices)		Chakrabarti and Tuchweber 1988	

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
7	Rat (Wistar)	1 or 2 wk 5 d/wk 4 h/d	Resp		376 M (nasal irritation during exposure)		Kumar et al. 2002a	
			Ocular		376 M (ocular irritation during exposure)			
8	Rat (Alpk: APfSD)	6 hr	Resp		500 F (reduction of aldrin epoxidase and cytochrome C reductase activity)		Odum et al. 1992	
9	Rat (CD-1)	2 wk 5 d/wk 6 hr/d	Bd Wt	1000 M			Xu et al. 2004	
10	Mouse (CD-1)	6 hr	Resp	20 F	100 F (vacuolization of Clara cells, reduction of P-450 activity)		Odum et al. 1992	
11	Mouse (CD-1)	2 wk 5 d/wk 6 hr/d	Resp		450 F (vacuolization of Clara cells, reduction of P-450 activity)		Odum et al. 1992	

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
12	Mouse (Hybrid)	7 d 8 h/d	Hepatic		1000 M (increased liver weight, minimal hepatocellular necrosis)		Ramdhan et al. 2008	
13	Mouse (B6C3F1)	30 min	Resp		500 M (vacuolization and dilation of endoplasmic reticulum in Clara cells)		Villaschi et al. 1991	
14	Dog (Beagle)	10 min	Cardio	5000 M		10000 M (7/12 ventricular fibrillation after epinephrine challenge, 1/12 cardiac arrest)	Reinhardt et al. 1973	
Immuno/ Lymphoret								
15	Mouse (CD-1)	3 hr		5 F	10 F (increased susceptibility to Streptococcus zooepidemicus)		Aranyi et al. 1986	
Neurological								
16	Human	2.5 hr		300 M			Ettema et al. 1975	
17	Human	~1 hr				3000 M (unconsciousness)	Longley and Jones 1963	

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
18	Human	5 d 7 hr/d			200	(headache, fatigue, drowsiness)			Stewart et al. 1970	
19	Human	2 hr		300 M			1000 M	(decreased depth perception and motor skills)	Vernon and Ferguson 1969	
20	Human	2.5 hr		200 M					Windemuller and Ettema 1978	
21	Rat (Wistar)	8 hr			3000	(lethargy)	4800	(anesthesia)	Adams et al. 1951	
22	Rat (Wistar)	3 d 8 hr/d or 4 hr/d		300 M	1000 M	(decreased wakefulness, decreased postexposure heart rate)	3000 M	(occasional seizures, postexposure arrhythmia)	Arito et al. 1993	
23	Rat (Long- Evans)	5 d 6 hr/d		2000 M			4000 M	(postexposure mid-frequency hearing loss, sedation)	Crofton and Zhao 1993	

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
24	Rat (Long- Evans)	Once 6 hr		4000 M	6000 M (14 dB increase in auditory threshold to 16 kHz)		Crofton and Zhao 1997	
25	Rat (Long- Evans)	5 d 6 hr/d		2400 M	3200 M (21 dB increase in auditory threshold for 16 kHz tone)		Crofton and Zhao 1997	
26	Rat (CFE)	10 d 5 d/wk 4 hr/d		1568 F		4380 F (ataxia)	Goldberg et al. 1964b	
27	Rat (NS)	6 hr		400 M	800 M (impaired swimming performance both with and without a load)		Grandjean 1963	
28	Rat (Wistar)	4 hr			250 M (decreased shock avoidance and Skinner box lever press)		Kishi et al. 1993	
29	Rat (pigmented)	1 hr			2754 (impaired oculomotor control)		Niklasson et al. 1993	

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
30	Rat (Sprague-Dawley)	4 d 6 hr/d			200 M (decreased brain RNA, hyperactivity)		Savolainen et al. 1977	
Reproductive								
31	Rat (Wistar)	2 wk 5 d/wk 4 hr/d			376 M (increased sperm abnormalities, decreased reproductive success)		Kumar et al. 2000b	
32	Rat (CD-1)	2 wk 5 d/wk 6 hr/d			1000 M (decreased numbers of sperm attaching to eggs)		Xu et al. 2004	
33	Mouse (C57Bl/ 6J)	5 d 6 hr/d		500 M			Allen et al. 1994	
34	Mouse (CD-1)	5 d 7 hr/d			100 M (6% increase in abnormal sperm morphology)		Beliles et al. 1980	
35	Mouse (CD-1)	1 d; 1, 2, 3, or 4 wk 5 d/wk 5 hr/d			1000 M (degeneration of epididymal epithelium)		Kan et al. 2007	
36	Mouse (C57BL/ 6N)	5 d 4 hr/d		200 M	2000 M (1% increase in abnormal sperm morphology)		Land et al. 1981	

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
Developmental								
37	Rat (Sprague-Dawley)	Gd 0-18 5 d/wk 7 hr/d		500			Beliles et al. 1980; Hardin et al. 1981	
38	Rat (Long- Evans)	Gd 0-20 7 d/wk 6 hr/d			1800 (decreased fetal weight, incomplete skeletal ossification)		Dorfmueller et al. 1979	
39	Rat (Sprague-Dawley)	Gd 6-15 7 hr/d		300			Schwetz et al. 1975	
40	Mouse (Swiss-Webster)	Gd 6-15 7 hr/d		300			Schwetz et al. 1975	
INTERMEDIATE EXPOSURE								
Systemic								
41	Monkey (Rhesus)	6 mo 5 d/wk 7 hr/d	Hepatic	400 M			Adams et al. 1951	
			Renal	400 M				
			Bd Wt	400 M				
42	Rat (Wistar)	6 mo 5 d/wk 7 hr/d	Hemato	400			Adams et al. 1951	
			Hepatic	400				
			Renal	400				
			Bd Wt	400				

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
43	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Bd Wt	2500			Albee et al. 1993, 2006	
44	Rat (Sprague-Dawley)	Gd 6-20 6 hr/d	Hepatic	600 F			Carney et al. 2006	
			Renal	600 F				
			Bd Wt	600 F				
45	Rat (Wistar)	12 or 24 wk 5 d/wk 4 hr/d	Endocr			376 M (decreases in serum testosterone and testicular 17-beta-hydroxy steroid dehydrogenase levels)	Kumar et al. 2000a	
46	Rat (Wistar)	8, 12, or 24 wk 5 d/wk 4 hr/d	Hepatic		376 M (histopathologic liver lesions)		Kumar et al. 2001a	
47	Rat (Wistar)	12 or 24 wk 5 d/wk 4 hr/d	Bd Wt		376 M (22-29% decreased body weight gain)		Kumar et al. 2001b	

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
48	Rat (Wistar)	28 or 90 d 5 d/wk 4 hr/d	Resp		376 M (histopathologic lung lesions)		Kumar et al. 2002b	
			Ocular		376 M (ocular irritation during exposure)			
49	Rat (Wistar)	10 wk 5 d/wk 8 hr/d	Hepatic	2000			Laib et al. 1979	
50	Rat (Wistar)	3 wk 5 d/wk 18 hr/d	Bd Wt		3000 (15% depressed body weight)		Muijser et al. 2000	
51	Rat (Sprague-Dawley)	90 d 24 hr/d	Resp	35			Prendergast et al. 1967	
			Cardio	35				
			Hemato	35				
			Hepatic	35				
			Renal	35				

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
52	Rat (Sprague-Dawley)	6 wk 5 d/wk 8 hr/d	Resp	712			Prendergast et al. 1967	
			Cardio	712				
			Hemato	712				
			Hepatic	712				
			Renal	712				
53	Rat (Sprague-Dawley)	4 wk 6 hr/d 5 d/wk	Hemato	1000 F			Woolhiser et al. 2006; Boverhof et al. 2013	
			Hepatic	300 F	1000 F (13% increased liver weight)			
			Renal	300 F	1000 F (17% increased kidney weight)			
			Bd Wt	1000 F				
54	Rat (CD-1)	6 wk 5 d/wk 6 hr/d	Bd Wt	1000 M			Xu et al. 2004	
55	Mouse (Hybrid)	8 wk 6 d/wk 4 hr/d	Bd Wt	2000 M			Kaneko et al. 2000	

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
56	Mouse (NMRI)	30 d 24 hr/d	Hepatic	37 M 150 F	75 M (increased BuChE activity, liver weight) 300 F (increased BuChE activity, liver weight)		Kjellstrand et al. 1983a	
			Renal	37 M 75 F	75 M (39% increased kidney weight) 150 F (23% increased kidney weight)			
			Bd Wt	75 M 150 F	150 M (body weights 10% lower than controls) 300 F (body weights 16% lower than controls)			
57	Gn Pig (NS)	6 mo 5 d/wk 7 hr/d	Hepatic	400			Adams et al. 1951	
			Renal	400				
			Bd Wt	100 M	200 M (body weights 18% lower than controls)			

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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	Rabbit (NS)	6 mo 5 d/wk 7 hr/d	Hepatic	400			Adams et al. 1951	
			Renal	400				
			Bd Wt	400				
Immuno/ Lymphoret								
59	Rat (Sprague-Dawley)	4 wk 6 hr/d 5 d/wk		300 F	1000 F (64% reduction in splenic anti-SRBC IgM response)		Woolhiser et al. 2006; Boverhof et al. 2013	
60	Mouse (Hybrid)	8 wk 6 d/wk 4 hr/d			500 M (decreased serum IgG)		Kaneko et al. 2000	
61	Mouse (B6C3F1)	30 wk (W)					Keil et al. 2009	MRL derived using HEC99 of 0.033 ppm from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model (see footnote b)
62	Mouse (NMRI)	30 d 24 hr/d		150	300 (41 and 24% decreased spleen weight in males and females, respectively)		Kjellstrand et al. 1983a	

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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								
63	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		800	2500 (cochlear focal hair cell loss; frequency-specific hearing deficit, particularly at 16 kHz)		Albee et al. 1993, 2006	
64	Rat (JCL- Wistar)	6 wk 5 d/wk 8 hr/d			50 M (decreased wakefulness during exposure, decreased postexposure sleeping heart rate)	100 M (decreased postexposure wakefulness, decreased time-averaged postexposure heart rate)	Arito et al. 1994a	
65	Rat (NS)	44 wk 5 d/wk 8 hr/d			400 M (decreased swimming speed)		Battig and Grandjean 1963	
66	Rat (Long- Evans)	4 wk 5 d/wk 6 hr/d		2400 M	3200 M (27 dB increase in auditory threshold to 16 kHz tone)		Crofton and Zhao 1997	
67	Rat (Long- Evans)	13 wk 5 d/wk 6 hr/d		1600 M	2400 M (21 dB increase in auditory threshold to 16 kHz tone)		Crofton and Zhao 1997	
68	Rat (CFE)	30 d 5 d/wk 4 hr/d			125 M (decreased shock avoidance)		Goldberg et al. 1964a	

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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	Rat (Wistar)	3 wk 5 d/wk 18 hr/d			1500 (reduced acoustic startle response)		Jaspers et al. 1993	
70	Rat (Wistar)	18 wk 5 d/wk 16 hr/d		500 M	1000 M (increased latency in visual discrimination task)		Kulig 1987	
71	Rat (Wistar)	3 wk 5 d/wk 18 hr/d			3000 (significantly decreased auditory sensitivity to 4-20 kHz sound)		Muijser et al. 2000	
72	Rat (Long- Evans)	12 wk 6 d/wk 12 hr/d		1600 M	3200 M (depressed amplitude of auditory-evoked potentials)		Rebert et al. 1991	
73	Rat (Fischer- 344)	3 wk 6 d/wk 12 hr/d			2000 M (depressed amplitude of auditory-evoked potentials)		Rebert et al. 1991	
74	Rat (Wistar)	5 wk 5 d/wk 6 hr/d			100 M (reduced social behavior: exploration, escape, submission)		Silverman and Williams 1975	

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
75	Rat (Wistar)	180 d 5 d/wk 4 h/d			376 M (increased spontaneous locomotor activity)		Waseem et al. 2001	
76	Rabbit (New Zealand)	12 wk 4 d/wk 4 hr/d			350 (altered amplitude of visual-evoked potentials)		Blain et al. 1992	
77	Rabbit (New Zealand albino)	12 wk 4 d/wk 4 h/d			350 M (decreased amplitude of oscillatory potentials and increased amplitude of a- and b-waves)		Blain et al. 1994	
78	Gerbil (Mongo- lian)	3 mo 24 hr/d			60 (astroglial hypertrophy)		Haglid et al. 1981	
Reproductive								
79	Rat (Wistar)	12 or 24 wk 5 d/wk 4 hr/d				376 M (decreased sperm concentration and motility, decreased serum testosterone, increased testicular cholesterol, decreased testicular glucose-6-phosphate dehydrogenase and 17-beta-hydroxy steroid dehydrogenase)	Kumar et al. 2000a	

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
80	Rat (Wistar)	5-10 wk 5 d/wk 4 hr/d			376 M (increased incidence of sperm abnormalities, decreased reproductive success)		Kumar et al. 2000b	
81	Rat (Wistar)	12 or 24 wk 5 d/wk 4 hr/d				376 M (testicular atrophy, decreased sperm count, decreased sperm motility)	Kumar et al. 2001b	
82	Rat (CD-1)	6 wk 5 d/wk 6 hr/d			1000 M (decreased numbers of sperm that attached to eggs)		Xu et al. 2004	
83	Mouse (CD-1)	4 wk 5 d/wk 6 h/d			1000 M (epithelial cell damage in the epididymis)		Forkert et al. 2002	
84	Mouse (CD-1)	1 d; 1, 2, 3, or 4 wk 5 d/wk 5 hr/d				1000 M (serious degeneration of epididymal epithelium, damaged sperm after 4 weeks of exposures)	Kan et al. 2007	

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
Developmental								
85	Rat (Sprague-Dawley)	Gd 6-20 6 hr/d		600			Carney et al. 2006	
86	Rat (Sprague-Dawley)	Throughout gestation (22 d)					Johnson et al. 2003	MRL derived using HEC99 of 0.0037 ppm from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model (see footnote b)
CHRONIC EXPOSURE								
Systemic								
87	Rat (Sprague-Dawley)	104 wk 5 d/wk 7 hr/d	Resp	600			Maltoni et al. 1988	
			Cardio	600				
			Gastro	600				
			Musc/skel	600				
			Hepatic	600				
			Renal	100 M 600 F	300 M (renal tubule meganucleocytosis)			
			Endocr	600				
			Dermal	600				
			Ocular	600				
			Bd Wt	600				

Table 3-1 Levels of Significant Exposure to Trichloroethylene - 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
Cancer								
88	Rat (Sprague-Dawley)	104 wk 5 d/wk 7 hr/d				100 M (CEL: Leydig cell tumors)	Maltoni et al. 1986	
89	Mouse (ICR)	104 wk 5 d/wk 7 hr/d				150 F (CEL: lung adenomas and adenocarcinomas)	Fukuda et al. 1983	
90	Mouse (NMRI)	18 mo 5 d/wk 6 hr/d				100 F (CEL: increased lymphomas)	Henschler et al. 1980	
91	Mouse (B6C3F1)	78 wk 5 d/wk 7 hr/d				600 F (CEL: pulmonary tumors)	Maltoni et al. 1986	
92	Mouse (Swiss-Webster)	78 wk 5 d/wk 7 hr/d				600 M (CEL: pulmonary tumors and hepatomas)	Maltoni et al. 1986	

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

b Study results used as support for the EPA (2011e) preferred chronic RfC of 0.0004 ppm for trichloroethylene and the ATSDR chronic-duration and intermediate-duration inhalation MRLs for trichloroethylene. The preferred chronic RfC of EPA is based on results of two critical studies for which individual candidate chronic RfCs were derived: A candidate chronic RfC of 0.00033 ppm for decreased thymus weight in female mice exposed to trichloroethylene in the drinking water for 30 weeks (Keil et al. 2009), and a candidate chronic RfC of 0.00037 ppm for fetal heart malformations in rats exposed to trichloroethylene via the maternal drinking water during gestation (Johnson et al. 2003). Derivation of the EPA preferred chronic RfC included route-to-route extrapolation that employed PBPK modeling. Selected details regarding EPA's methodology for derivation of the preferred chronic RfC using results from the two critical studies are presented in Appendix A.

Bd Wt = body weight; BuChe = butyrylcholinesterase; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); dB = decibels; Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gd = gestation day; Gn Pig = guinea pig; HEC99 = 99th percentile estimate of human equivalent concentration; Hemato = hematological; hr = hour(s); IgG = Immunoglobulin G; IgM = Immunoglobulin M; Immuno/Lymphoret = immunological/lymphoreticular; kHz = kiloHertz; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; PBPK = physiologically-based pharmacokinetic; ppm = parts per million; Resp = respiratory; SRBC = sheep red blood cell; wk = week(s).

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

Acute (≤14 days)

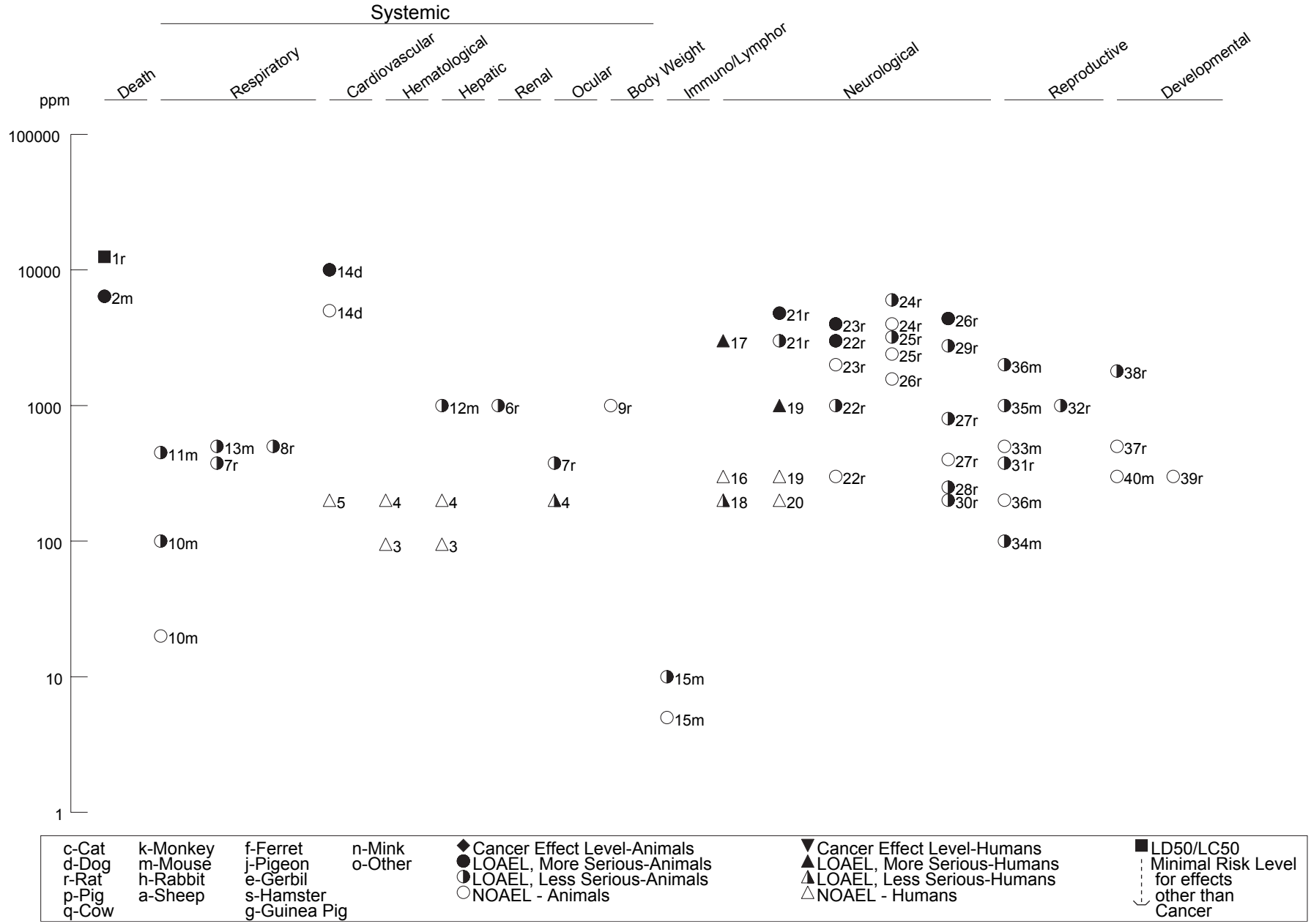


Figure 3-1 Levels of Significant Exposure to Trichloroethylene - Inhalation *(Continued)*

Intermediate (15-364 days)

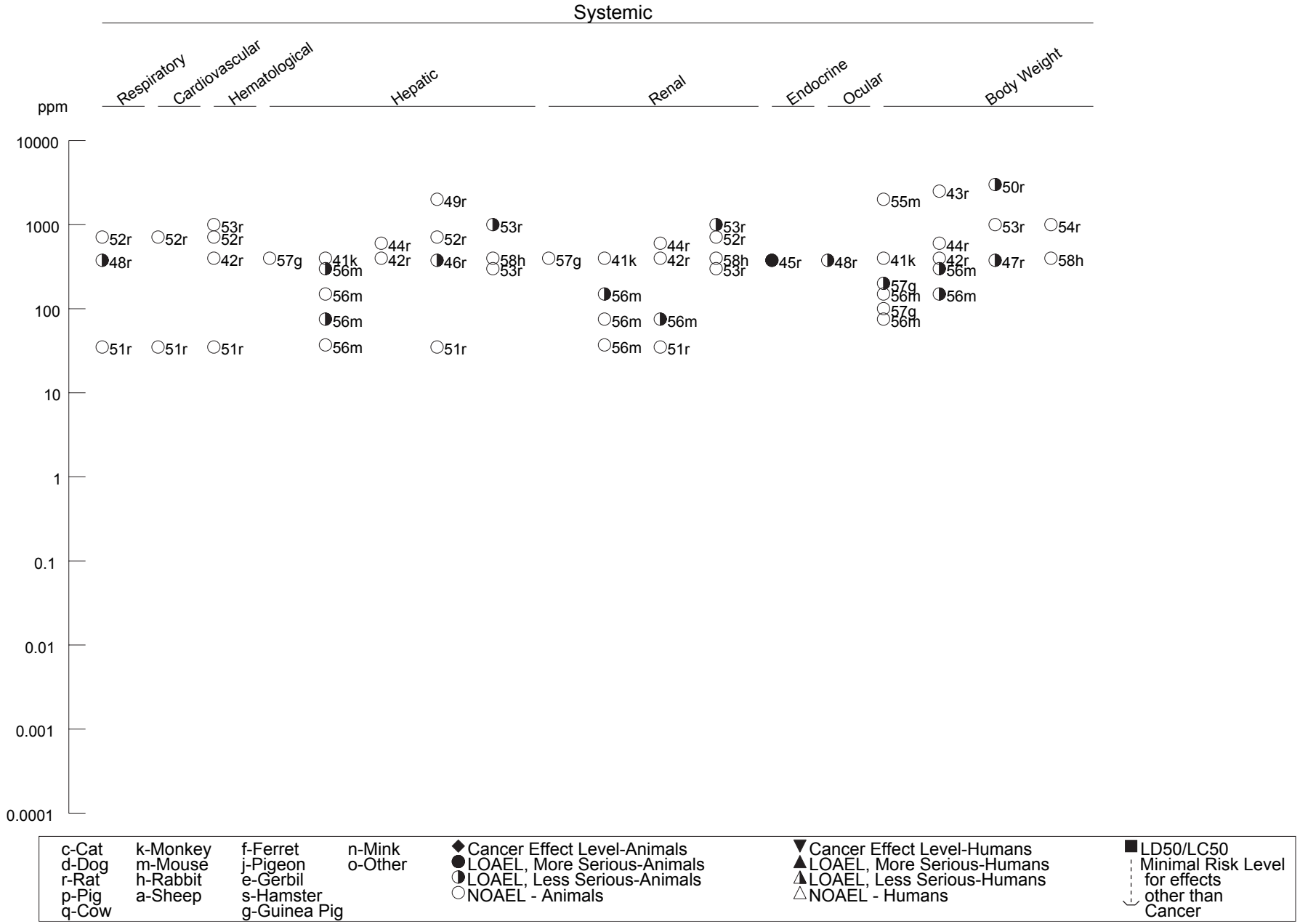


Figure 3-1 Levels of Significant Exposure to Trichloroethylene - Inhalation *(Continued)*

Intermediate (15-364 days)

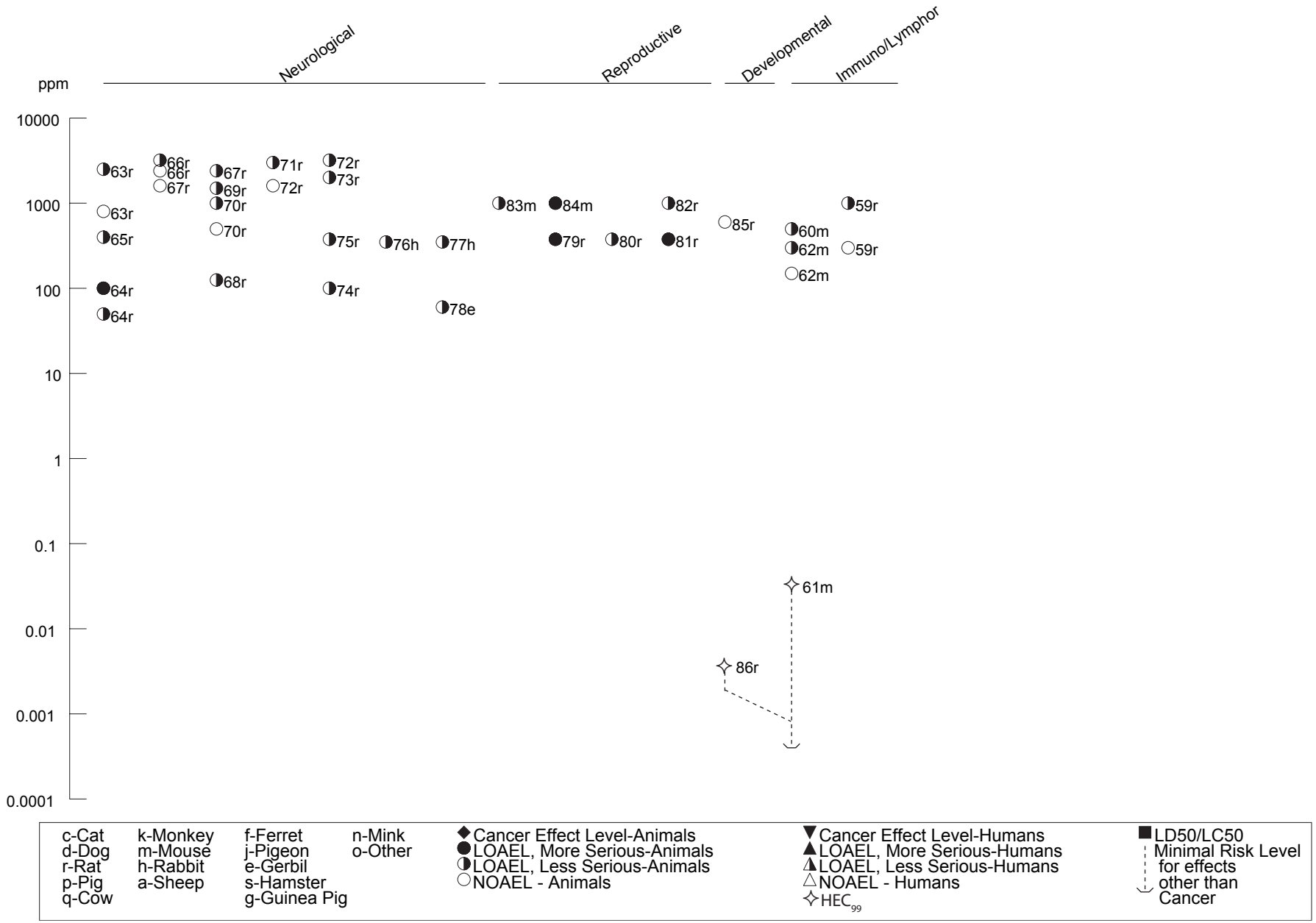
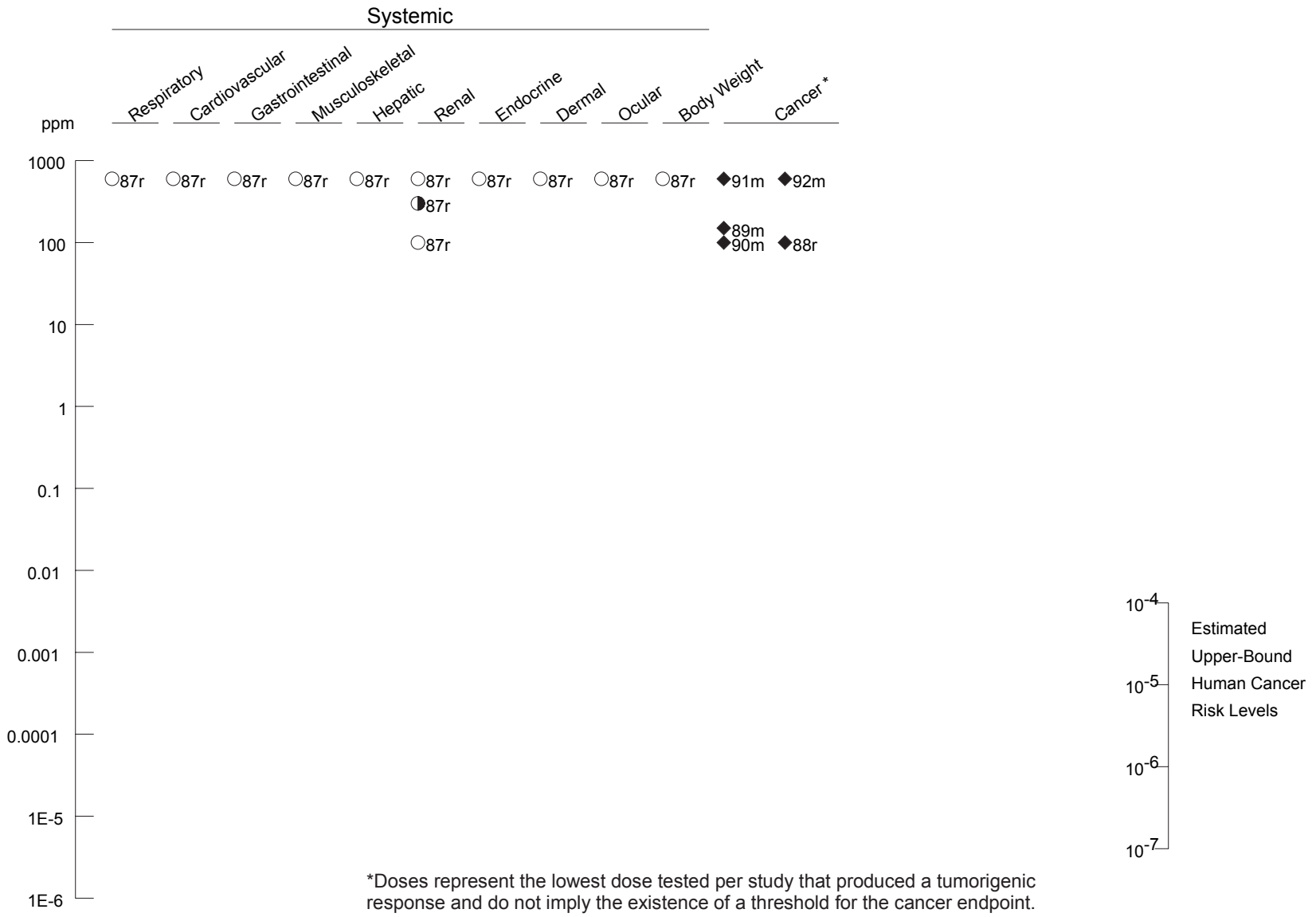


Figure 3-1 Levels of Significant Exposure to Trichloroethylene - Inhalation *(Continued)*

Chronic (≥365 days)



reported in studies of gun manufacturing workers exposed to solvents including trichloroethylene (Cakmak et al. 2004; Saygun et al. 2007), but the specific role of trichloroethylene in these symptoms could not be established.

Morphology of lung cells and activity of cytochrome P-450 (enzymes that metabolize xenobiotics) in the lungs have been studied in rats and mice exposed to trichloroethylene. Results of animal studies demonstrate that inhaled trichloroethylene can cause damage to Clara cells, which are nonciliated epithelial cells of the lung that produce a protective secretory protein, provide cytochrome P450 enzymes that assist in the metabolism of xenobiotics, and serve a function in regeneration of bronchiolar epithelium (see Reynolds and Malkinson 2010). A 30-minute inhalation exposure to 500 ppm resulted in vacuole formation and endoplasmic reticulum dilation specifically in Clara cells of the bronchial tree (Villaschi et al. 1991). Similar Clara cell-specific damage was observed in mice after a 6-hour exposure to 100 ppm trichloroethylene (Odum et al. 1992). A reduction in pulmonary cytochrome P-450 activity was also observed. After mice were exposed to 450 ppm trichloroethylene for 5 days, the Clara cell effects resolved, but after a 2-day break in the exposure, the effect returned (Odum et al. 1992). Rats, which have a lower abundance and different distribution of Clara cells than mice, exhibited no cell damage at 500 ppm, although P-450 activity was reduced following a 6-hour exposure (Odum et al. 1992). Kumar et al. (2002b) reported bronchiolitis and alveolitis in rats exposed to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 28 or 90 days; marked edema, presence of mononuclear cells, and unspecified emphysematous changes were noted after 90 days. These rats also exhibited signs of nasal irritation during exposures.

Cardiovascular Effects. Exposure of 15 male volunteers to 200 ppm trichloroethylene for 2.5 hours had no effect on heart rate or sinus rhythm (Windemuller and Ettema 1978). Electrocardiograms of workers exposed to trichloroethylene in the range of 38–172 ppm for periods ranging from <1 to >5 years did not show any adverse effects (El Ghawabi et al. 1973). A few case studies of persons who died following acute occupational exposure to trichloroethylene have revealed cardiac arrhythmias to be the apparent cause of death (Bell 1951; Kleinfeld and Tabershaw 1954; Smith 1966). In one case report, a woman had erratic heart action and abnormal electrocardiogram readings following exposure in the workplace (Milby 1968). Ventricular extrasystoles (also known as preventricular contractions or PVCs) were observed in a 34-year-old male worker during a workday in which personal monitoring revealed trichloroethylene levels between 50 and 100 ppm; the worker had no history of heart ailments and monitoring at the beginning of the workday and during a day without trichloroethylene exposure revealed no abnormalities (Konietzko and Elster 1973). In a cohort mortality of 14,457 aircraft maintenance

workers employed for at least 1 year between 1952 and 1956, a significant excess of death from ischaemic heart disease (SMR 108; 95% CI 103–113) was reported for a group of 6,153 workers with reported occupational exposure to trichloroethylene compared to a referent group of workers not exposed to any chemical (Blair et al. 1998). The follow-up period was 1952–1990; the trichloroethylene-exposed workers were likely exposed to other chemicals as well. A case-control study of 98 workers reported an increased risk of pulmonary veno-occlusive disease based on an adjusted odd ratio (OR, 95% CI) of 8.2 (1.4–49.4; p=0.022) (Montani et al. 2015). Although the risk estimate was adjusted for age, sex, and smoking history, exposure to other solvents was not considered as a potential confounder.

Inhalation of very high concentrations of trichloroethylene in incidents of poisonings (Dhuner et al. 1957; Gutch et al. 1965), or during its use as an anesthetic agent (Pembleton 1974; Thierstein et al. 1960), has been reported to lead to cardiac arrhythmias. The mechanism is unclear, but high doses of hydrocarbons such as trichloroethylene could act upon the heart to cause cardiac sensitization to catecholamines. This is supported by animal studies. For example, dogs (Reinhardt et al. 1973) and rabbits (White and Carlson 1979, 1981, 1982) exposed to very high concentrations of trichloroethylene (5,000 or 10,000 ppm, and 3,000 ppm, respectively) for ≤1 hour showed increased arrhythmias when injected intravenously with epinephrine. In animals, trichloroethylene itself, rather than its metabolites, is apparently responsible for the cardiac sensitization because chemicals that inhibit the metabolism of trichloroethylene increase its potency, while chemicals that enhance the metabolism of trichloroethylene decrease its potency (White and Carlson 1979, 1981).

No histopathological changes were observed in the hearts of squirrel monkeys, rats, guinea pigs, dogs, or rabbits exposed to 700 ppm trichloroethylene 8 hours/day, 5 days/week for 6 weeks, or to 35 ppm continuously for 6 weeks (Prendergast et al. 1967). Histopathological changes were also not observed in the hearts of rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988).

Gastrointestinal Effects. Case reports indicate that acute inhalation exposure to trichloroethylene results in nausea and vomiting (Buxton and Hayward 1967; Clearfield 1970; David et al. 1989; DeFalque 1961; Gutch et al. 1965; Milby 1968). Anorexia, nausea, and vomiting have also been reported as chronic effects of occupational exposure to trichloroethylene (El Ghawabi et al. 1973). The exposure levels were not measured. Anorexia and vomiting were reported in a woman chronically exposed to occupational levels between 40 and 800 ppm (Schattner and Malnick 1990). Trichloroethylene-induced effects on the autonomic nervous system may contribute to these effects (Grandjean et al. 1955). Cases of pneumatosis

cystoides intestinalis (a rare condition characterized by gas-filled cysts in the submucosa of the small intestine) seen in Japanese lens cleaners and polishers were attributed to trichloroethylene exposure in the workplace (Nakajima et al. 1990a).

Histopathological changes in the gastrointestinal tract were not observed in rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988).

Hematological Effects. There are limited data on hematological effects of trichloroethylene in humans. A study of humans exposed to 200 ppm trichloroethylene for a short period (7 hours/day for 1 or 5 days) revealed no adverse effects on blood cell counts or sedimentation rates (Stewart et al. 1970). Blood cell counts were also not affected in volunteers exposed to 1,000 ppm trichloroethylene for 2 hours (Vernon and Ferguson 1969). Volunteers inhaling trichloroethylene vapor at 95 ppm for 4 hours showed only an increase in neutrophil enzyme levels (alkaline and acid phosphatases, naphthol-AS-D esterase) (Konietzko and Reill 1980). The toxicological significance of this effect is unknown, however, because enzyme level changes may merely be the result of the nonspecific stimulation of metabolizing enzymes. No effects on hemoglobin levels or red blood cell counts were observed in workers exposed to trichloroethylene in the range of 38–172 ppm for periods ranging from <1–>5 years (El Ghawabi et al. 1973).

Various minor hematological effects have been noted in animals. Rats exposed to 50–800 ppm of trichloroethylene continuously for 48 or 240 hours showed time- and dose-related depression of delta-aminolevulinate dehydratase activity in liver, bone marrow, and erythrocytes (Fujita et al. 1984; Koizumi et al. 1984). Related effects included increased delta-aminolevulinic acid (ALA) synthetase activity, reduced heme saturation of tryptophan pyrrolase and reduced cytochrome P-450 levels in the liver, and increased urinary excretion of ALA and coproporphyrin. Since hemoglobin concentration in erythrocytes did not change, these changes are not considered to be adverse. Dogs exposed to 200 ppm trichloroethylene for 1 hour by tracheal intubation exhibited decreased leukocyte counts (Hobara et al. 1984). No effects on hematology examinations were noted in squirrel monkeys, rats, guinea pigs, dogs, or rabbits exposed to 700 ppm trichloroethylene 8 hours/day, 5 days/week for 6 weeks, or to 35 ppm continuously for 6 weeks (Prendergast et al. 1967). Hematological effects were also not observed in rats exposed intermittently for intermediate durations at 1,000 ppm (Boverhof et al. 2013), 400 ppm (Adams et al. 1951), or 55 ppm (Kimmerle and Eben 1973a).

Musculoskeletal Effects. Muscle necrosis was reported within 3 hours following the collapse of a 36-year-old female factory worker who was overcome by trichloroethylene vapors used to degrease metal; the exposure included a dermal component (Thorburn et al. 2004). Trichloroethylene exposure can cause nervous system effects that result in secondary effects on muscle strength, especially in the face (Leandri et al. 1995). See Section 3.2.1.4 for further discussion of nervous system effects following trichloroethylene exposure.

Histopathological changes in the thigh muscle were not observed in rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988).

Hepatic Effects. There is some evidence for trichloroethylene-induced hepatotoxic effects in humans. However, much of this information is limited by the fact that the exposure levels associated with these effects were usually not reported, and the individuals may have been exposed to other substances as well. Reports that support the liver as a target of trichloroethylene toxicity are summarized below.

Multiple case reports implicate trichloroethylene as a liver toxicant. A 37-year-old male with occupational exposure to trichloroethylene and a reportedly unprotected high-level acute exposure to trichloroethylene vapors during the preparation of a solvent mixture presented to a hospital in a jaundiced condition and died several weeks later; acute massive liver necrosis was noted at autopsy (Joron et al. 1955). Acute hepatic necrosis was also seen in a degreaser who died after being exposed to trichloroethylene for at least 6 weeks (Priest and Horn 1965). Two case studies of people hospitalized after intentional acute inhalation of very high concentrations of trichloroethylene showed liver damage at autopsy in one and hepatocyte degeneration revealed by liver biopsy in the other (Clearfield 1970). In contrast, James (1963) saw only small foci of fatty degeneration in the liver of a man who had intentionally inhaled trichloroethylene during a 10-year span. Other case studies reported liver effects such as jaundice, hepatomegaly, hepatosplenomegaly, hepatitis, and liver failure in patients with occupational or nonoccupational exposure to trichloroethylene (Anagnostopoulos et al. 2004; Caprioli et al. 2001; Chae et al. 1999, 2003; Chittasobhaktra et al. 1997; Goon et al. 2001; Ha et al. 2009; Huang et al. 2006; Jung et al. 2012; Kamijima et al. 2007; Nakayama et al. 1988; Pantucharoensri et al. 2004; Thiele et al. 1982; Xu et al. 2009).

There are reports of fatal hepatic failure in eclamptic pregnant women following trichloroethylene anesthesia (DeFalque 1961). Exposure concentrations and durations were not provided. Women who were exposed to 1,000 ppm of trichloroethylene during surgery for Caesarean sections exhibited no

evidence of liver toxicity (Crawford and Davies 1975). Although liver function tests were not completed, 250 neurosurgery patients, anesthetized with trichloroethylene for 3–5-hour periods, showed no evidence of liver damage during the postoperative period (Brittain 1948). Pembleton (1974) reviewed data on 550 patients who had undergone trichloroethylene anesthesia for a variety of operative procedures. For 100 of these patients, a number of pre- and postoperative liver function tests were reported. Four of 100 patients had a postoperative rise in serum glutamic-oxaloacetic transaminase (aspartate aminotransferase; AST), which returned to normal within 2 or 3 days. One patient had a doubling of the AST level, which also returned to normal by day 3. Other liver function tests evidently remained within normal ranges. A significant increase in the metabolism of the drug, paracetamol, was observed in patients anesthetized with trichloroethylene, indicating that determining the proper dosage in such cases may not be straightforward because of effects on liver function (Ray et al. 1993). Overall, the available data indicate that controlled trichloroethylene anesthesia produces minimal effects on the liver.

Other case reports indicate that exposure to trichloroethylene in the workplace can cause changes in blood and urine indices of liver function and possibly cause liver pathology (Graovac-Leposavic et al. 1964). Acute hepatitis developed in a woman occupationally exposed to between 40 and 800 ppm over a period of several years (Schattner and Malnick 1990). Changes in levels of serum liver enzymes (Nagaya et al. 1993; Rasmussen et al. 1993b; Xu et al. 2009) and bile acids (Driscoll et al. 1992; Neghab et al. 1997) among individuals exposed to trichloroethylene in the workplace were indicative of liver toxicity. A case report of four workers who had dermal reactions to trichloroethylene exposure showed no adverse liver function in three persons, but an enlarged liver in one worker (Bauer and Rabens 1974). Among 14 workers exposed to trichloroethylene at an unspecified concentration above the occupational standard, enlarged liver was observed in 3 workers, increased serum transaminase activity was observed in 9 workers, and liver biopsies of 13 workers revealed fatty acid deposition in 11 workers (Schuttmann 1970).

There was no clear evidence of liver effects within a group of 289 British workers who exhibited trichloroethylene-induced neurological effects; no information was provided regarding trichloroethylene exposure levels (McCarthy and Jones 1983). No significant association was found between occupational exposure to trichloroethylene and death from liver cirrhosis in multiple cohort mortality studies (ATSDR 2004; Blair et al. 1998; Boice et al. 1999, 2006; Garabrant et al. 1988; Morgan et al. 1998; Radican et al. 2008; Ritz 1999).

Liver function tests were normal in volunteers exposed for 5 days to 95 ppm for 4 hours/day (Konietzko and Reill 1980) or 200 ppm for 7 hours/day (Stewart et al. 1970).

Inhalation of trichloroethylene for acute or intermediate periods can cause liver enlargement in laboratory animals. This effect is usually reversible when exposure ceases. Histological changes were observed in some studies but not in others. Liver weight and plasma butyrylcholinesterase (BuChE) activity were increased in various strains of mice exposed to 37–300 ppm continuously for 30 days (Kjellstrand et al. 1983a, 1983b). In this study, histological examinations revealed misshapen, enlarged, and vacuolated hepatocytes. After 4 months of postexposure recovery, liver weight and serum BuChE activity had returned to normal; the only remaining histopathological effect was that of hepatocyte enlargement. Male mice were more sensitive to the hepatic effects than female mice. In male mice, the liver effects were observed at 75 ppm with a NOAEL of 37 ppm, while in female mice, the liver effects occurred at 300 ppm with a NOAEL of 150 ppm. The study authors suggested that the effects were not toxicologically significant. Another study in rats reported a dose-effect relationship between trichloroethylene exposure concentrations (50–800 ppm) or duration and inhibition of liver ALA dehydratase activity following continuous 48-hour and 10-day exposures. However, the toxicological significance of these effects is not known because the changes occurred in the absence of gross liver injury (Koizumi et al. 1984). In related studies, mice, rats, and gerbils were exposed continuously for up to 30 days to 150 ppm of trichloroethylene (Kjellstrand et al. 1981). The study authors reported increased relative liver weight in all species and treatment groups, but the effect was more pronounced in the mice (60–80% enlargement) than the rats or gerbils (20–30%). Examination of mice 5 and 30 days after cessation of treatment indicated that the increase in liver weight had decreased. Limitations of this study include lack of histopathologic evaluation of liver tissue and limitations in methodology used to record and evaluate body weight data. Kumar et al. (2001a) reported significantly increased liver weight and hepatocellular fatty and necrotic liver lesions in male rats exposed to trichloroethylene vapors at 376 ppm for 4 hours/day 5 days/week for 8, 12, or 24 weeks; the liver lesions became progressively more severe with duration, but quantitative data were not included in the study report. Ramdhan et al. (2008) reported concentration-related increased liver weight (43–64% higher than controls) and minimal to moderate hepatocellular necrosis in male wild type (CYP2E1+/+) mice exposed to trichloroethylene vapors at 1,000 or 2,000 ppm for 8 hours/day on 7 consecutive days; similarly-exposed CYP2E1-null mice exhibited no signs of exposure-related liver effects, indicating that the liver effects in the wild type mice are associated with CYP2E1-mediated metabolism. In a study designed to assess the role of human and mouse PPARα in trichloroethylene-induced liver effects, male wild-type (mPPARα), PPARα-null, and humanized PPARα (hPPARα) mice on Sv/129 background were exposed to trichloroethylene by

inhalation at 0, 1,000, or 2,000 ppm 8 hours/day for 7 days (Ramdhan et al. 2010). Trichloroethylene-exposed mice of each cell line exhibited increased plasma alanine aminotransferase (ALT) and AST activities, hepatocellular inflammation and necrosis, and elevated nuclear factor-kappa B p52 mRNA and protein. Hepatic lipid accumulation, increased expression of triglyceride-synthesizing enzymes, diacyl-glycerol acyltransferases, and PPARγ were observed in the PPARα-null and hPPARα mice, but not the mPPARα mice. Rats, guinea pigs, rabbits, dogs, and squirrel monkeys were exposed to 35 ppm trichloroethylene continuously for 90 days or to 712 ppm 8 hours/day, 5 days/week for 6 weeks. Although liver weight was not determined, gross and histopathological examinations of the liver were unremarkable (Prendergast et al. 1967). In rats exposed to 55 ppm trichloroethylene intermittently (8 hours/day, 5 days/week) for 14 weeks, increased liver weight was observed, but there were no effects on hepatic function or gross appearance of the liver (Kimmerle and Eben 1973a). Histology of the liver was not examined in this study. Rats, guinea pigs, rabbits, and Rhesus monkeys exposed intermittently to 400 ppm of trichloroethylene for 6 months (173 exposures in 243 days) exhibited increased liver weight, but there were no gross or histological hepatic alterations (Adams et al. 1951). An increase in nucleoside-5-triphosphatase-deficient foci (considered to be preneoplastic) was not observed in the livers of newborn rats exposed to 2,000 ppm trichloroethylene 8 hours/day, 5 days/week for 10 weeks (Laib et al. 1979). No histopathological changes were observed in the livers of rats exposed to 300 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988). Only slightly (but statistically significant) increased liver weight was observed in female rats intermittently exposed to trichloroethylene vapors at 1,000 ppm for 4 weeks (Boverhof et al. 2013) or pregnant rats exposed for 6 hours/day on GDs 6–20 at 600 ppm (Carney et al. 2006); histopathologic liver examinations were not performed.

Renal Effects. Trichloroethylene may have effects in the kidney; however, studies in humans are limited by having poor or no exposure data and by concomitant exposure to other chemicals. There was no evidence of kidney damage in 250 neurosurgery patients who underwent prolonged trichloroethylene anesthesia (Brittain 1948), nor in 405 women who had Caesarean sections and were subjected to trichloroethylene anesthesia (Crawford and Davies 1975).

There are few reports of renal dysfunction in workers exposed to trichloroethylene. One case report indicates that a man using trichloroethylene in de-inking operations (for 8 hours) developed acute renal failure due to acute allergic interstitial nephritis with secondary tubular necrosis (David et al. 1989). Acute renal failure was reported in one man acutely exposed to trichloroethylene, although the man was also known to have a history of excessive abuse of alcohol (Gutch et al. 1965). Proteinuria was reported in a man who intentionally inhaled a spot-remover containing trichloroethylene and petroleum solvents

(Clearfield 1970). Renal toxicity, as indicated by changes in urinary proteins and N-acetyl-β-d-glucos-aminidase (NAG) (Brogren et al. 1986; Brüning et al. 1999; Carrieri et al. 2007; Nagaya et al. 1989b; Selden et al. 1993), have been found in workers exposed to trichloroethylene and other chemicals in the workplace. The increase in these markers of kidney effects suggests that trichloroethylene may affect both glomeruli and renal tubules. In a study of 80 trichloroethylene-exposed workers and 45 unexposed workers within several factories in China, the exposed workers exhibited urinary kidney molecule-1 (KIM-1) levels that were 50% higher than control levels (p=0.01) (Vermeulen et al. 2012). KIM-1 is a transmembrane protein expressed in dedifferentiated proximal renal tubular epithelial cells within damaged regions (Huo et al. 2010) and has been shown to be a more sensitive biomarker of renal damage than traditional biomarkers of renal injury (serum creatinine and blood urea nitrogen [BUN]) in rat studies (Vaidya et al. 2010). Personal trichloroethylene exposure measurements taken during a 2-week period prior to the collection of urine indicated a mean trichloroethylene exposure level of 22.2 ppm; measurements from 96% of the exposed workers were below the OSHA 8-hour TWA permissible exposure limit of 100 ppm. Evaluation of other markers of kidney toxicity (alpha-GST, Pi-GST, vascular endothelial growth factor, NAG, and creatinine) resulted in p-values of 0.98, 0.09, 0.99, 0.94, and 0.27, respectively. The study authors indicated that the mean Pi-GST level among the trichloroethylene-exposed workers was indicative of a borderline statistically significant effect (Vermeulen et al. 2012).

Green et al. (2004) assessed renal dysfunction in a cross-sectional study of 70 workers exposed to trichloroethylene and 54 age- and sex-matched individuals without trichloroethylene exposure by measuring urinary levels of NAG and albumin. Urinary trichloroacetic acid (TCA) concentration was used to estimate trichloroethylene exposure level (mean 32 ppm; range 0.5–252 ppm). Urinary levels of NAG and albumin were significantly higher in the trichloroethylene-exposed workers, although neither parameter was correlated with exposure level or duration. Evidence of increased urinary formate, methylmalonate, and glutathione S-transferase α activity in the exposed workers, although within the control range, indicate that higher exposure levels would likely have resulted in more clear evidence of trichloroethylene-induced kidney effects.

Radican et al. (2006) performed a retrospective cohort study of end-stage renal disease in aircraft workers exposed to trichloroethylene and other hydrocarbons by matching an occupational database to the U.S. Renal Data System and examining the all-cause end-stage renal disease using multivariate Cox regression. The evaluation spanned the years 1973–2002; the time period during which exposure occurred was not reported. Among 6,532 aircraft workers with reported trichloroethylene exposure and a group of 3,327 referents with no reported chemical exposure, an approximately 2-fold increased risk of

end-stage renal disease was observed for the trichloroethylene-exposed aircraft workers (hazard ratio [HR] 1.92; 95% CI 1.03–3.59) for the period of 1973–1999. For the period of 1973–2000, increased risk of end-stage renal disease in the trichloroethylene-exposed workers was noted among those workers with 5–25 unit-years of exposure (HR 2.48; 95% CI 1.20–5.15), workers with indirect low/intermittent exposures (HR 2.47; 95% CI 1.17–5.19), and workers with indirect peak/infrequent exposures (HR 3.66; 95% CI 1.25–10.74). For workers exposed for periods <5 years or >25 years, HRs were 1.73 (95% CI 0.86–3.48) and 1.65 (95% CI 0.82–3.35), respectively. Taken together, the results provide evidence of trichloroethylene-induced renal effects.

Jacob et al. (2007) evaluated a possible association between progression of primary glomerulonephritis to end-stage renal disease among 269 patients and exposure to trichloroethylene based on self-reported job description. For those patients considered to have been occupationally exposed to any level of trichloroethylene (n=20), six patients exhibited progression to end-stage renal disease (HR 2.5; 95% CI 0.9–6.5). Among 10 of the patients with assumed high-level exposure, an HR of 2.7 (95% CI 0.7–10.1) was reported. This study is limited by the lack of measured trichloroethylene levels and the small numbers of trichloroethylene-exposed participants. No evidence was found for associations between trichloroethylene and noncancer kidney effects in other cohort studies (Boice et al. 2006; Lipworth et al. 2011; Silver et al. 2014).

Exposure of rats to extremely high levels (≥1,000 ppm) for periods of <1 day led to the dysfunction of the tubular and glomerular regions of the nephron, as indicated by increases in urinary glucose, proteins, glucosaminidase, gamma glutamyl transpeptidase, and serum urea nitrogen (Chakrabarti and Tuchweber 1988). Mensing et al. (2002) reported increased urinary levels of high-molecular-weight proteins and albumin (biomarkers of glomerular damage) and NAG and low-molecular-weight proteins (biomarkers of proximal tubule damage) in male rats exposed to trichloroethylene vapors at 500 ppm, 6 hours/day, 5 days/week for 6 months. Histopathologic examinations of the kidneys revealed perivascular, interstitial inflammation and glomerulonephritis. Increased kidney weight has been found in rats, mice, and gerbils repeatedly or continuously exposed to trichloroethylene vapors in the range of 50–1,000 ppm for 4–14 weeks (Boverhof et al. 2013; Kimmerle and Eben 1973a; Kjellstrand et al. 1981, 1983a, 1983b). However, the toxicological significance of the increased organ weight is uncertain because no histopathological changes were observed and no functional tests were performed. Adams et al. (1951) reported significantly increased kidney weight in rats and rabbits repeatedly exposed to trichloroethylene vapors at 3,000 ppm for 36 days and in rats exposed at 400 ppm for as long as 243 days; however, there was no histopathological evidence of exposure-related renal effect. Prendergast et al. (1967) found no

histopathological evidence of trichloroethylene-induced renal effects in groups of rats, guinea pigs, rabbits, dogs, and squirrel monkeys repeatedly exposed by inhalation for 6 weeks at a concentration of 3,825 mg/m^3 (688 ppm); organ weight data were not provided in the study report. Male rats, but not female rats, that were exposed to 300 ppm trichloroethylene in a chronic study showed renal tubular megalonucleocytosis (Maltoni et al. 1986, 1988). The study authors considered that this histopathological change might be a precancerous lesion; however, no kidney tumors were observed. The serious shortcomings of these chronic studies are discussed in Section 3.2.1.7.

Endocrine Effects. In occupational studies of men who used trichloroethylene to degrease electronic equipment, increasing years of exposure to trichloroethylene were associated with increased serum dehydroepiandrosterone sulphate (a metabolite of the endogenous steroid hormone dehydroepiandrosterone) and decreases in serum levels of testosterone, follicle-stimulating hormone, and sex-hormone binding globulin (Chia et al. 1997; Goh et al. 1998). Serum androstenedione, cortisol, and aldosterone levels were in normal ranges. In the study of Goh et al. (1998), the serum insulin level among those workers with <2 years of exposure (40.8 mLU/L) was notably higher than that of unexposed controls (9.6 mLU/L); however, insulin levels returned to normal among workers exposed for longer periods. There is suggestive evidence of an association between exposure to trichloroethylene and menstrual cycle disturbances (including amenorrhea) (Bardodej and Vyskocil 1956; Sagawa et al. 1973; Zielinski 1973).

No histopathological changes in the pituitary gland, adrenal glands, or pancreas were observed in rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988). Significantly decreased serum testosterone (31–48% less than that of controls) and decreased testicular 17β-hydroxy steroid dehydrogenase were noted in rats exposed to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 12 or 24 weeks (Kumar et al. 2000a).

Dermal Effects. Dermal effects of trichloroethylene exposure in humans are usually the consequence of direct skin contact with concentrated solutions, but occupational exposure also involves vapor contact. Adverse effects have not been reported from exposure to dilute aqueous solutions. Humans who were experimentally exposed to 200 ppm of trichloroethylene vapor for 7 hours experienced dry throats (40% of the subjects), beginning after 30 minutes (Stewart et al. 1970). The subjects experiencing these symptoms did not experience them when exposed in the same manner on 5 other consecutive days. These effects are presumed to be due to direct contact with the vapor.

Generalized skin disorders, manifested as irritation and rashes, have resulted from occupational exposure to trichloroethylene (Bauer and Rabens 1974; Chittasobhaktra et al. 1997; El Ghawabi et al. 1973; Huang et al. 2006; Kamijima et al. 2007; Pantucharoensri et al. 2004; Xu et al. 2009). An exfoliative dermatitis (Goh and Ng 1988), scleroderma (Czirjak et al. 1993), and eosinophilic fasciitis (Hayashi et al. 2000), thought to have immune components, have been reported in persons occupationally exposed to trichloroethylene. Refer to Section 3.2.1.3 for information regarding occupational exposure to trichloroethylene and immunological responses.

Histopathological changes in the skin were not observed in rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988).

Ocular Effects. Humans who were experimentally exposed to 200 ppm of trichloroethylene vapor for 7 hours experienced mild eye irritation (20% of the subjects), beginning after 30 minutes (Stewart et al. 1970). The subjects experiencing these symptoms did not again experience them when exposed in the same manner on 5 other consecutive days. Itchy, watery eyes (Bauer and Rabens 1974; El Ghawabi et al. 1973) and inflamed eyes (Schattner and Malnick 1990) have also been reported following contact with the vapor.

Ocular irritation was observed during exposures of rats to trichloroethylene vapors at 376 ppm (Kumar et al. 2002a, 2002b). Histopathological changes in the eyes were not reported in rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988).

Body Weight Effects. Body weight loss has been reported in humans occupationally exposed to trichloroethylene for intermediate or chronic durations at concentrations resulting in neurological effects (Mitchell and Parsons-Smith 1969; Schattner and Malnick 1990).

Exposure to trichloroethylene vapors resulted in depressed body weight or body weight gain in some studies of laboratory animals. Kumar et al. (2001b) reported >20% depressed body weight gain in male rats exposed to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 12 or 24 weeks. In other rat studies, no body weight effects were observed following intermittent or continuous exposure to trichloroethylene vapors at exposure levels in the range of 400–2,500 ppm for 2 weeks to as much as 2 years (Adams et al. 1951; Albee et al. 2006; Boverhof et al. 2013; Carney et al. 2006; Maltoni et al. 1988; Prendergast et al. 1967; Xu et al. 2004). In a group of male mice exposed to trichloroethylene continuously at 150 ppm for 30 days, mean body weight was 10% lower than that of controls (Kjellstrand

et al. 1983a). There was no effect on body weight of similarly-exposed females; however, the next higher exposure level (300 ppm) resulted in 18 and 16% lower mean body weight in males and females, respectively. In another mouse study (Kaneko et al. 2000), exposure of males to trichloroethylene at 2,000 ppm, 4 hours/day, 6 days/week for 8 weeks had no effect on body weight. Male guinea pigs exposed to 200 ppm trichloroethylene 7 hours/day, 5 days/week for 6 months exhibited 18% lower body weight than controls; however, there was no effect on female guinea pigs similarly exposed to 400 ppm (Adams et al. 1951). Body weight was not affected in Rhesus monkeys or rabbits exposed to 400 ppm 7 hours/day, 5 days/week for 6 months (Adams et al. 1951).

3.2.1.3 Immunological and Lymphoreticular Effects

Occupational exposure to trichloroethylene may involve both inhalation and dermal routes. Results of numerous case reports indicate that people can develop hypersensitivity-type reactions to trichloroethylene (Chae et al. 1999, 2003; Conde-Salazar et al. 1983; Czirjak et al. 1993; Goh and Ng 1988; Goon et al. 2001; Ha et al. 2009; Hayashi et al. 2000; Jung et al. 2012; Kamijima et al. 2007, 2008; Nakayama et al. 1988; Phoon et al. 1984; Raşcu et al. 2003; Waller et al. 1994; Xu et al. 2009) that may involve skin, mucous membranes, and the liver. Phoon et al. (1984) reported on five cases of individuals who developed generalized erythema and maculopapular lesions with exfoliation, conjunctivitis (corneal ulcers in one case), and liver dysfunction; all had been occupationally-exposed to trichloroethylene for 2–5 weeks. Although patch testing of one case about 6 months later provided negative results, it was suggested that adverse effects were the result of a hypersensitivity response to trichloroethylene because exposure levels were described as “not very high” and other workers in the same environments were not affected. Goon et al. (2001) reported a case in which a trichloroethylene-exposed worker presented with dermal lesions, irritation of mucous membrane, and liver dysfunction; it was suggested that the condition be named trichloroethylene hypersensitivity syndrome. Other investigators have reported similar cases (e.g., Chae et al. 2003; Ha et al. 2009; Jung et al. 2012). Dermal sensitivity was confirmed with patch testing in three cases (Conde-Salazar et al. 1983; Ha et al. 2009; Nakayama et al. 1988).

Iavicoli et al. (2005) reported alterations of the immune system, expressed as significantly altered serum levels of selected cytokines (increased interleukin-2 and interferon-γ and decreased interleukin-4), in a group of factory workers who were exposed to trichloroethylene at a mean workplace air concentration of 35 ± 14 mg/m^3 (6.3 ppm) for at least 3 years during degreasing processes. The exposed group was compared to a group of workers not directly involved in the degreasing process and a group of nonexposed office workers. Immune function was not tested in this study. Bassig et al. (2013) reported

significantly decreased serum interleukin-10 in a group of 71 workers exposed to trichloroethylene when compared to a group of 78 unexposed workers; the magnitude of the decrease was 70%. The magnitude was >60% among those workers exposed at levels <12 ppm. In another study that included a cohort of 80 trichloroethylene-exposed workers and 45 unexposed control workers, significantly decreased serum IgG and IgM levels were reported for the exposed workers (17.5 and 38%, respectively, lower than controls) (Zhang et al. 2013).

There is some evidence for an association between occupational exposure to trichloroethylene and the occurrence of scleroderma (systemic sclerosis, a chronic autoimmune disease primarily of the skin) (Diot et al. 2002; Garabrant et al. 2003; Nietert et al. 1998). A meta-analysis of these studies resulted in combined ORs of 2.5 (95% CI 1.1–5.4) for any exposure in men and 1.2 (95% CI 0.58–2.6) in women (Cooper et al. 2009; EPA 2011e). Increased risk of scleroderma may be easier to detect in trichloroethylene-exposed male workers than female workers because, within various populations, women are on average approximately 3 times more likely than men to develop scleroderma (Chifflot et al. 2008). Evaluation of a potential association between occupational exposure to trichloroethylene and the occurrence of scleroderma in a case-control study of 100 scleroderma patients and 300 controls resulted in a reported OR of 2.26 (95% CI 0.95–5.26) (Marie et al. 2014). Limiting the evaluation to those cases (n=8) and controls (n=7) with a high cumulative score for trichloroethylene exposure, the OR was 3.63 (95% CI 1.15–12.09).

Occupational exposure to trichloroethylene was associated with decreases in selected lymphocyte subsets among trichloroethylene-exposed workers (n=80) at factories in China that used trichloroethylene for cleaning a variety of materials and products; controls consisted of 96 unexposed age- and sex-matched workers from other industries (Hosgood et al. 2012; Lan et al. 2010). Full-shift personal air monitoring was performed to assess trichloroethylene exposure levels. The study authors noted significantly lower total numbers of lymphocytes, T cells, CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells among the trichloroethylene-exposed workers (Lan et al. 2010). When the trichloroethylene-exposed workers were categorized according to exposure level, those in the higher exposure category (≥12 ppm; mean 38 ppm) exhibited more marked decreases in total lymphocytes and lymphocyte subsets than those in the lower exposure category (<12 ppm; mean 5 ppm). Relative to unexposed controls, the trichloroethylene-exposed group of workers exhibited 8% decreased CD4+ naïve T cell count (p=0.056), 17% decreased CD8+ naïve T cell count (p=0.0002), and 20% decreased CD4+ effective memory T cell count (p=0.001) (Hosgood et al. 2012). These results suggest that trichloroethylene toxicity may include immunosuppression by depressing the capacity to respond to antigens. Analysis of serum concentrations

of IgG, IgM, and IgE from the 80 trichloroethylene-exposed workers and 45 of the unexposed controls revealed significantly ($p<0.01$) decreased IgG and IgM in the trichloroethylene-exposed workers (approximately 18 and 38%, respectively, lower than controls), but no significant effect on serum IgE (Zhang et al. 2013). Similar decreases in IgG and IgM were observed when controls were compared to those workers exposed to trichloroethylene levels either <12 or ≥12 ppm.

Some animal studies provide evidence for trichloroethylene-induced immunosuppression. A 64% reduction in splenic anti-SRBC IgM response was observed in female rats exposed to trichloroethylene vapors at 1,000 ppm, 6 hours/day, 5 days/week for 4 weeks; the NOAEL for immunological effects was 300 ppm (Boverhof et al. 2013). Kaneko et al. (2000) reported exposure concentration-related decreased serum IgG levels, liver inflammation, splenomegaly, and hyperplasia of lymphatic follicles in male mice of an autoimmune-prone strain repeatedly exposed to trichloroethylene at concentrations ≥500 ppm for 8 weeks. Male and female mice repeatedly exposed to trichloroethylene vapors at 300 ppm for 8 weeks exhibited significantly decreased spleen weight (41 and 24%, respectively, less than those of controls); the NOAEL was 150 ppm (Kjellstrand et al. 1983a). Mice exposed to trichloroethylene for 3 hours at ≥10 ppm with simultaneous streptococcal aerosol challenge had increased susceptibility to pulmonary infection with *Streptococcus zooepidemicus* (Aranyi et al. 1986). Increased susceptibility was not observed at 5 ppm following a single 3-hour exposure, or five daily 3-hour exposures. Histopathological effects on the spleen were not observed in squirrel monkeys, rats, guinea pigs, dogs, or rabbits exposed to 700 ppm trichloroethylene 8 hours/day, 5 days/week for 6 weeks, or to 35 ppm continuously for 90 days (Prendergast et al. 1967).

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

3.2.1.4 Neurological Effects

Studies evaluating neurological effects in humans and animals exposed during gestation are discussed in Section 3.2.1.6 (Developmental Effects).

Experimental exposure studies have attempted to associate various neurological effects in humans with specific trichloroethylene exposure levels. Voluntary exposures of 1–4 hours resulted in complaints of drowsiness at 27 ppm and headache at 81 ppm (Nomiyama and Nomiyama 1977). These are very low

exposure levels, but the results are questionable because of the use of only three test subjects per dose, lack of statistical analysis, sporadic occurrence of the effects, lack of clear dose-response relationships, and discrepancies between the text and summary table in the report. Therefore, this study is not presented in Table 3-1. No effects on visual perception, two-point discrimination, blood pressure, pulse rate, or respiration rate were observed at any vapor concentration in this study. Other neurobehavioral tests were not performed, and the subjects were not evaluated following exposure.

Effects noted from inhalation of trichloroethylene vapors by male volunteers include impaired visual-motor coordination (measured by groove-type hand steadiness, depth perception, and pegboard tests) at 1,000 ppm for 2–2.5 hours (Vernon and Ferguson 1969). Increases in heart and breathing rates were noted when trichloroethylene was inhaled simultaneously with ethanol ingestion at 200 ppm (Windemuller and Ettema 1978). This latter study found no effect without ethanol ingestion. An 8-hour exposure (two 4-hour exposures separated by 1.5 hours) to 110 ppm was reported to result in decreased performance on tests of perception, memory, reaction time, and manual dexterity (Salvini et al. 1971). However, a later attempt to replicate these results found no effects other than fatigue and drowsiness (Stewart et al. 1974a), so the original results remain in doubt.

In contrast to the above reports of acute exposure effects, reports of no effect in humans include no psychomotor impairment at 95 ppm (Konietzko et al. 1975a), no change in visual choice, pursuit rotor, or subjective feelings at 200 ppm (Windemuller and Ettema 1978), and no change in reaction time, hand steadiness, or other behavioral parameters at 300 ppm (Ettema et al. 1975). Each of these studies involved an exposure of <4 hours. No change in reaction time or short-term memory function was seen in 15 subjects exposed to 1,080 mg/m^3 (200 ppm) for 3 days, 70 minutes/day (Gamberale et al. 1976). Somewhat longer exposures of 5 days resulted in psychological changes at 100 ppm as measured by standard psychometric tests (Triebig et al. 1977). Motor and dexterity tests were normal in five to six volunteers exposed to 200 ppm for 5 days, 7 hours/day, although they did complain of fatigue and drowsiness (Stewart et al. 1970). Half of the subjects also indicated that, on one or more occasions after exposure, greater mental effort was required to perform the tests.

In cases of acute accidental or intentional overexposure to trichloroethylene vapors, actual exposure levels are not typically quantified. Trichloroethylene-induced neurological effects include euphoria, giddiness, lethargy, confusion, dizziness, headache, nausea, difficulty swallowing, facial effects that indicate possible trigeminal nerve damage (including sensation deficits, jaw weakness, increased blink reflex latency), which may be irreversible, memory deficits, and unconsciousness (Adamek and Krupiński 2007;

Buxton and Hayward 1967; Carrieri et al. 2007; Clearfield 1970; Feldman 1970; Feldman et al. 1985; James 1963; Lawrence and Partyka 1981; Lachnit and Pietschmann 1960; Leandri et al. 1995; Longley and Jones 1963; Milby 1968; Miller et al. 2002; Pembleton 1974; Thierstein et al. 1960; Troutman 1988). These types of uncontrolled case studies are of limited value in determining the exposure levels associated with the effects of trichloroethylene inhalation under usual occupational and environmental exposures. Also, the lack of information on the subjects' preexisting health and the possibility of effects from other chemicals to which the subjects were exposed further confound the usefulness of this information.

Intermediate- and chronic-duration occupational and nonoccupational exposures to trichloroethylene have produced neurological effects similar to those found in acute exposure situations. Workers chronically exposed to levels between 38 and 172 ppm reported symptoms of sleepiness, dizziness, headache, and nausea, but no apparent trigeminal nerve disorders (El Ghawabi et al. 1973). In a study of Dutch workers regularly exposed to no more than 35 ppm (the Dutch threshold limit value), investigators found no evidence of trichloroethylene-induced trigeminal nerve impairment as measured by blink reflex, but did report an increased latency (38 ms longer than that of controls) for the masseter reflex (another measure of trigeminal nerve function) (Ruijten et al. 1991). A case study of a retired metal degreaser who had been exposed to between 8 and 170 mg/m^3 (1.5 and 32 ppm) for 1–2 hours/day over a period of 20 years reported symptoms of headache, forgetfulness, vertigo, nausea, and loss of feeling in hands and feet persisting for 4 years after retirement (Kohlmuller and Kochen 1994). However, this worker had also been exposed to elevated levels due to accidental spills several times during his career, and it may have been that these few incidences of acute, high-level exposure were more significant factors related to his symptoms, rather than the chronic, low-level exposure. Caprioli et al. (2001) reported loss of strength and polyneuropathy in a woman who had been exposed to trichloroethylene during a 3-month period of degreasing and antiquing processes (7–8 hours/day) in a poorly-ventilated garage.

Murata et al. (2010) reported a significant association ($p<0.001$) between eyes open static postural sway and urinary trichloroethanol in an investigation of 57 workers exposed to trichloroethylene for periods of 0.1–37 years at maximum estimated ambient concentrations <22 ppm; a control group consisted of 60 subjects. Total tremor intensities in nondominant hands differed significantly ($p=0.039$) among three groups of the workers, divided according to cumulative exposure index. Ambient trichloroethylene air concentrations were estimated using the equation $Y=8.37X+17.12$, where X is trichloroethylene in air and Y is total trichloro-compounds (TTC; sum of the trichloroethylene urinary metabolites, trichloroethanol and TCA) (Ogata et al. 1971). Murata et al. (2010) reported a mean TTC level of 4.2 mg/L (range 0.6–

192.6) in the urine from exposed workers; TTC was not detected in the urine of the control subjects. The results of Murata et al. (2010) indicate that even relatively low levels of occupational exposure to trichloroethylene may affect neuromotor function.

Chronic exposure in the workplace has been associated with damage to cranial nerves in several cases (Bardodej and Vyskocil 1956; Barret et al. 1987; Cavanagh and Buxton 1989). Persons who died from overexposure have shown degeneration of cranial nuclei in the brain stem (Buxton and Hayward 1967). Sanz et al. (2008) reported a case of disabling myoclonic encephalopathy with progression to thalamic and cerebellar involvement in a 25-year-old woman with a history of 18 months of occupational exposure to trichloroethylene; neurological symptoms persisted after the woman left the job.

Other reported neurological effects of chronic occupational exposure to unquantified trichloroethylene levels include memory loss (Grandjean et al. 1955; Smith 1966), mood swings (Barret et al. 1987; Milby 1968; Rasmussen et al. 1993d), trigeminal neuropathy (Barret et al. 1987; Feldman et al. 1992; Mitchell and Parsons-Smith 1969; Smith 1966), cranial nerve VIII damage and decreased psychomotor function (Konietzko 1979), impaired acoustic-motor function (Rasmussen et al. 1993c), and psychotic behavior with impaired cognitive function (Steinberg 1981). The study by Feldman et al. (1992) found that the neuropathic effects of trichloroethylene appear to be specific to the trigeminal nerves, rather than generalized. For instance, chronic exposure to trichloroethylene resulted in no change in conduction velocity measured in the radial and ulnar nerves (Triebig et al. 1978). Sympathetic nerve activity, as measured by changes in serum dopamine-β-hydroxylase activity, was normal in workers occupationally exposed to trichloroethylene levels of about 22 ppm (Nagaya et al. 1990). However, some cranial nerves, other than the trigeminal, have shown an exposure-related effect, including the facial (Feldman et al. 1985), olfactory (Rasmussen et al. 1993a), and acoustic nerves. Interestingly, Rasmussen et al. (1993a) reported no significant association ($p=0.42$) between length of exposure and trigeminal nerve effect. There is some evidence that effects on trigeminal nerve function may be due to dichloroacetylene (a trichloroethylene combustion product formed under conditions of high alkalinity or temperature during volatilization of trichloroethylene (Albee et al. 1997, 2006; Barret et al. 1991, 1992; Laureno 1993; Reichert et al. 1976); in one set of animal studies, trigeminal nerve effects were more prominent following exposure to dichloroacetylene than trichloroethylene (Barret et al. 1991, 1992).

Goldman et al. (2012) examined possible associations between exposure to solvents and risk of Parkinson's disease (a neurodegenerative motor disorder). Ninety-nine twin pairs discordant for Parkinson's disease were interviewed regarding lifetime occupations and hobbies; exposures to six

specific solvents were estimated independent of case status. Ever exposure to trichloroethylene was associated with increased risk of Parkinson's disease (OR 6.1; 95% CI 1.2–33; p=0.034).

Trichloroethylene was once used as a surgical anesthetic (Hewer 1943). Some patients were reported to have experienced trigeminal neuropathy following anesthesia using trichloroethylene in association with soda-lime (Humphrey and McClelland 1944). The reaction of trichloroethylene with the soda-lime was thought to have produced dichloroacetylene, which triggered neuropathies in 13 patients over a 4-month period in a county hospital. No new cases were discovered for 3 months after the discontinuation of the use of soda-lime. In another study, Pembleton (1974) found trichloroethylene to be a satisfactory anesthetic using an open technique without soda-lime. A mixture of nitrous oxide and 1,000 ppm of trichloroethylene has been used for obstetrical anesthesia (Crawford and Davies 1975). No adverse effects on infants or their mothers were noted. Trichloroethylene was also used, with variable success, in the treatment of painful symptoms of trigeminal neuralgia (Glaser 1931).

Studies on the neurological effects of acute trichloroethylene inhalation in animals have produced results similar to those observed in human studies. In rats, exposures of ≤8 hours have resulted in decreased electric shock avoidance and frequency of lever press in a Skinner box at 250 ppm (Kishi et al. 1993), decreased swimming time but no change in shuttle box or maze performance at 800 ppm (Grandjean 1963), suppressed reaction to visual stimulus at 14,800 mg/m^3 (2,754 ppm) (Niklasson et al. 1993), lethargy at 3,000 ppm (Adams et al. 1951), and full anesthesia at 4,800 ppm (Adams et al. 1951). Ataxia was observed in rats exposed to 4,380 ppm trichloroethylene 4 hours/day, 5 days/week for 10 days, but not at an exposure level of 1,568 ppm (Goldberg et al. 1964b). Most of these effects were found to be reversible when the exposure period ended. Rats that had been conditioned to climb a rope to a feeding trough in response to a signal exhibited no change in response latency after an 11–14-hour exposure to 200 ppm trichloroethylene, although a significant increase in spontaneous climbs in the absence of a signal was seen (Grandjean 1960). The study authors indicated that this may have been due to increased disinhibition or increased excitability. Exposures of rats for 3 days (4 or 8 hours/day) to 1,000 ppm trichloroethylene resulted in disturbed sleep cycles, while seizures, abnormal electroencephalographic (EEG) activity, and post-exposure cardiac arrhythmia were seen at 3,000 ppm (Arito et al. 1993).

Some animal studies included evaluation of effects of exposure concentration versus time on nervous system function; the results indicate that concentration, rather than time of exposure, is more important in determining effects. In one study, rats were trained to perform a signal detection task that involved the pressing of two levers for food reward: one lever when a light flashed and the second lever produced

food when there was no signal (Bushnell 1997). The trained rats were exposed to 0, 400, 800, 1,200, 1,600, 2,000, or 2,400 ppm trichloroethylene for 0.33, 0.67, or 1 hour. Response times were significantly increased only at 2,400 ppm at 0.67 and 1 hour. Sensitivity was significantly decreased at 2,400 ppm at all exposure times. At 0.33 hour, sensitivity was not affected at the other concentrations. At 0.67 hour, sensitivity was significantly decreased at 2,000, and 1,200 ppm, and at 1 hour, sensitivity was significantly decreased at 2,000, 1,600, and 1,200 ppm. Sensitivity was not affected at any point of time at 800 ppm, and this concentration is considered the NOAEL for this study. In a companion study, it was noted that rats developed tolerance to trichloroethylene during 2 weeks of intermittent exposure as reflected by improvement in performance of the signal detection task following repeated exposures (Bushnell and Oshiro 2000). Boyes et al. (2003, 2005) reported trichloroethylene-induced decreased amplitude of visual evoked potentials in rats repeatedly exposed to trichloroethylene vapors at concentrations in the range of 1,000–5,000 ppm; the results of these studies indicated that momentary brain trichloroethylene level (not exposure duration) is an appropriate dose metric to predict these effects. Results of other studies designed to assess trichloroethylene-induced visual effects include changes in visual evoked potentials (Blain et al. 1992) and electroretinal responses to flash stimulation (Blain et al. 1994) in rabbits exposed to 350 ppm trichloroethylene for 12 weeks (4 days/week, 4 hours/day).

Hearing loss in the mid-frequency range (8–20 kHz) is another effect observed in rats exposed to trichloroethylene. Crofton and Zhao (1993) found significant hearing loss, which persisted for up to 14 weeks post-exposure, exclusively in the 8–16-kHz range when Long-Evans rats were exposed to 4,000 ppm 6 hours/day for 5 days. Rats exposed to 3,500 ppm for 5 days and tested at a wide range of frequencies (0.5–40 kHz) exhibited hearing loss only up to a frequency of 16 kHz, confirming that the effect is specific to the mid-frequency range (Crofton et al. 1994). Assessment of relationships between exposure concentration and duration in the observed trichloroethylene-induced hearing loss in rats included exposures to trichloroethylene vapors using 6-hour exposure times and either single exposure, repeated exposures for 5 days, or exposures 5 days/week for 4 or 13 weeks (Boyes et al. 2000; Crofton and Zhao 1997). Following the final exposure period, the auditory threshold to a 16 kHz tone was measured and compared to that of a group of air-exposed rats. A single 6-hour exposure at 6,000 ppm resulted in a 14 dB increase in the 16 kHz threshold (NOAEL 4,000 ppm). Significantly increased 16 kHz threshold was noted at 3,200 ppm in the groups exposed for 5 days or 4 weeks, and 13 weeks of exposures at 2,400 ppm resulted in a 21 dB increase in the 16 kHz threshold (NOAEL 1,600 ppm). No hearing loss was detected after a 5-day exposure to 1,500 ppm, as measured by brainstem auditory evoked response, but a substantial effect was seen when this level was combined with 500 ppm styrene (Rebert et al. 1993). Hearing loss at 20 kHz only was measured in Wistar rats exposed 18 hours/day, 5 days/week

for 3 weeks to 3,000 ppm and a reduced acoustic startle response was observed in rats at 1,500 ppm (Jaspers et al. 1993). A depressed auditory sensory evoked potential amplitude was seen in F344 rats exposed to 2,000 ppm for 3 weeks and 3,200 ppm for 12 weeks (Rebert et al. 1991). This latter study found no effect at 1,600 ppm in Long-Evans rats and thus set the response threshold at about 2,000 ppm trichloroethylene. F344 rats exposed to 2,500 ppm trichloroethylene for 13 weeks (5 days/week, 6 hours/day) exhibited a decrease in tone pip auditory response primarily at 16 kHz, along with a loss of cochlear hair cells (NOAEL 800 ppm) (Albee et al. 1993, 2006). Similar ototoxic effects were reported by Muijser et al. (2000) following exposure of rats to trichloroethylene at 3,000 ppm for 18 hours/day, 5 days/week for 3 weeks. Fechter et al. (1998) reported that the ototoxicity of trichloroethylene in rats could be accounted for by loss of spiral ganglion cells in the middle turn of the cochlea.

Other studies assessed clinical signs of trichloroethylene-induced behavioral effects. After 10 days of exposure, reduced social behavior and reduced exploratory behavior were observed in rats exposed to 100 ppm trichloroethylene 6 hours/day 5 days/week for a total of 5 weeks (Silverman and Williams 1975). Waseem et al. (2001) exposed rats to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 180 days and noted significantly increased spontaneous locomotor activity. In rats exposed to 50 or 100 ppm trichloroethylene 8 hours/day, 5 days/week for 6 weeks, effects on sleep patterns were observed (Arito et al. 1994a). At 50 ppm, decreased wakefulness was observed during the exposure. Effects remaining at 22 hours after the end of the 6-week exposure included decreased heart rate during sleep at 50 ppm and decreased wakefulness at 100 ppm (Arito et al. 1994a). An 18-week exposure (16 hours/day, 5 days/week) to 1,000 ppm resulted in increased latency in visual discrimination tasks, but not in spontaneous activity, coordinated movement, grip strength, or peripheral nerve conduction time (Kulig 1987). Impaired swimming behavior was observed in rats exposed to 400 ppm trichloroethylene 8 hours/day, 5 days/week for 44 weeks (Battig and Grandjean 1963). An increased level of exploratory activity immediately after exposure, attributed to reduced anxiety on the part of the rats, was also observed in this study. Decreased avoidance was observed in rats exposed to 125 ppm trichloroethylene 4 hours/day, 5 days/week for 30 days (Goldberg et al. 1964a).

One study evaluated the effect of trichloroethylene on heart rate. Among rats of various ages, the normal age-related decrease in heart rate and circadian rhythm amplitude, as well as the incidence of spontaneous bradyarrhythmias, were exacerbated by an 8-hour exposure to 300 ppm of trichloroethylene, followed by exposure to 1,000 ppm for 8 hours 7 days later (Arito et al. 1994b).

Biochemical changes have also been noted in the brains of animals after an inhalation exposure to trichloroethylene. Decreased brain ribonucleic acid (RNA) content was seen in rats exposed to 200 ppm for 6 hours/day for 4 days (Savolainen et al. 1977). Open-field activity, preening, and rearing were increased in these rats at 1 hour, but not 17 hours, post-exposure. In gerbils, continuous exposure to 60 ppm trichloroethylene for 3 months, followed by a recovery period of 4 months, resulted in increased brain S100 protein content, consistent with astroglial hypertrophy and proliferation (Haglid et al. 1981). Exposure to 320 ppm produced significantly elevated DNA content in the cerebellar vermis and sensory motor cortex. It is not known whether such effects reflect adverse changes.

The highest NOAEL values and all LOAEL values from each reliable study 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

Possible associations between exposure to organic solvents (including trichloroethylene) and measures of fertility and fecundity have been assessed to some extent in occupationally-exposed men and women. Increases in miscarriages have been reported among nurses exposed to unspecified concentrations of trichloroethylene and other chemicals in operating rooms (Corbett et al. 1974). The occurrence of miscarriages could not conclusively be attributed to trichloroethylene because there was concomitant exposure to other chemicals. A retrospective case-control study conducted in humans compared spontaneous abortion rates among women who had been exposed occupationally or nonoccupationally to trichloroethylene and other solvents to rates among women without solvent exposure (Windham et al. 1991). The authors observed approximately three times the risk of spontaneous abortion with exposure to trichloroethylene. This risk increased further when women with less than a half hour of exposure to trichloroethylene each week were excluded from the analysis. However, a consistent dose-response relationship was not observed, and most of the women were exposed to a variety of solvents, not just trichloroethylene. Other epidemiologic studies have evaluated possible associations between occupational exposure of women to organic solvents (including trichloroethylene) and measures of fertility including time-to-pregnancy, spontaneous abortion, and menstrual cycle disturbance (Bardodej and Vyskocil 1956; Corbett et al. 1974; Lindbohm et al. 1990; Sallmén et al. 1995; Taskinen et al. 1994; Windham et al. 1991; Zielinski 1973). Some of these studies provide suggestive evidence of an association between exposure to trichloroethylene and reduced fecundability (Sallmén et al. 1995) and menstrual cycle disturbances (including amenorrhea) (Bardodej and Vyskocil 1956; Sagawa et al. 1973; Zielinski 1973).

Studies in men include assessments of reproductive behavior, sperm quality, and fertility. Bardodej and Vyskocil (1956) reported decreased potency or unspecified sexual disturbances in a group of 75 men employed in dry cleaning or metal degreasing processes. El Ghawabi et al. (1973) reported decreased libido in a group of 30 men employed in a money printing shop for up to 5 years and exposed to trichloroethylene at 38–172 ppm; however, the study authors indicated that the decreased libido was likely due to fatigue and sleepiness. Within two groups of men (n=85) exposed to trichloroethylene during degreasing of electronics at a mean trichloroethylene air concentration of 29.6 ppm (range 9–131 ppm, determined by 8-hour personal air sampling for 12 of the men), a decreased percentage of normal sperm morphology was reported for 48 of the workers with higher levels of trichloroethylene exposure (as determined by urinary TCA ≥25 mg/g creatinine) compared to 37 of the workers with lower levels of trichloroethylene exposure (Chia et al. 1996; 1997; Goh et al. 1998). There was no effect on sperm volume, density, or motility; however, prevalence of hyperzoospermia increased with increasing urinary TCA level. Sallmén et al. (1998) found no effect on male fertility in a study that examined paternal occupational exposure to trichloroethylene and time-to-pregnancy among their wives. Levels of exposure were determined by questionnaire and urinary TCA levels; however, the presentation of data regarding exposure categories and fertility outcomes precludes meaningful dose-response assessment. Forkert et al. (2003) identified trichloroethylene and its metabolites in the seminal fluid of eight mechanics exposed to trichloroethylene for at least 2 years and diagnosed with clinical infertility. Neither trichloroethylene nor its metabolites were detected in the seminal fluid of five other clinically infertile men at the same clinic who had not been occupationally exposed to trichloroethylene; furthermore, the study did not include controls exhibiting normal fertility. As noted in Section 3.2.2.2 (Endocrine Effects), there is some evidence of an association between occupational exposure to trichloroethylene and decreases in serum levels of testosterone, follicle-stimulating hormone, and sex-hormone binding globulin (Chia et al. 1997; Goh et al. 1998).

Studies in animals demonstrate the toxicity of trichloroethylene to the male reproductive system. Repeated exposures of male rats at trichloroethylene concentrations of 376–1,000 ppm for as little as 1–2 weeks resulted in effects that included degeneration of epididymal epithelium (Kan et al. 2007), increases in abnormal sperm and decreased reproductive success (Kumar et al. 2000b), and decreased numbers of sperm capable of attaching to eggs *in vitro* (Xu et al. 2004). Kumar et al. (2000a, 2000b, 2001b) exposed male rats to trichloroethylene at 376 ppm for 4 hours/day, 5 days/week for up to 24 weeks and noted testicular atrophy and decreases in sperm count and motility. Forkert et al. (2002) reported epididymal epithelium damage in mice exposed to trichloroethylene vapors at 1,000 ppm,

6 hours/day, 5 days/week for 4 weeks. Other mice exposed to 2,000 ppm of trichloroethylene, 4 hours/day for a 5-day period, exhibited a significant increase in abnormal sperm morphology of 1% 28 days after the exposure (NOAEL 200 ppm) (Land et al. 1981). A 6% increase in abnormal sperm was observed 4 weeks, but not 4 days or 10 weeks, after mice were exposed to 100 ppm trichloroethylene 7 hours/day for 5 days (Beliles et al. 1980). Based on the time after exposure at which sperm were affected, the study authors indicated that trichloroethylene damages sperm precursor cells but that spermatogonia were either unaffected or were capable of recovery. Reproductive performance was not tested in most of the animal studies. Another mouse study tested the effects of a 5-day exposure (6 hours/day) on spermatid micronuclei frequency; no effects were observed at exposure levels of up to 500 ppm, the highest concentration tested (Allen et al. 1994). These results were interpreted as evidence that trichloroethylene did not cause meiotic chromosome breakage or loss. No treatment-related reproductive effects were seen in female rats exposed to 1,800 ppm trichloroethylene for 2 weeks (6 hours/day, 7 days/week) before mating (Dorfmueller et al. 1979).

The highest NOAEL values and all LOAEL values from each reliable study 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

No increase in malformed babies was observed among approximately 2,000 fathers and mothers exposed to unspecified concentrations of trichloroethylene in the workplace (Tola et al. 1980).

A retrospective case-control study conducted in humans compared spontaneous abortion rates among women who had been exposed occupationally or nonoccupationally to trichloroethylene and other solvents to rates among women without solvent exposure (Windham et al. 1991). The authors observed about a 3-fold increase in risk of spontaneous abortion associated with exposure to trichloroethylene. This risk increased further when women with less than a half hour of exposure to trichloroethylene per week were excluded from the analysis. However, a consistent dose-response relationship was not observed, and most of the women were exposed to a variety of solvents other than trichloroethylene. In this same study, the relationship between exposure to halogenated solvents during the first 20 weeks of pregnancy and fetal growth were examined. No association between exposure to solvents and decreased fetal growth was observed. However, the number of small infants was too low to specifically assess trichloroethylene exposures, and most fetal growth would occur after the first 20 weeks of pregnancy.

No associations were observed between occupational exposure to trichloroethylene and rates of spontaneous abortion among women who reported occupational exposure to organic solvents including trichloroethylene (OR 0.6 [95% CI 0.2–2.3]; based on 4 exposed cases and 3 controls and adjusted for exposure to other solvents) (Lindbohm et al. 1990), or women whose husbands were exposed to trichloroethylene (OR 1.0 [95% CI 0.6–2.0]; based on 17 exposed cases and 35 referents and adjusted for exposure to other solvents) (Taskinen et al. 1989). However, these studies are limited by small incidences of spontaneous abortion.

Yauck et al. (2004) reported results of a case-control study of 4,025 infants born to mothers in Milwaukee, Wisconsin, between 1997 and 1999. The study included a trichloroethylene-exposed group (defined as residing within a 1.32-mile radius of a trichloroethylene-emitting site) and a nonexposed group (residing outside a 1.32-mile radius of a trichloroethylene-emitting site). Using nonexposed mothers <38 years of age as the referent, there was no significant increased risk of congenital heart defects in children from trichloroethylene-exposed mothers <38 years of age (OR 0.9; 95% CI 0.6–1.2). However, a 6.2-fold increased risk of congenital heart defects was noted for children of trichloroethylene-exposed mothers who were ≥38 years of age at delivery (OR 6.2; 95% CI 2.6–14.5), and a 1.9-fold increased risk of congenital heart defects was also noted for children of unexposed mothers who were ≥38 years of age at delivery (OR 1.9; 95% CI 1.1–3.5). These results indicate that maternal age at delivery may influence the risk of congenital heart defects in children of trichloroethylene-exposed mothers.

Analyses of birth outcome were performed in the Endicott, New York area where residents may have been exposed to volatile organic compounds (VOCs) via soil vapor intrusion (migration of contamination through the soil into structures through cracks in building foundations) (ATSDR 2006, 2008; Forand et al. 2012). Groundwater sampling performed following a 1979 spill of 4,100 gallons of 1,1,1-trichloroethane at a manufacturing facility revealed a large plume of contaminants including trichloroethylene (NYSDEC 2003). Initially, it was assumed that the VOC-contaminated groundwater was not of particular health concern because residential drinking water was supplied primarily from wells outside the plume area. Subsequently, it was determined that exposure could occur via soil vapor intrusion; soil vapor sampling initiated in 2000 revealed that trichloroethylene was the predominant contaminant in the soil vapor above the plume region where levels typically ranged from 100 to 10,000 µg/m^3 (18–1,800 ppb) (McDonald and Wertz 2007; NYSDEC 2003). Trichloroethylene levels in indoor air samples in the plume area ranged from 0.18 to 140 µg/m^3 (0.0324–25.2 ppb) (Agency for Toxic Substance and Disease Registry 2006; NYSDEC 2003). Sixty-seven percent of the measured indoor trichloroethylene samples were higher than

the upper 95th percentile trichloroethylene level of 3.3 µg/m^3 (0.59 ppb) determined from data compiled from 15 U.S. indoor air studies that measured background concentrations of VOCs in homes not expected to be influenced by soil vapor intrusion (EPA 2011g). The evaluations of ATSDR (2006, 2008) and Forand et al. (2012) included assessment of birth outcomes among those residents in the plume area compared to birth outcomes in the rest of New York State exclusive of New York City.

In the evaluation by ATSDR (2006, 2008), total cardiac defects were twice as prevalent as expected (standardized prevalence ratio [SPR] 2.02; 95% CI 1.23–3.11). There were no cases of neural tube defects, orofacial clefts, or choanal atresia in the study area, and results of spontaneous fetal death analysis did not support an association between living in the exposure area and increased risk of fetal death.

In the evaluation of Forand et al. (2012), adjusted rate ratios were elevated for low birth weight (rate ratio 1.36; 95% CI 1.07–1.73; n=76), small for gestational age (rate ratio 1.23; 95% CI 1.03–1.48; n=117), term low birth weight (rate ratio 1.68; 95% CI 1.20–2.34; n=37), cardiac defects (rate ratio 2.15; 95% CI 1.27–3.62; n=15), and conotruncal defects (rate ratio 4.91; 95% CI 1.58–15.24; n=3). It was noted that residual socioeconomic confounding may have contributed to low birth weight outcomes.

A case-control study evaluated the risk of autism spectrum disorder in a population of children exposed during gestation and early life in southwestern Pennsylvania (Talbott et al. 2015). Trichloroethylene was one of numerous solvents and chemicals measured in air. Trichloroethylene concentrations were stratified by quartile and ranged from approximately 71 mg/m^3 for the second quartile to approximately 83 mg/m^3 for the fourth quartile. Cases (n=217), born 2005–2009, were compared to matched controls (n=224). The ORs for quartiles 2 through 4 were similar; the OR (95% CI) for the fourth quartile was 1.22 (0.68–2.17).

Pregnant laboratory animals have been exposed to trichloroethylene vapors, but no conclusive studies have been encountered that clearly indicate teratogenic effects. There were no indications of trichloroethylene exposure-related developmental effects in pups of rat or mouse dams exposed to 100–600 ppm of trichloroethylene during gestation (Beliles et al. 1980; Carney et al. 2006; Hardin et al. 1981; Healy et al. 1982; Schwetz et al. 1975). Decreased fetal weight and incomplete skeletal ossification were observed in offspring of rats exposed to 1,800 ppm trichloroethylene 6 hours/day on GDs 0–20 (Dorfmueller et al. 1979). Activity measurements completed in the offspring at ages 10, 20, and 100 days did not show an effect of trichloroethylene exposure. Developmental effects were not observed in

offspring of mice exposed to 300 ppm trichloroethylene 7 hours/day on GDs 6–15 (Schwetz et al. 1975). Although not statistically significant, four rabbit fetuses in 2 of 23 litters had external hydrocephalus (Beliles et al. 1980; Hardin et al. 1981). Because this effect is rarely observed in control rabbits, the study authors indicated that it was suggestive of a teratogenic effect, although it was not conclusive. Therefore, this study is not presented in Table 3-1 or Figure 3-1.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in 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 trichloroethylene has been evaluated in numerous epidemiological studies and experimental animal studies. HHS has classified trichloroethylene as "*known to be a human carcinogen"* based on sufficient evidence of carcinogenicity from humans (NTP 2016). IARC (2014) has classified trichloroethylene as "carcinogenic to humans" based on sufficient evidence in humans (Group 1). EPA (2011e) has characterized trichloroethylene as "carcinogenic in humans by all routes of exposure."

Epidemiological Studies. A large number of cohort and case-control studies have assessed possible associations between inhalation exposure to trichloroethylene and cancer, with comprehensive reviews conducted by NTP (2016), EPA (2011e), and IARC (2014). NTP (2016) concluded that trichloroethylene causes kidney cancer in humans based on consistent results of epidemiological studies and has a causal association with non-Hodgkin's lymphoma based on results of several epidemiological studies; however, the epidemiological evidence for non-Hodgkin's lymphoma is less consistent than for kidney cancer. For other cancer types, NTP (2016) concluded that evidence from epidemiological studies is inadequate to evaluate associations. Conclusions of the EPA (2011e) Toxicological Review regarding epidemiological evidence for cancer are similar to the conclusions of NTP (2016): convincing evidence for a causal relationship for trichloroethylene and kidney cancer; strong evidence for a causal relationship for non-Hodgkin's lymphoma, but less consistent that that for kidney cancer; limited evidence for liver cancer; and less evidence for other cancer types. IARC (2014) concluded that the epidemiological evidence for kidney cancer is sufficient to establish a causal relationship, and "positive associations" have been observed for non-Hodgkin's lymphoma and liver cancer. The National Research Council of the National Academy of Sciences (NRC 2006, 2009) concluded that there is inadequate/insufficient evidence to determine associations between trichloroethylene and hepatobiliary cancer and non-Hodgkin's

lymphoma. Furthermore, NRC (2006) concluded that exposure to trichloroethylene at levels relevant to the general public is not likely to induce liver cancer in humans. Recently published reviews on the carcinogenicity of trichloroethylene in humans and laboratory animals, and the role of trichlorethylene biotransformation in mutagenicity and carcinogenicity, may be consulted for additional information (Cichocki et al. 2016; Lash et al. 2014; Rusyn et al. 2014).

Table 3-2 provides an overview of selected epidemiological studies, including information on study types (e.g., cohort, case-control), study 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 (2011e) selected for inclusion in meta-analyses on kidney cancer, non-Hodgkin's lymphoma, and liver cancer;
- studies on other cancer end points (cancers other than kidney, liver, and non-Hodgkin's lymphoma) meeting the following criteria as listed in EPA (2011e): cohort or case-control study design; evaluation of incidence or mortality; adequate selection in cohort studies of exposure and control groups and of cases and controls in case-control studies; trichloroethylene exposure potential inferred to each subject and quantitative assessment of trichloroethylene exposure assessment for each subject by reference to industrial hygiene records indicating a high probability of trichloroethylene use, individual biomarkers, job-exposure matrices, or obtained from subjects using questionnaire (case-control studies); and
- studies meeting the EPA (2011e) criteria that were published after 2011.

For additional details and reviews of these and other epidemiological studies assessing the potential carcinogenicity of trichloroethylene, the EPA Integrated Risk Information System (IRIS) Toxicological Review for Trichloroethylene (EPA 2011e), IARC (2014), and NTP (2016) may be consulted. Additional information is also provided in an assessment on studies of drinking water contaminants, including trichloroethylene, at U.S Marine Corp Base at Camp Lejeune conducted by ATSDR (2017b).

As summarized in Table 3-2, selected studies included 9 meta-analyses, 1 pooled case-control study, 12 cohort studies, and 32 case-control studies. Study populations were from numerous countries, including the United States, Canada, and several European countries. Cohort studies evaluated general worker populations, microelectronics/machine workers, and aircraft and aerospace workers. The Radican et al. (2008) cohort study is a follow-up of Blair et al. (1998). Most case-control studies evaluated various cancer end points in adult worker populations from numerous industries. Three case-control studies examined cancer in children of exposed workers (DeRoos et al. 2001; McKinney et al. 1991; Shu et al. 1999).

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

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Meta-analyses			
Alexander et al. 2006; Workers from 8 studies	JEM and/or urine trichloroethylene	Not reported for individual studies	Strengths[b]: large number of participants; results consistent across studies Limitations[b]: participants likely exposed to other chemicals and solvents; no information on potential impact of confounding factors
Alexander et al. 2007; Workers from 15 studies	JEM and/or urine trichloroethylene	Not reported for individual studies	Strengths[b]: large number of participants Limitations[b]: participants likely exposed to other chemicals and solvents; no information on adjustments for potential confounding factors
EPA 2011a; Scott and Jinot 2011 Workers from 24 studies	JEM and/or urine trichloroethylene	"Most studies" considered age and sex	Strengths: includes numerous well-controlled studies; large number of participants; evaluated publication bias Limitations: low-to-moderate heterogeneity for NHL data
Hansen et al. 2013; Workers from 3 Nordic studies	urine trichloroethylene	Age; sex; country; calendar year	Strengths[b]: large number of participants; prospective design; long follow-up period; used national registry for cancer Limitations[b]: lack of information on potential confounders (smoking, alcohol use); no information on duration of exposure
Karami et al. 2013 Workers from 28 studies	JEM and/or urine trichloroethylene	Not reported for individual studies	Strengths[b]: participants had known trichloroethylene exposure; low misclassification bias; exposure classification accounted for exposure to other solvents Limitations[b]: most studies lacked subject-specific exposure measurements; use of biomarker measurements may not reflect long-term exposure levels; study selection bias
Kelsh et al. 2010; Workers from 20 studies	JEM and/or urine trichloroethylene	Not reported for individual studies	Strengths[b]: examined heterogeneity across studies; conducted sensitivity and influence analysis Limitations[b]: no information on potential impact of confounding factors; lack of quantitative exposure assessment

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

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Mandel et al. 2006; Workers from 7 studies	JEM	Not reported for individual studies	Strengths[b]: known trichloroethylene exposure; assessed heterogeneity Limitations[b]: variability across studies; limited exposure assessments; inconsistent results across studies; no adjustments for potential confounding factors
Ojajärvi et al. 2001; Workers from 5 studies	JEM and/or urine trichloroethylene	Not reported for individual studies	Strengths[b]: participants had known trichloroethylene exposure; publication bias unlikely Limitations[b]: no adjustments for potential confounding factors; exposure to other chemicals
Wartenberg et al. 2000; Workers from 4 studies	JEM and/or urine trichloroethylene	"Few traditional confounding variables (e.g., smoking, alcohol consumption)" were assessed in individual studies	Strengths[b]: High confidence in trichloroethylene exposure; long follow-up periods (17–36 years) Limitations[b]: exposure to other solvents; no assessment of other potential risk factors; short-term urine measurements of trichloroethylene does not reflect long-term exposure; "traditional" confounding factors not considered
Cohort studies			
Anttila et al. 1995; Workers (Finland)	Urine levels of trichloroethylene; no quantitative exposure	Age; sex; calendar year	Strengths: long follow-up period (26 years); data obtained from Finnish registries Limitations: limited statistical power; length of exposure uncertain; selection of participants not described; potential exposure to multiple solvents
Axelson et al. 1994; Male workers (Sweden)	Urine levels of trichloroethylene; no quantitative exposure	Age; calendar year	Strengths: biological monitoring conducted Limitations: exposure was considered "low" in most participants; uncertainty regarding duration of exposure; selection of participants not described
Blair et al. 1998; Aircraft workers (United States)	JEM; no quantitative exposure	Age; sex; race; date of hire; calendar year of death	Strengths[b]: large worker cohort; use of internal comparisons to minimize selection and socioeconomic bias; extended follow-up period Limitations[b]: exposures to multiple chemicals; no information on other risk factors (smoking, alcohol use, diet)

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene 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; no monitoring data; exposure to other solvents
Boice et al. 2006; Aircraft workers (United States)	JEM; no quantitative exposure	Birth year; year of hire; potential hydrazine exposure	Strengths: long follow-up period (up to 50 years); accounted for exposure to hydrazine Limitations: referent population not identified; no air or biological monitoring; possible exposure misclassification; did not adjust for smoking
Buhagen et al. 2016; Workers (Norway)	JEM; no quantitative exposure	None reported	Strengths[b]: long observation period (up to 50 years) Limitations[b]: exposure to other chemicals and solvents; did not adjusted for age, race, smoking, or other potential confounding factors
Hansen et al. 2001; Workers (Denmark)	Trichloroethylene in urine or breath; no quantitative exposure	Age; sex; calendar year	Strengths: biological monitoring to determine exposure; medical records obtained from national surveillance program Limitations: measurements of trichloroethylene below the level of detection for 5% of participants; did not adjust for smoking or exposure to other chemicals
Morgan et al. 1998; Workers (United States)	JEM; semi-quantitative exposure	Age; sex; race; calendar year	Strengths: semi-quantitative exposure Limitations: potential exposure misclassification
Raaschou-Nielsen et al. 2003; Workers (Denmark)	JEM; no quantitative exposure	Age; sex; calendar year	Strengths: medical records obtained from national surveillance program Limitations: only a small fraction of the cohort exposed to trichloroethylene; no monitoring data; did not adjust for smoking or exposure to other chemicals

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

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Radican et al. 2008; Aircraft maintenance workers (United States); follow-up to Blair et al. 1998	JEM; no quantitative exposure	Age; sex; race	Strengths[b]: large study population; long follow-up period (1952–2000) Limitations[b]: small number of trichloroethylene-exposed deaths and reduced statistical power; did not control for smoking or exposure to other chemicals and solvents; exposure based on job descriptions and other historical information may result in misclassification of exposure
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
Zhao et al. 2005; Aerospace workers (United States)	JEM; no quantitative exposure	Time since first employment; SES; age at event	Strengths[b]: use of cancer registry; evaluated incidence and mortality Limitations[b]: potential exposure misclassification; no information on jobs held before or after employment at facility; no adjustment for smoking; exposure to other chemicals and solvents
Pooled case-control studies			
Cocco et al. 2013; Workers (4 European studies)	JEM; semi-quantitative exposure	Age; sex; study area	Strengths[b]: large study size; high-quality exposure assessment; no heterogeneity across studies; histological confirmed diagnosis Limitations[b]: small number of exposed cases; individual studies used different designs and controls; did not assess exposure to other chlorinated solvents; did not adjust for other confounders (smoking, education, BMI, family history of hematopoietic cancers)

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

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Case-control studies			
Brüning et al. 2003; Workers (Germany)	JEM; no quantitative exposure	Age; gender; smoking	Strengths[b]: exposure assessment classified for each participant using JEM Limitations[b]: small number of participants; could not assess confounding from other chemicals or solvents; did not control for hypertension; potential for exposure misclassification
Charbotel et al. 2006; Workers (France)	JTEM; semi-quantitative exposure	Age; sex; BMI; smoking	Strengths: high exposure prevalence; detailed exposure assessment Limitations: low participation rate
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; semi-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
Cocco et al. 2010; Workers (multiple countries)	JEM; no quantitative exposure	Age; gender; education; study center	Strengths: detailed exposure assessment Limitations: low response rate from two study centers
Costantini et al. 2008; Workers (Italy)	JEM; no quantitative exposure	Age; gender; education; study area	Strengths[b]: detailed exposure assessment Limitations[b]: none reported

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

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
DeRoos et al. 2001; Children (United States and Canada)	Self-reported exposure and JEM; no quantitative exposure	Child's age; maternal race; maternal age; maternal education	Strengths[b]: evaluation of exposure misclassification Limitations[b]: potential for "false negative" exposure classification
Dosemeci et al. 1999; Workers (United States)	JEM; no quantitative exposure	Age; smoking; hypertension; diuretic use; use of anti-hypertension medication; BMI	Strengths: large sample size; detailed work and task histories Limitations: lack of direct exposure information; potential exposure misclassification due to next-of-kin interviews
Dumas et al. 2000; Workers (Canada)	JEM; no quantitative exposure	Age; education; respondent status; smoking; beer consumption; BMI	Strengths[b]: histologically confirmed cancer incidence Limitations[b]: potential exposure misclassification; limited statistical power due to low exposure prevalence; small number of participants; included several non-occupational variables as co-variates
Fredriksson et al. 1989; Workers (Sweden)	JEM; no quantitative exposure	Age; sex; scoring index of physical activity	Strengths: use of cancer registry to define diagnosis of rectal cancer; obtained specific information regarding job duties for all jobs Limitations: exposure potential obtained from mailed questionnaires; potential for exposure misclassification; low exposure prevalence to trichloroethylene
Gold et al. 2011; Workers (United States)	JEM; hours of weekly exposure; estimated cumulative exposure	Sex; age; race; education; cancer registry	Strengths[b]: use of detailed occupational information to improve assessment of solvent exposure Limitations[b]: 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
Greenland et al. 1994; Workers (United States)	JEM; no quantitative exposure	Age; year of death	Strengths: none reported Limitations: high likelihood of misclassification bias; deaths likely to be underestimated; missing information from approximately 35% of participants for participants with death in the earlier years; low statistical power

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

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
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
Heineman et al. 1994; Workers (United States)	JEM; no quantitative exposure	Age; year of death; study area	Strengths: large sample size; detailed work histories, including tasks; comprehensive exposure analysis Limitations: lack of direct exposure information; potential exposure inaccuracies for information obtained from next of kin
Kernan et al. 1999; Workers (United States)	JEM; no quantitative exposure	Age; metropolitan status; region of residence; marital status	Strengths: large sample size (total cases: 63,097; total controls: 252,386) Limitations: likely exposure misclassification; total cases per race and sex not reported
Krishnadasan et al. 2007; Workers (Denmark)	JEM; semi-quantitative exposure	Age at diagnosis; occupational activity; pay status; other chemicals (benzene, polycyclic aromatic hydrocarbons, mineral oil, hydrazine)	Strengths: long follow-up period for morality; provided semi-quantitative exposure assessment (low, moderate, high); adjustment for exposure to other chemicals Limitations: potential for exposure misclassification; did not control for race; smoking history not available for all participants
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]: almost all participants exposed to other solvents; small number of exposed women compared to exposed men, leading to wide confidence intervals
McKinney et al. 1991; Children of workers (United Kingdom)	JEM; no quantitative exposure	Age; sex; region of residency at diagnosis	Strengths: none reported Limitations: low prevalence of trichloroethylene exposure; discordant pairs limited statistical power
Miligi et al. 2006; Workers (Italy)	JEM; no quantitative exposure	Age; sex; education; area	Strengths: none reported Limitations: low statistical power due to low prevalence of exposure; bias likely due to unblinded interviewers

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

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Moore et al. 2010; Workers (4 European countries)	JEM; no quantitative exposure	Age; sex; center	Strengths: high confidence in exposure Limitations: low prevalence of exposure
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
Nordstrom et al. 1998; Workers (Sweden)	JEM; no quantitative exposure	Age; sex; county of residence	Strengths: histologically confirmed cases; use of national cancer registry Limitations: limited statistical power due to low exposure prevalence and small number of participants
Persson and Fredriksson 1999; Workers (Sweden)	JEM; no quantitative exposure	Age; sex	Strengths: histologically confirmed cases; use of national cancer registry Limitations: small number of participants; potential for exposure misclassification
Pesch et al. 2000; 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: Most cases did not have substantial exposure
Pesch et al. 2000; 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. 2011; Workers (United States)	JEM; semi-quantitative exposure	Age; sex; race; education; group and center	Strengths: detailed exposure assessment; histologically confirmed cases; estimated semi-quantitative exposure Limitations: potential misclassification

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

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
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
Saberi Hosnijeh et al. 2013; Workers (Europe)	JEM; semi-quantitative exposure	Age at recruitment; sex; country; smoking status; alcohol intake	Strengths[b]: long follow-up period Limitations[b]: no information on duration of exposure; lack of information on full occupational histories; potential for exposure misclassification
Shu et al. 1999; Children of workers (United States, Canada, and Australia)	JEM; no quantitative exposure	Child's age at diagnosis; sex; year of diagnosis; maternal age and education	Strengths: none reported Limitations: potential misclassification; no description of jobs with possible trichloroethylene exposure; low prevalence of exposure to trichloroethylene limits statistical power
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

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

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Wang et al. 2009; Workers (United States)	JEM; no quantitative exposure	Age; race; family history of hematopoietic cancers; alcohol consumption	Strengths: validated JEM Limitations: potential for exposure misclassification; low prevalence of high intensity exposure limits statistical power

[a]Unless otherwise noted, study strengths and limitations were noted by EPA (2011e).
[b]Study strengths and limitations were noted by the study authors.

BMI = body mass index; HPV = 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

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 trichloroethylene concentrations in individual workplaces. One pooled case-control study (Cocco et al. 2013), one cohort study (Morgan et al. 1998), and five case-control studies (Charbotel et al. 2006; Christensen et al. 2013; Krishnadasan et al. 2007; Purdue et al. 2011; Saberi-Hosnijeh et al. 2013) provided semi-quantitative estimates of exposure. The remaining studies provided qualitative descriptions of exposure (e.g., exposed/not exposed, probable, substantial, low-moderate-high) based on job-exposure matrices and/or occupational history from union records, census records, and/or participant questionnaires. Exposure conditions most likely differ widely between study populations (e.g., exposure levels, peak exposures), which could explain different study outcomes. For most study participants, it is likely that exposure included other solvents or chemicals.

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. Most studies adjusted risk estimates for age, sex, and race. Studies by Christensen et al. (2013), Neta et al. (2012), and Silver et al. (2014) provided the most comprehensive assessment of confounders, and other studies considered several confounders (Dosemeci et al. 1999; Dumas et al. 2000; Krishnadasan et al. 2007; Mattei et al. 2014). For carcinogenicity assessments of trichloroethylene, it is important to consider the potential influence of exposure to other solvents and chemicals (EPA 2012a). However, relatively few studies considered smoking status (Brüning et al. 2003; Charbotel et al. 2006; Dosemeci et al. 1999; Dumas et al. 2000; Mattei et al. 2014; Neta et al. 2012; Pesch et al. 2000; Purdue et al. 2017; Saberi-Hosnijeh et al. 2013) or concomitant exposure to other chemicals (Boice et al. 2006; Christensen et al. 2013; Hadkhale et al. 2017; Krishnadasan et al. 2007; Mattei et al. 2014; Neta et al. 2012; Silver et al. 2014). Only one study considered family history of cancers as a confounding factor (Wang et al. 2009). One study did not list any confounding factors (Buhagen et al. 2016).

Study results based on cancer type are shown in the following figures: kidney cancer (Figure 3-2); non-Hodgkin's lymphoma (Figure 3-3); liver cancer (Figure 3-4); esophageal cancer (Figure 3-5); stomach cancer (Figure 3-6); colorectal cancer (Figure 3-7); bladder cancer (Figure 3-8); pancreatic cancer (Figure 3-9); lung cancer (Figure 3-10); breast cancer (Figure 3-11); female reproductive cancer (Figure 3-12); male reproductive cancer (Figure 3-13); central nervous system cancer (Figure 3-14); multiple myeloma (Figure 3-15); and leukemia (Figure 3-16).

Figure 3-2. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Kidney Cancer

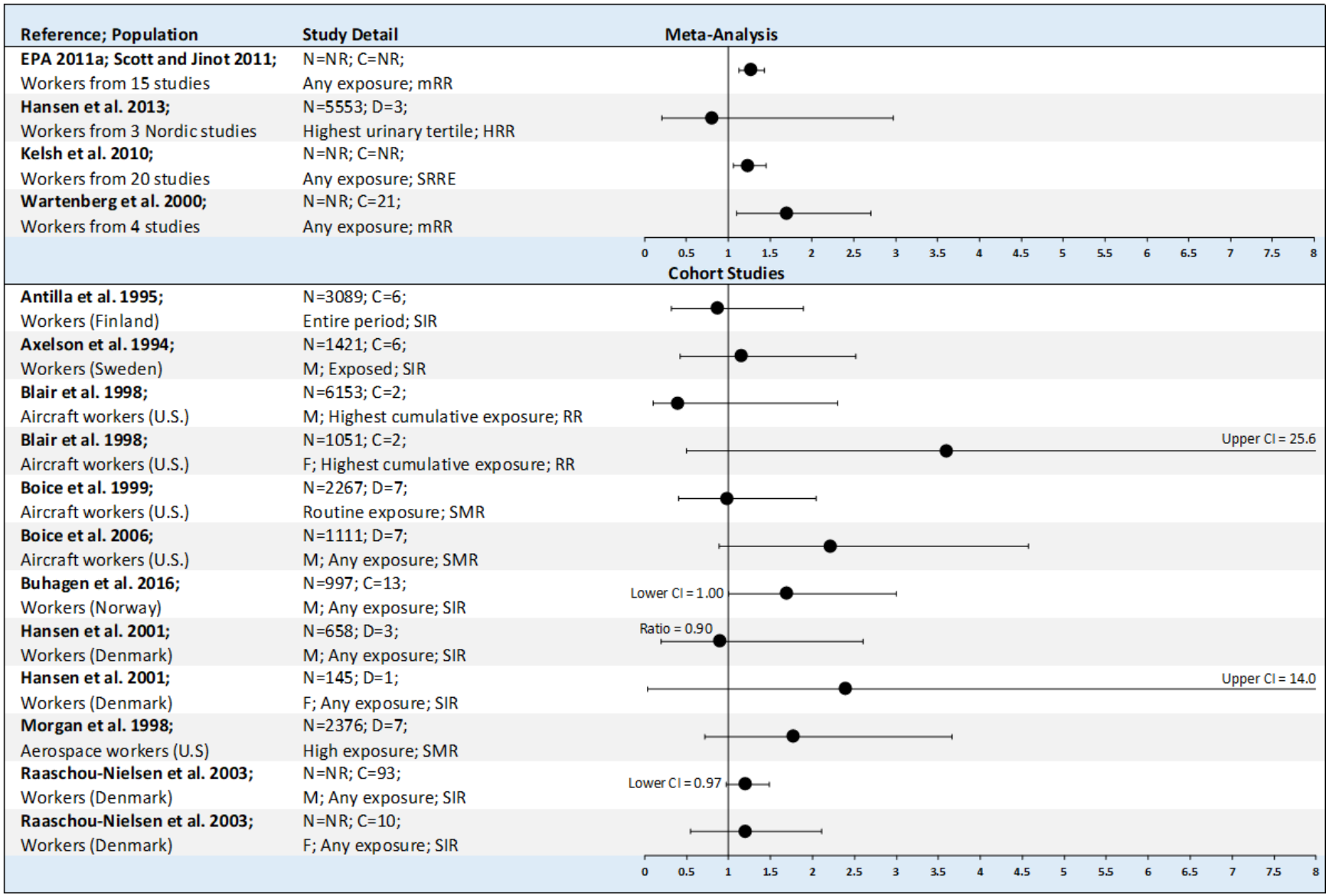
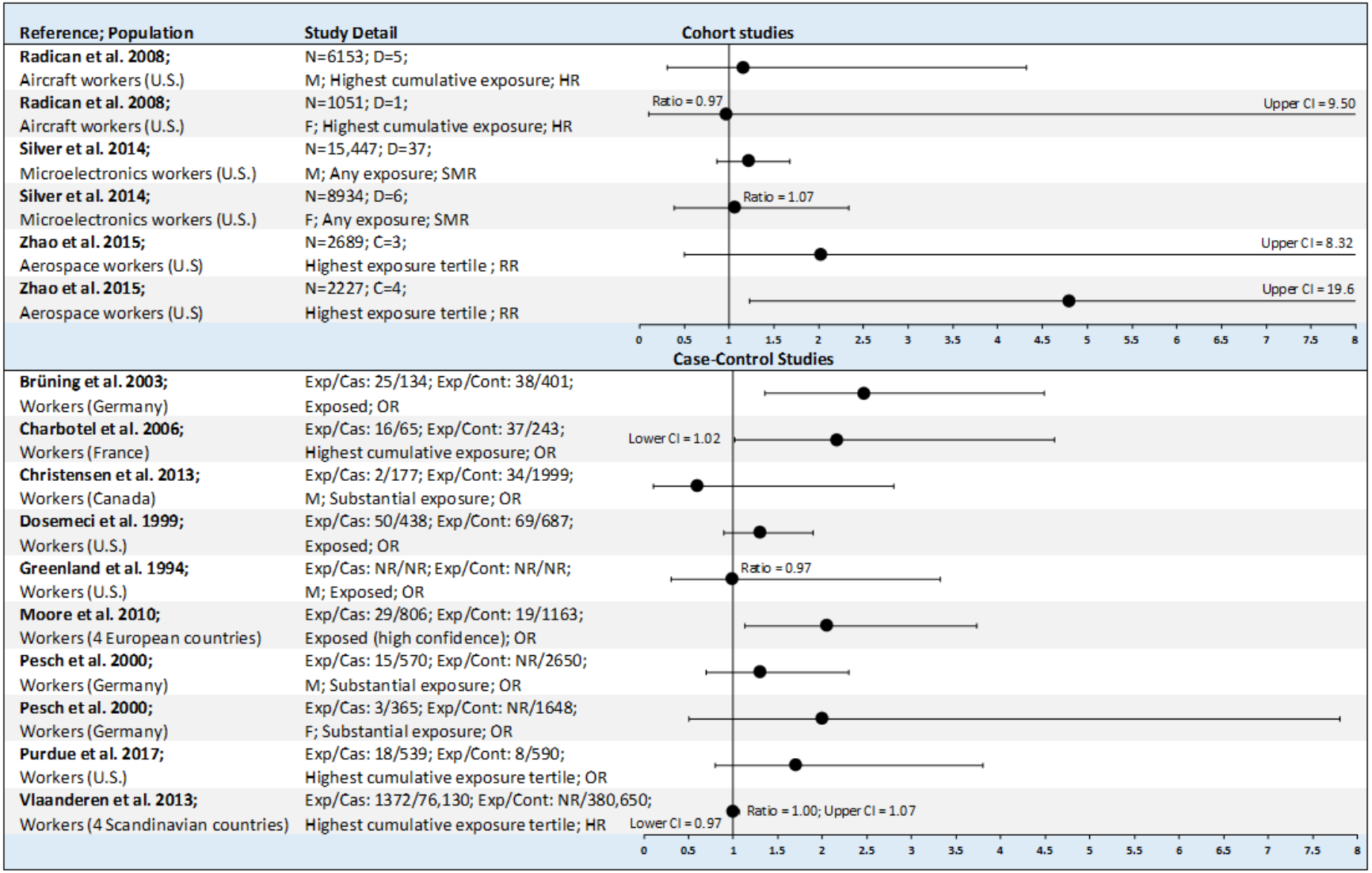


Figure 3-2 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Kidney Cancer



= risk estimate and 95% CI

C = number with kidney cancer; CI = confidence interval; D = number of deaths due to kidney 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; mRR = meta relative risk; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRRE = summary relative risk estimate

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

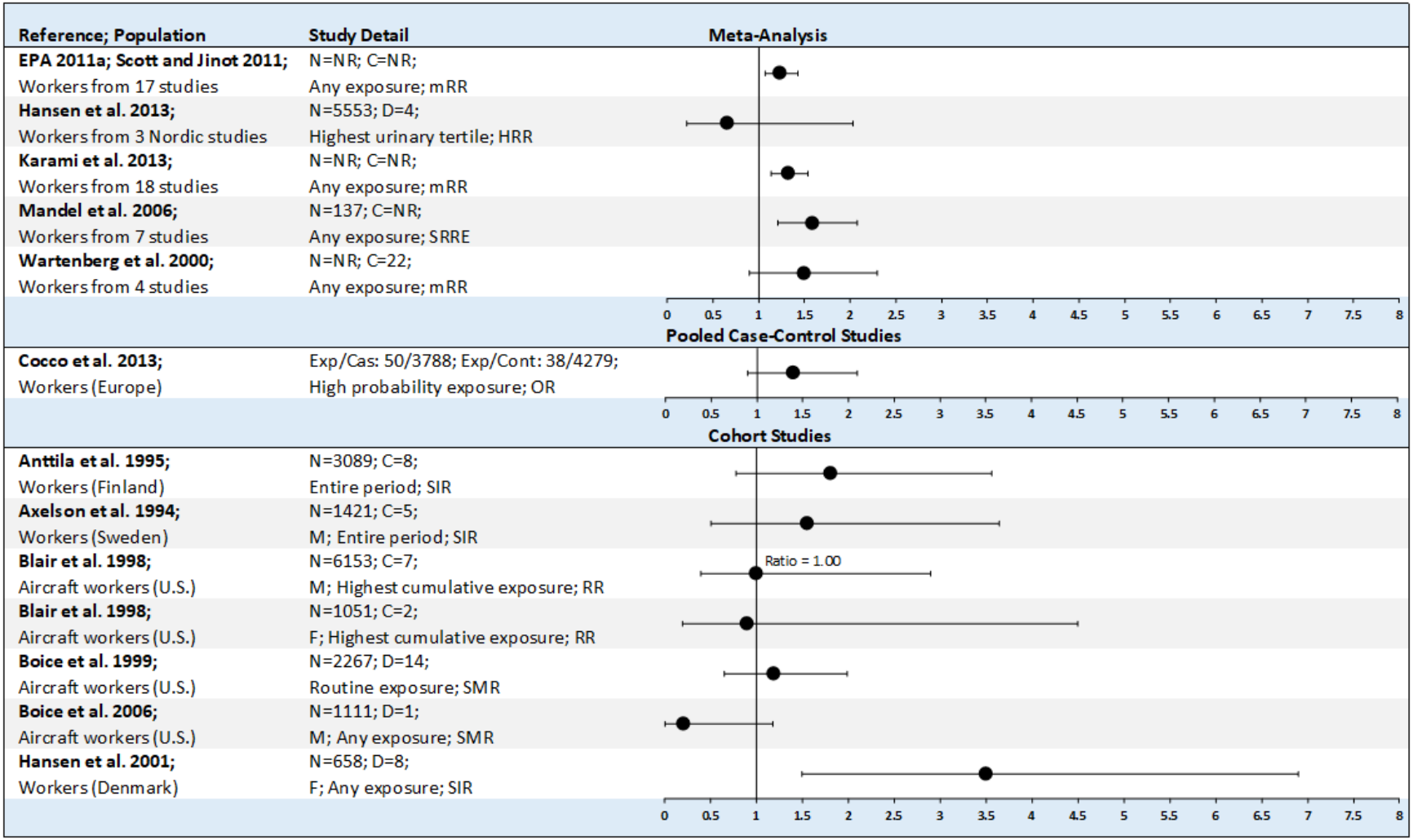
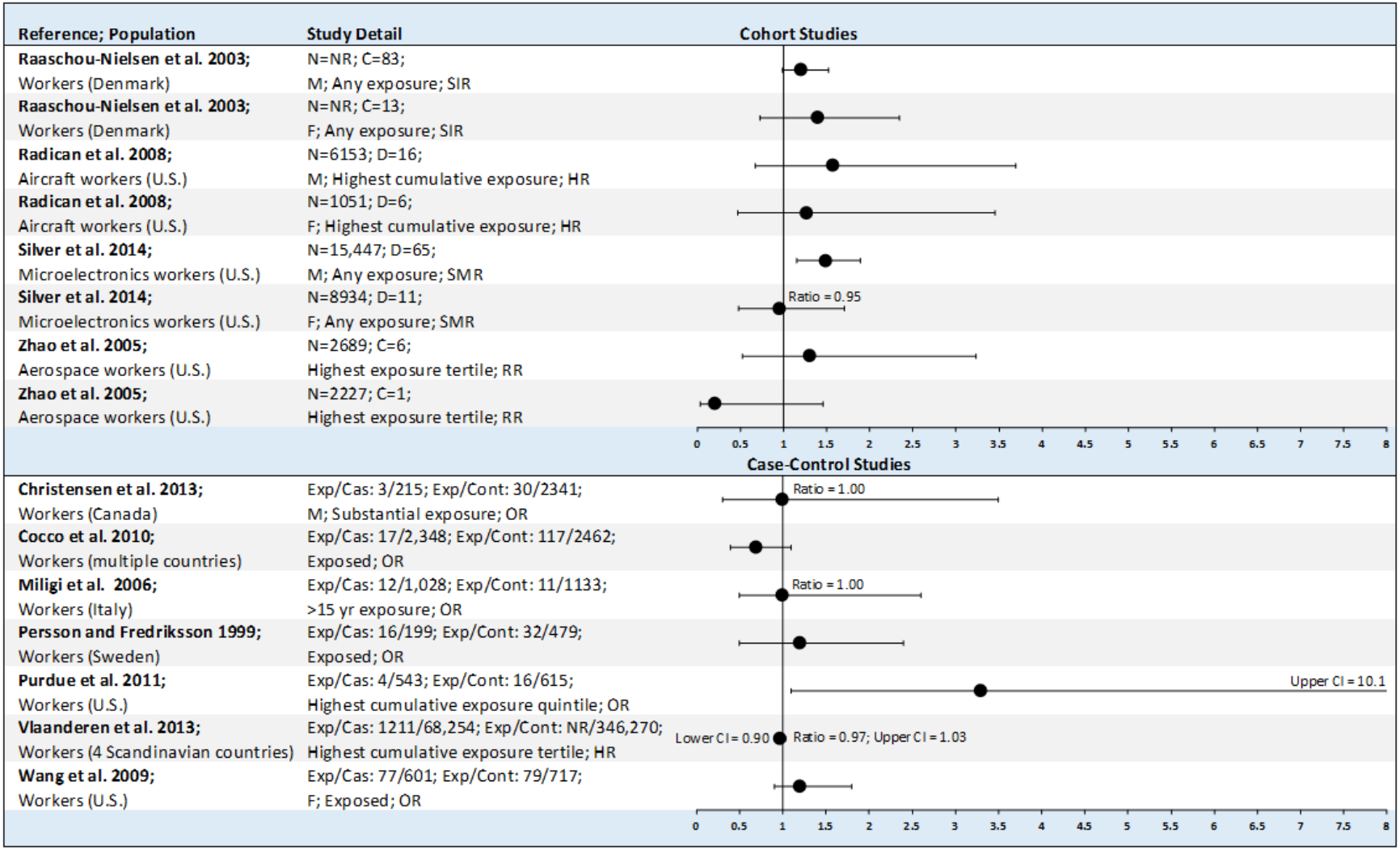


Figure 3-3 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Non-Hodgkin's Lymphoma



= risk estimate and 95% CI

C = number with non-Hodgkin's lymphoma; CI = confidence interval; D = number of deaths due to non-Hodgkin's lymphoma; 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; mRR = relative risk ratio; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRRE = summary relative risk estimate; yr = year

Figure 3-4. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Liver Cancer

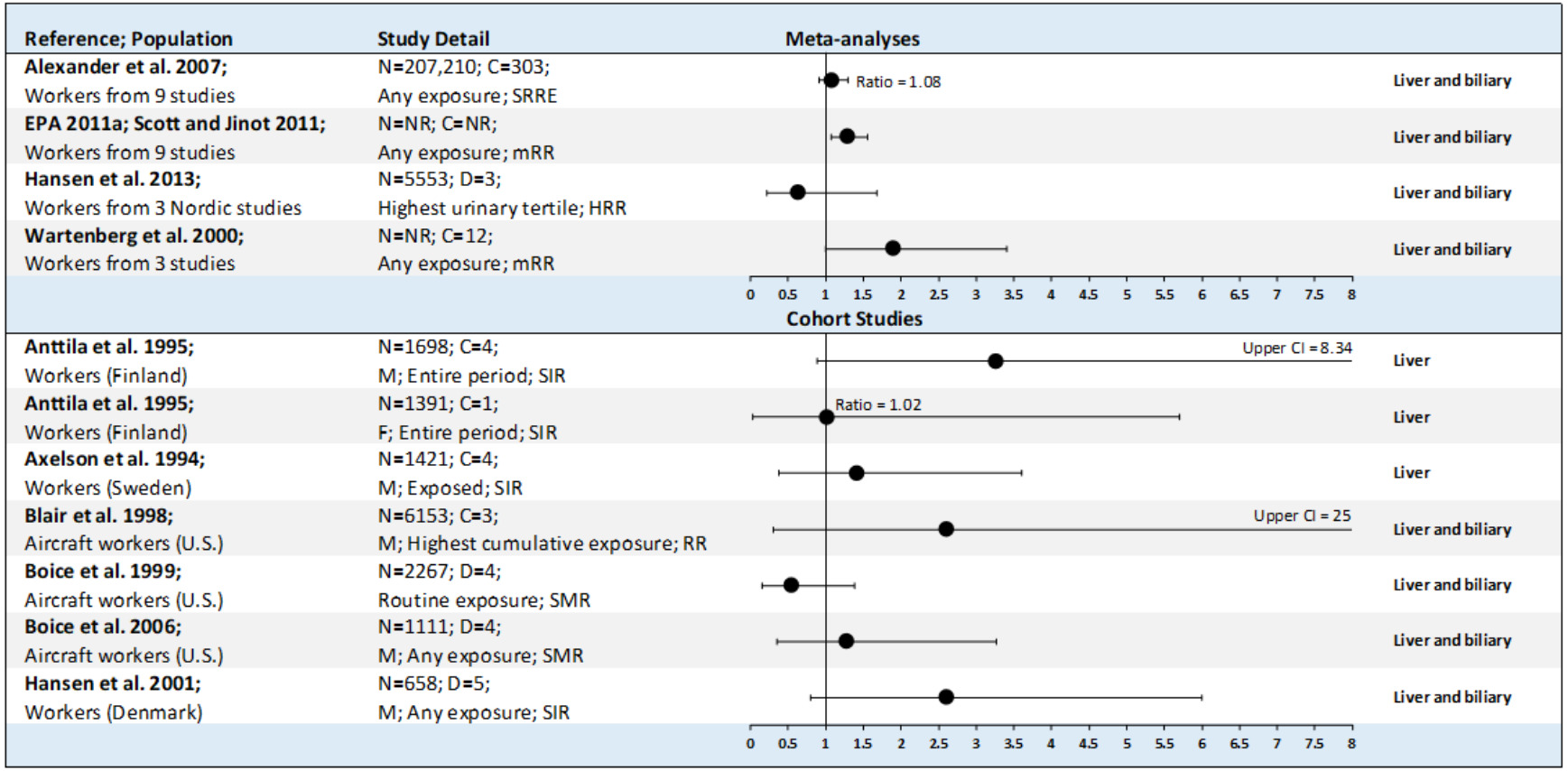


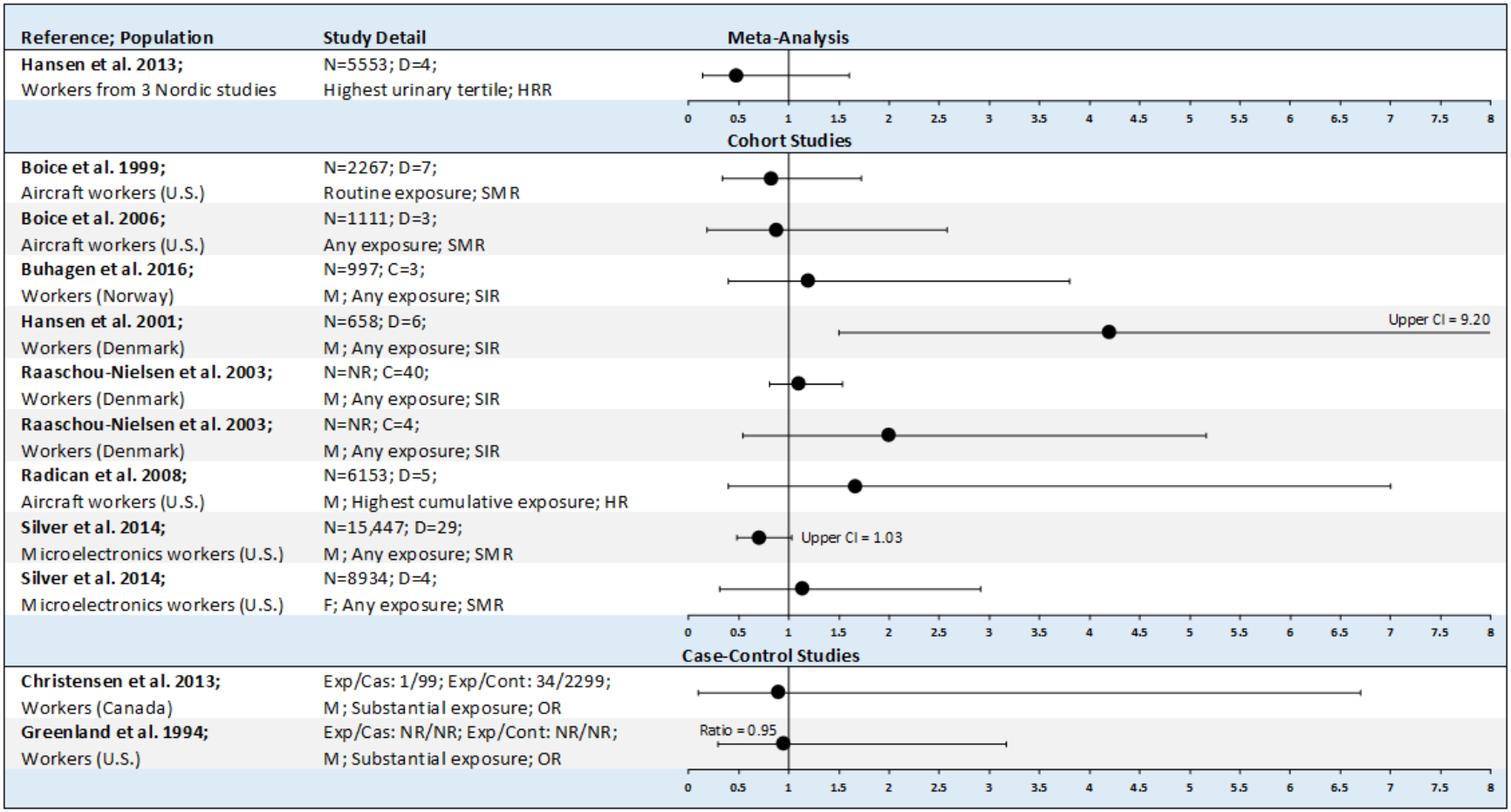
Figure 3-4 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Liver Cancer

Reference; Population	Study Detail	
Cohort Studies		
Morgan et al. 1998; Aerospace workers (U.S.)	N=2376; D=3; High exposure; SMR	Lower CI = 0.78; Ratio = 0.78 — Liver and biliary
Raaschou-Nielsen et al. 2003; Workers (Denmark)	N=NR; C=27; M; Any exposure; SIR	Ratio = 1.10 — Liver
Raaschou-Nielsen et al. 2003; Workers (Denmark)	N=NR; C=7; F; Any exposure; SIR	Liver
Radican et al. 2008; Aircraft workers (U.S.)	N=6153; D=12; M; Highest cumulative exposure; HR	Liver and biliary
Radican et al. 2008; Aircraft workers (U.S.)	N=1051; D=2; F; Highest cumulative exposure; HR	Ratio = 0.98 — Liver and biliary
Silver et al. 2014; Microelectronics workers (U.S.)	N=15,447; D=19; M; Any exposure; SMR	Liver and biliary
Silver et al. 2014; Microelectronics workers (U.S.)	N=8934; D=9; F; Any exposure; SMR	Liver and biliary
		0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8
Case-Control Studies		
Christensen et al. 2013; Workers (Canada)	Exp/Cas: 1/33; Exp/Cont: 38/1834; M; Substantial exposure; OR	Upper CI = 18.00 — Liver
Greenland et al. 1994; Workers (U.S.)	Exp/Cas: NR/NR; Exp/Cont: NR/NR; M; Exposed; OR	Liver
Vlaanderen et al. 2013; Workers (4 Scandinavian countries)	Exp/Cas: 422/23,896; Exp/Cont: NR/119,480; Highest cumulative exposure tertile; HR	Lower CI = 0.90; Ratio = 1.00; Upper CI = 1.10 — Liver
		0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8

—●— = risk estimate and 95% CI

C = number with liver cancer; CI = confidence interval; D = number of deaths due to liver 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; mRR = meta relative risk; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRRE = summary relative risk estimate

Figure 3-5. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Esophageal Cancer



= risk estimate and 95% CI

C = number with esophageal cancer; CI = confidence interval; D = number of deaths due to esophagael 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 = number of participants; NR = not reported; OR = odds ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-6. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Stomach Cancer[a]

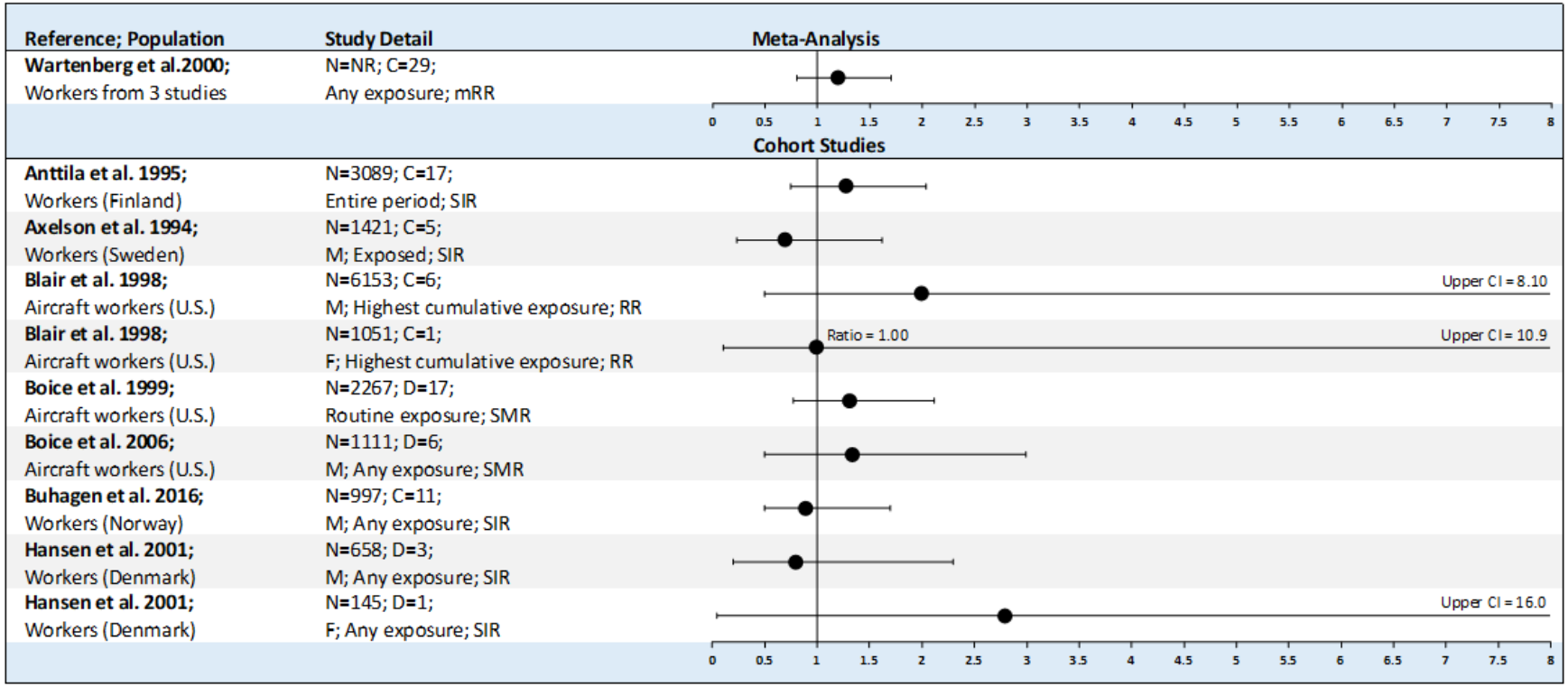
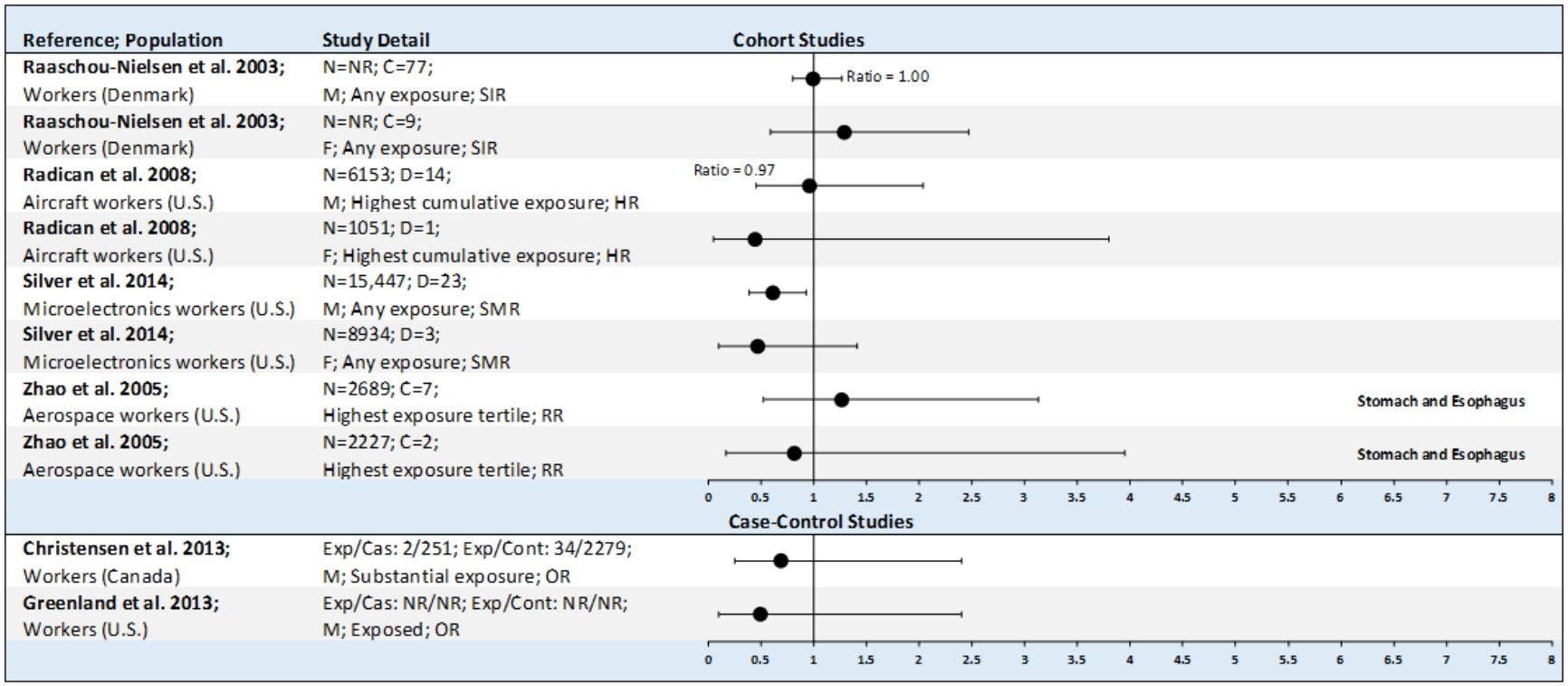


Figure 3-6 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Stomach Cancer[a]



[a]Unless otherwise noted, risk estimates are for stomach cancer only

—●— = risk estimate and 95% CI

C = number with stomach cancer; CI = confidence interval; D = number of deaths due to stomach 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; mRR = meta relative risk; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-7. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Colorectal Cancer

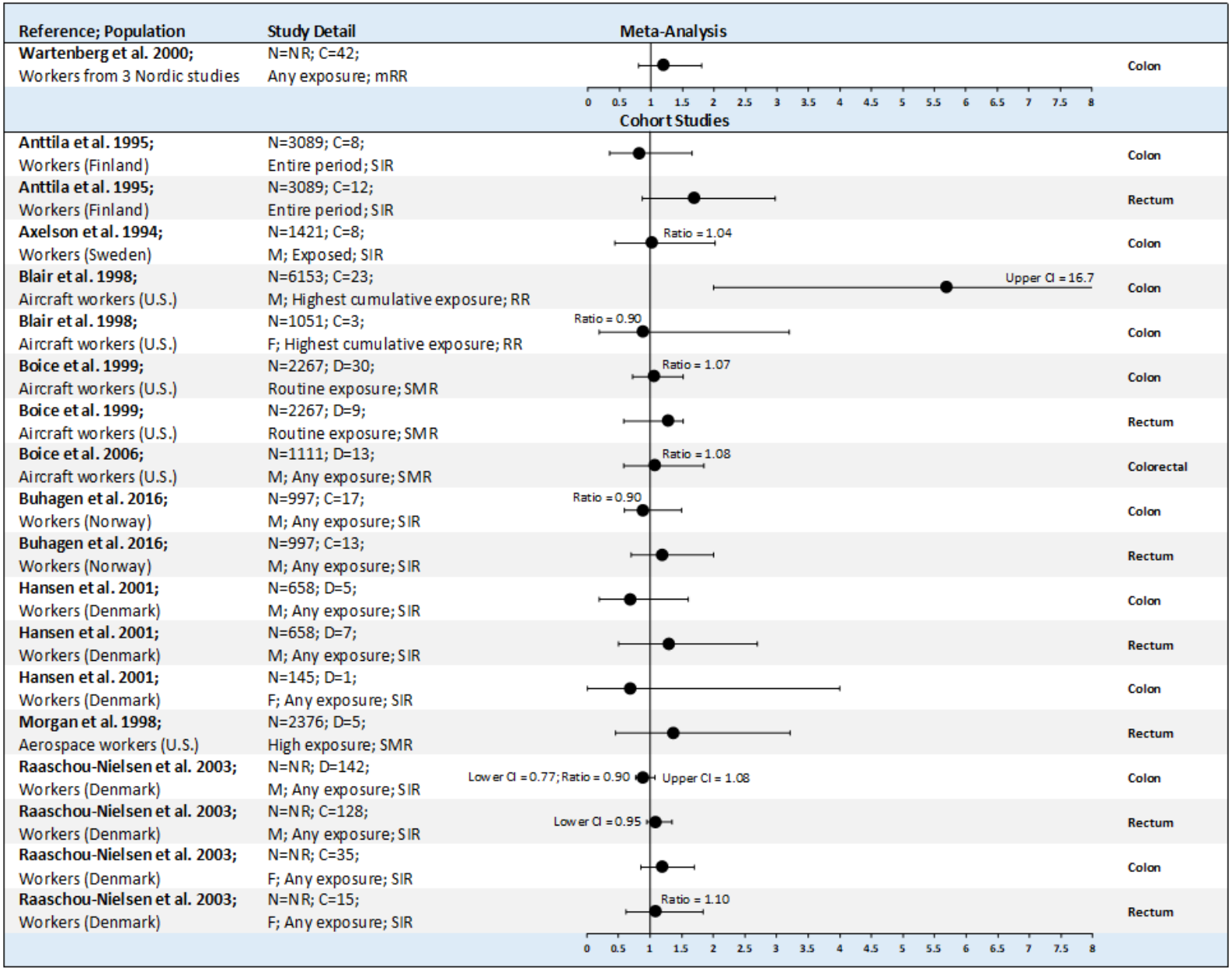
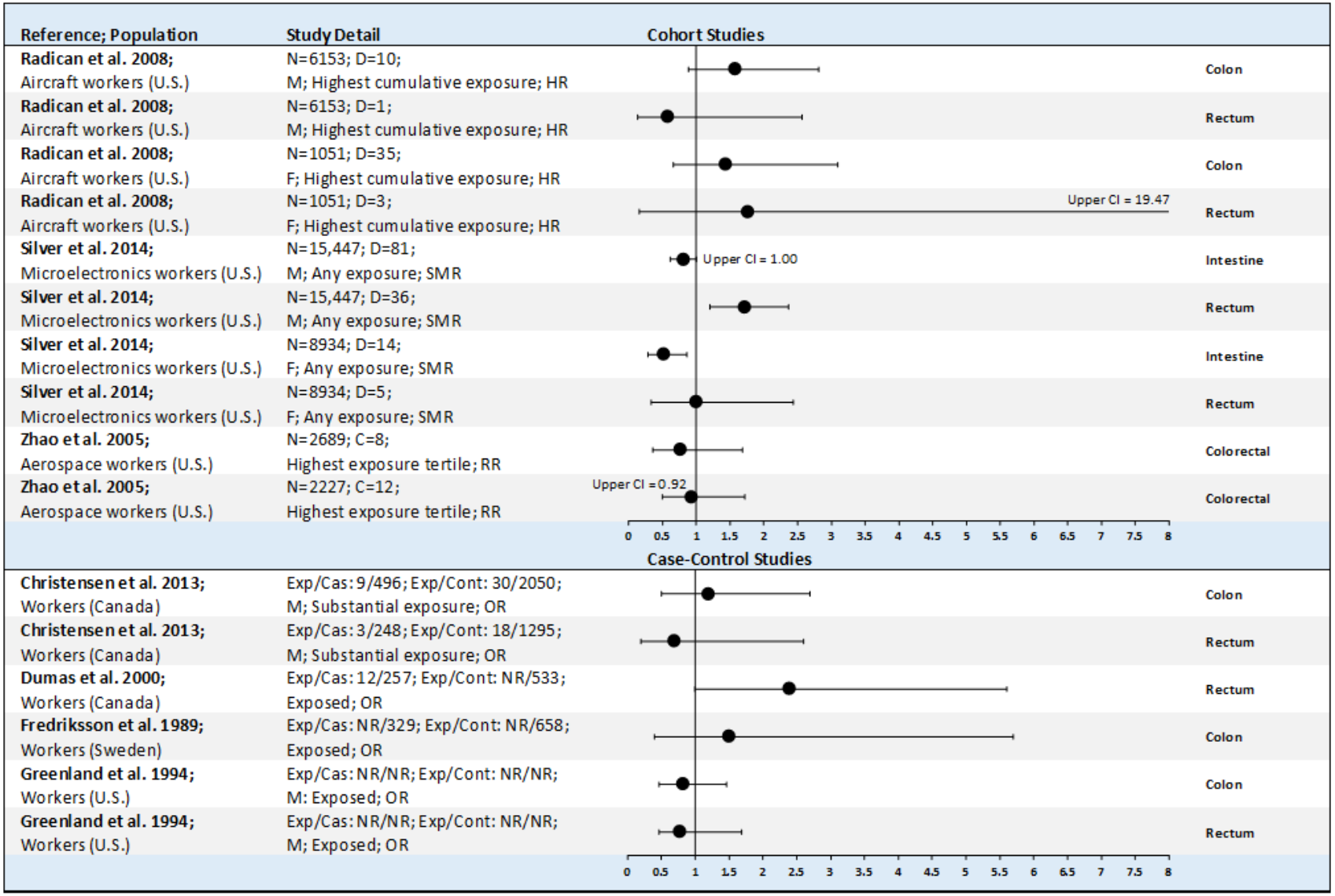


Figure 3-7 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Colorectal Cancer



= risk estimate and 95% CI

C = number with colorectal cancer; CI = confidence interval; D = number of deaths due to colorectal 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; mRR = relative risk ratio; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-8. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Bladder Cancer

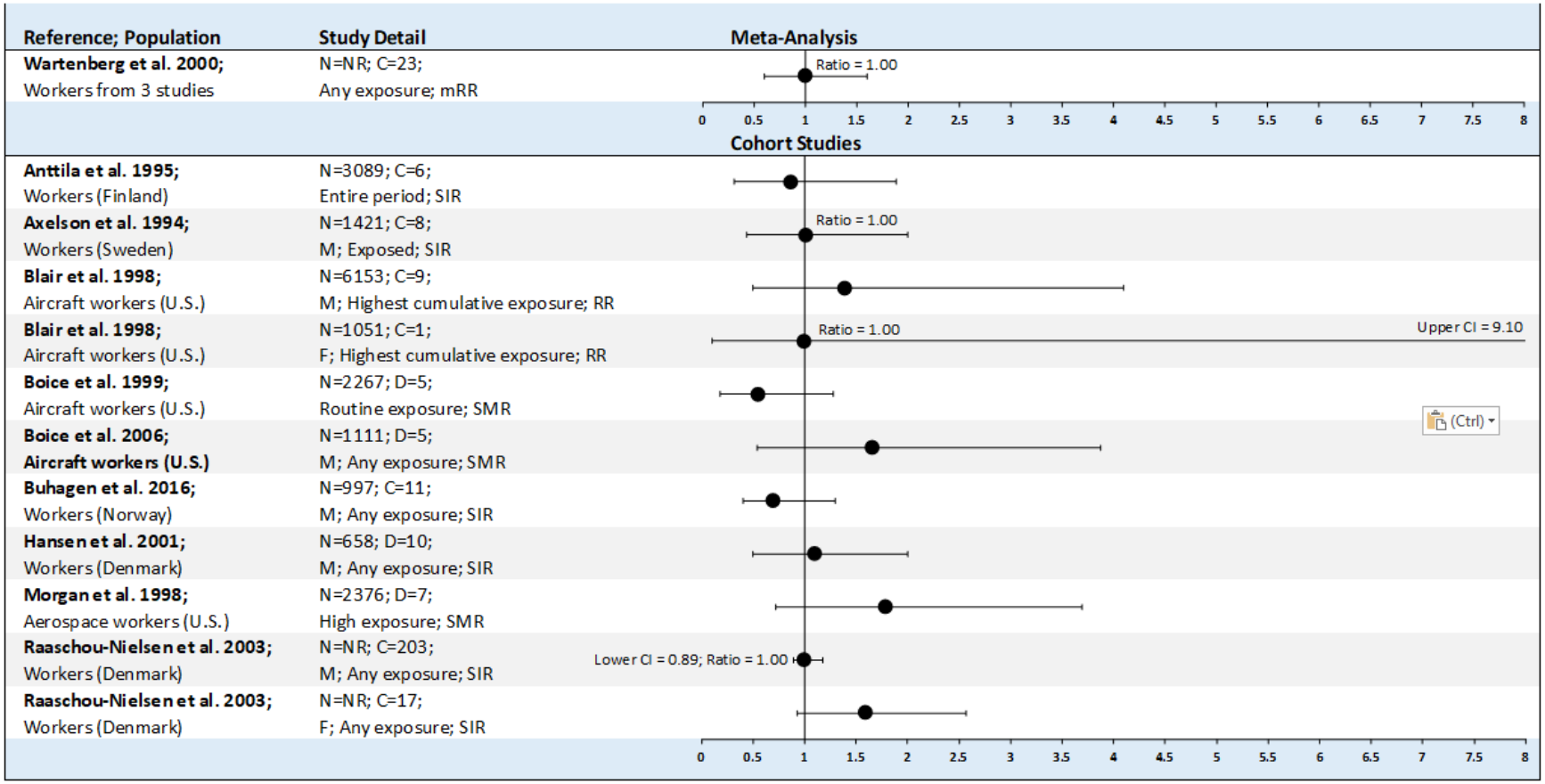
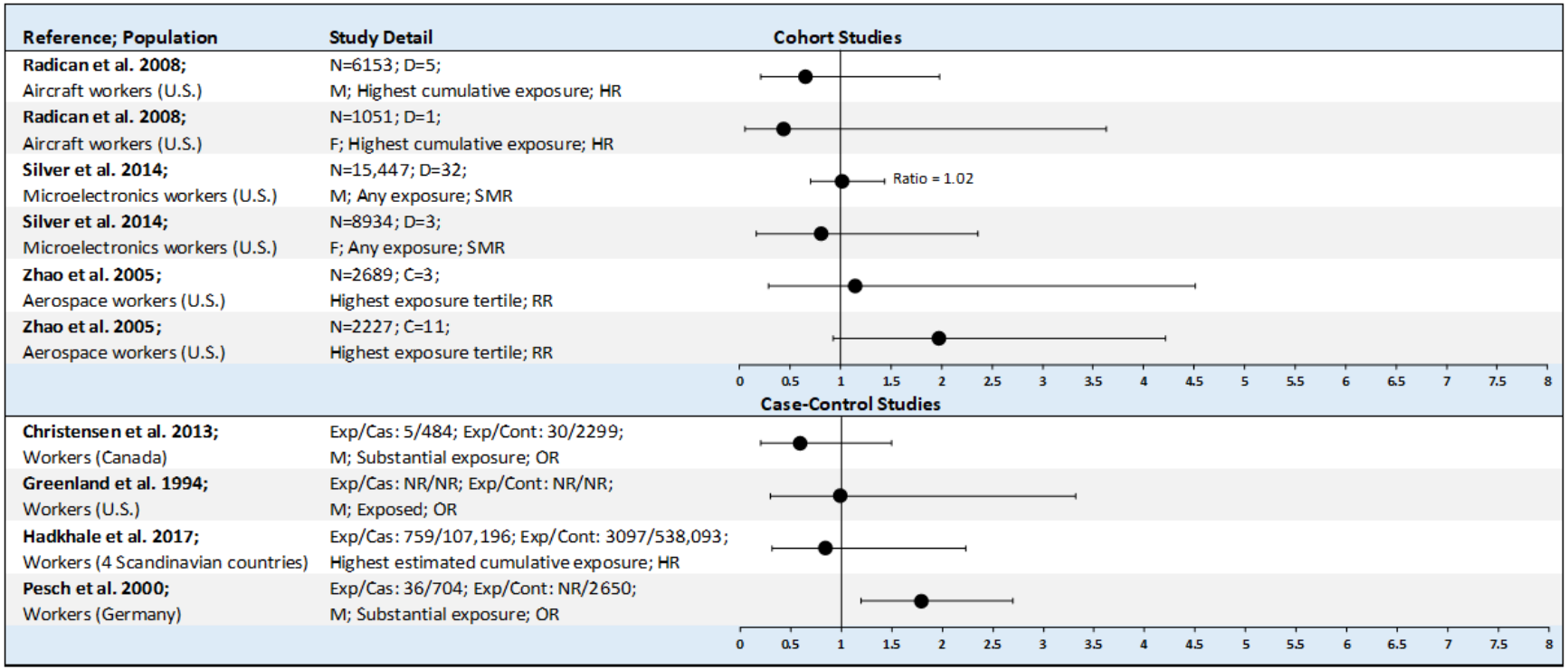


Figure 3-8 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Bladder Cancer



= risk estimate and 95% CI

C = number with bladder cancer; CI = confidence interval; D = number of deaths due to bladder 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; mRR = meta relative risk; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-9. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Pancreatic Cancer

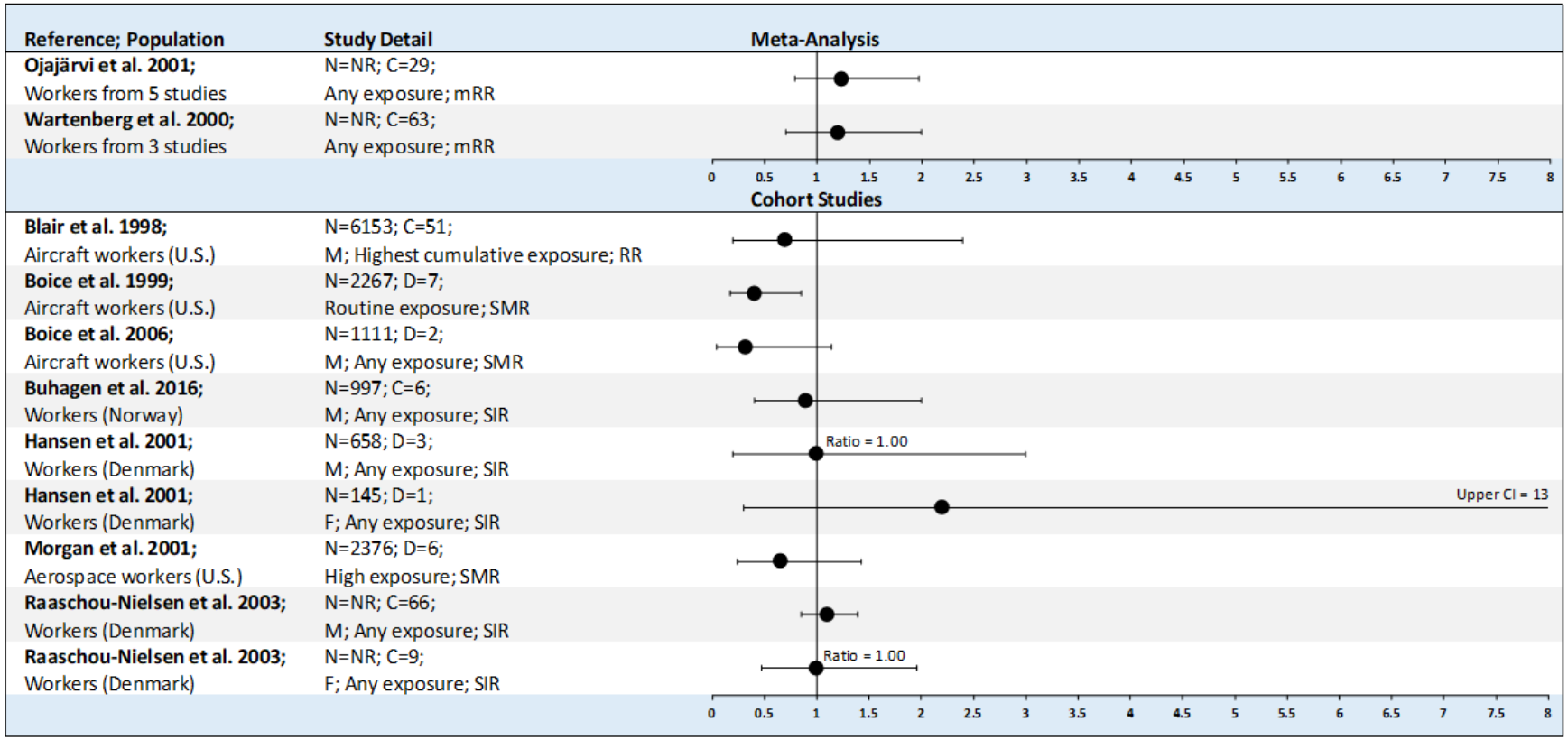
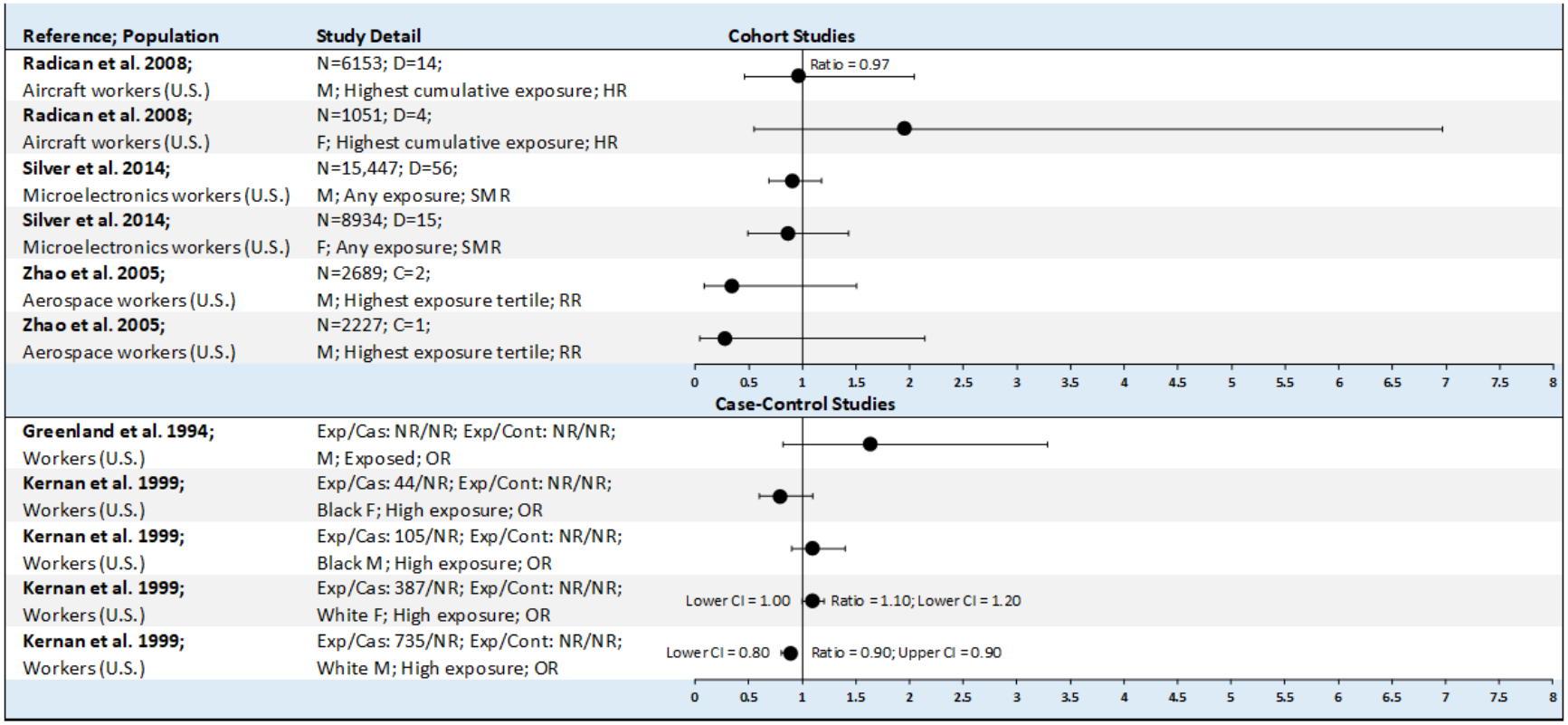


Figure 3-9 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Pancreatic Cancer



= risk estimate and 95% CI

C = number with pancreatic cancer; CI = confidence interval; D = number of deaths due to pancreatic 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; mRR = meta relative risk; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-10. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Lung Cancer

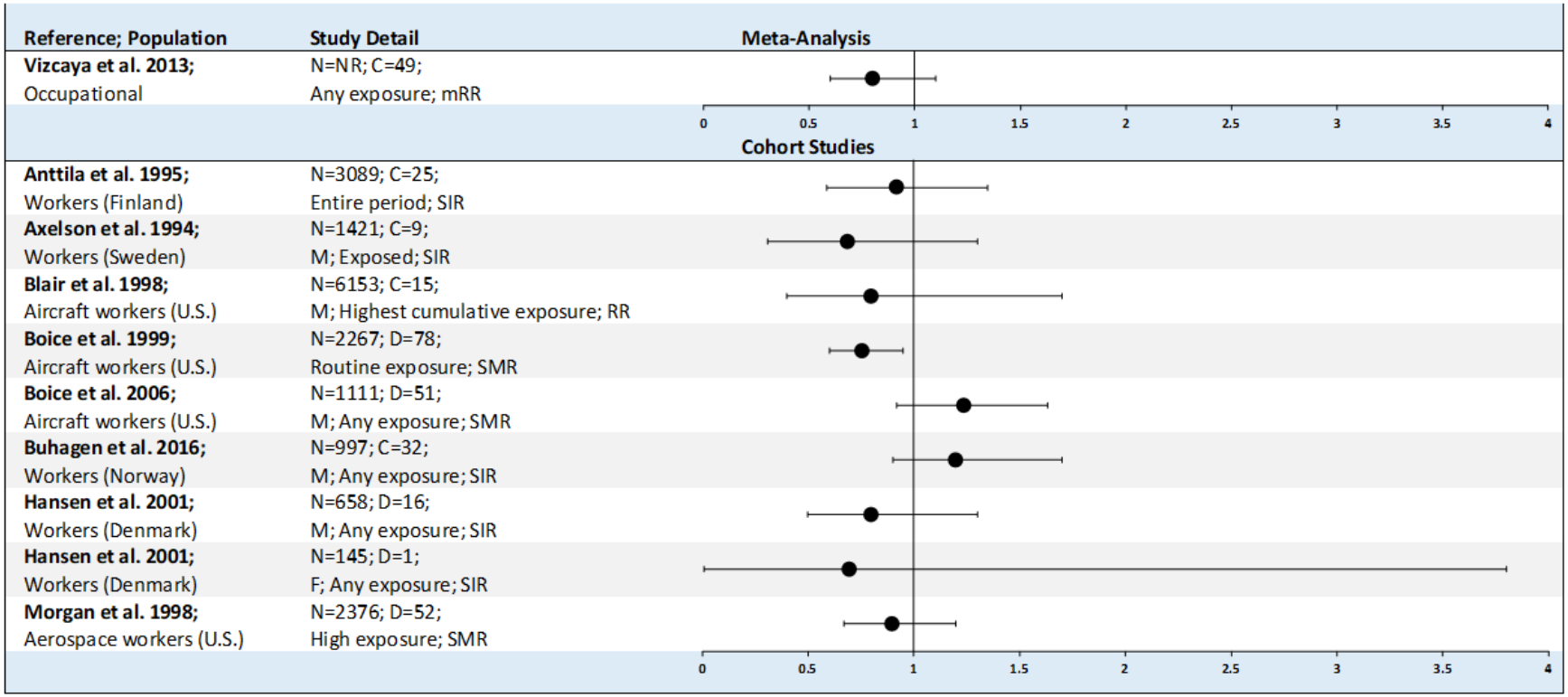
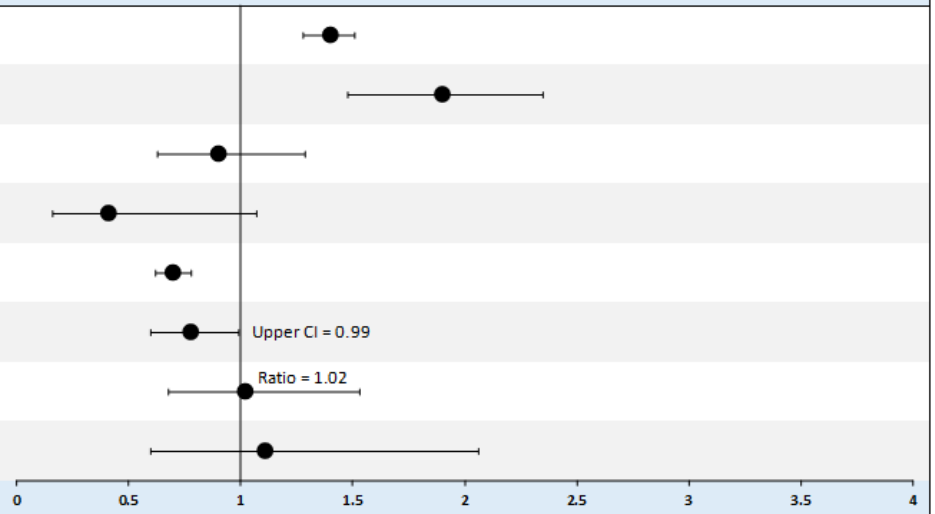


Figure 3-10 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Lung Cancer

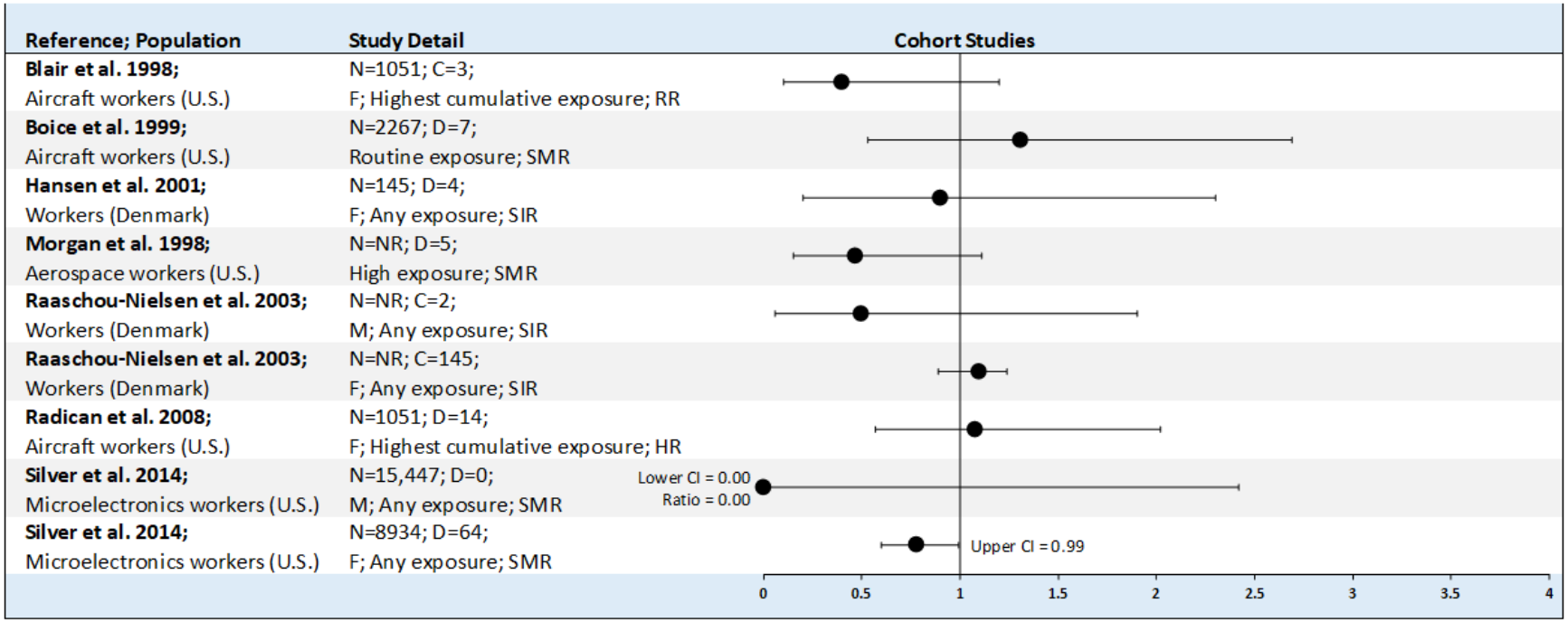
Reference; Population	Study Detail
Cohort Studies	
Raaschou-Nielsen et al. 2003; Workers (Denmark)	N=NR; C=559; M; Any exposure; SIR
Raaschou-Nielsen et al. 2003; Workers (Denmark)	N=NR; C=73; F; Any exposure; SIR
Radican et al. 2008; Aircraft workers (U.S.)	N=6153; D=67; M; Highest cumulative exposure; HR
Radican et al. 2008; Aircraft workers (U.S.)	N=1051; D=5; F; Highest cumulative exposure; HR
Silver et al. 2014; Microelectronics workers (U.S.)	N=15,447; D=287; M; Any exposure; SMR
Silver et al. 2014; Microelectronics workers (U.S.)	N=8934; D=64; M; Any exposure; SMR
Zhao et al. 2005; Aerospace workers (U.S.)	N=2689; C=33; Highest exposure tertile; RR
Zhao et al. 2005; Aerospace workers (U.S.)	N=2227; C=14; Highest exposure tertile; RR
Case-Control Studies	
Greenland et al. 1994; Workers (U.S.)	Exp/Cas: NR/NR; Exp/Cont: NR/NR; M; Exposed; OR
Mattei et al. 2014; Workers (France)	Exp/Cas: 556/2274; Exp/Cont: 614/2780; M; Exposed; OR
Mattei et al. 2014; Workers (France)	Exp/Cas: 30/622; Exp/Cont: 39/760; F; Exposed; OR



= risk estimate and 95% CI

C = number with lung cancer; CI = confidence interval; D = number of deaths due to lung 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; mRR = relative risk ratio; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

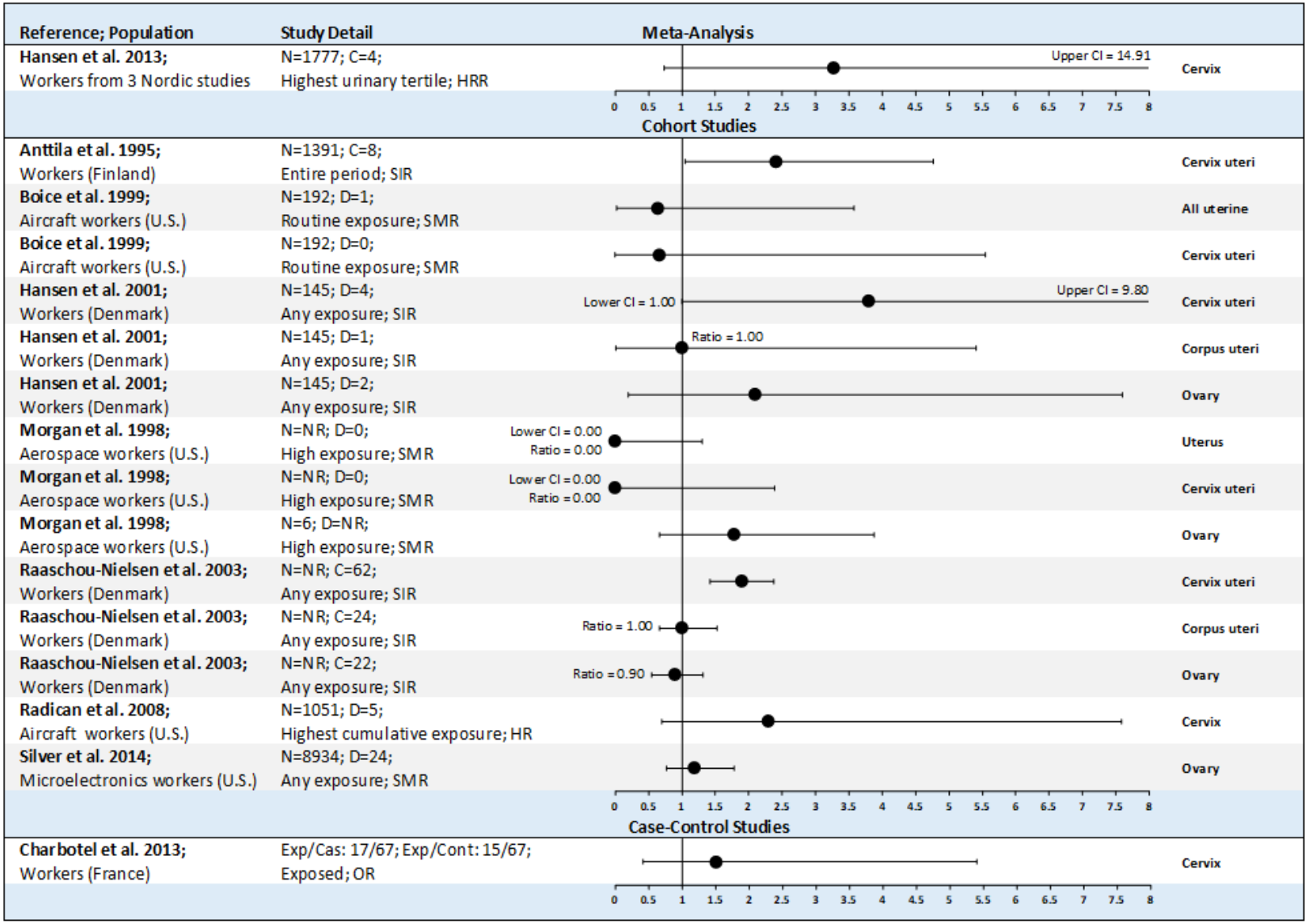
Figure 3-11. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Breast Cancer



= risk estimate and 95% CI

C = number with breast cancer; CI = confidence interval; D = number of deaths due to breast cancer; F = females; HR = hazard ratio; M = males; N = number of participants; NR = not reported; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-12. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Female Reproductive Cancer



= risk estimate and 95% CI

C = number with reproductive cancer; CI = confidence interval; D = number of deaths due to female reproductive cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; HR = hazard ratio; N = number of participants; NR = not reported; OR = odds ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-13. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Male Reproductive Cancer

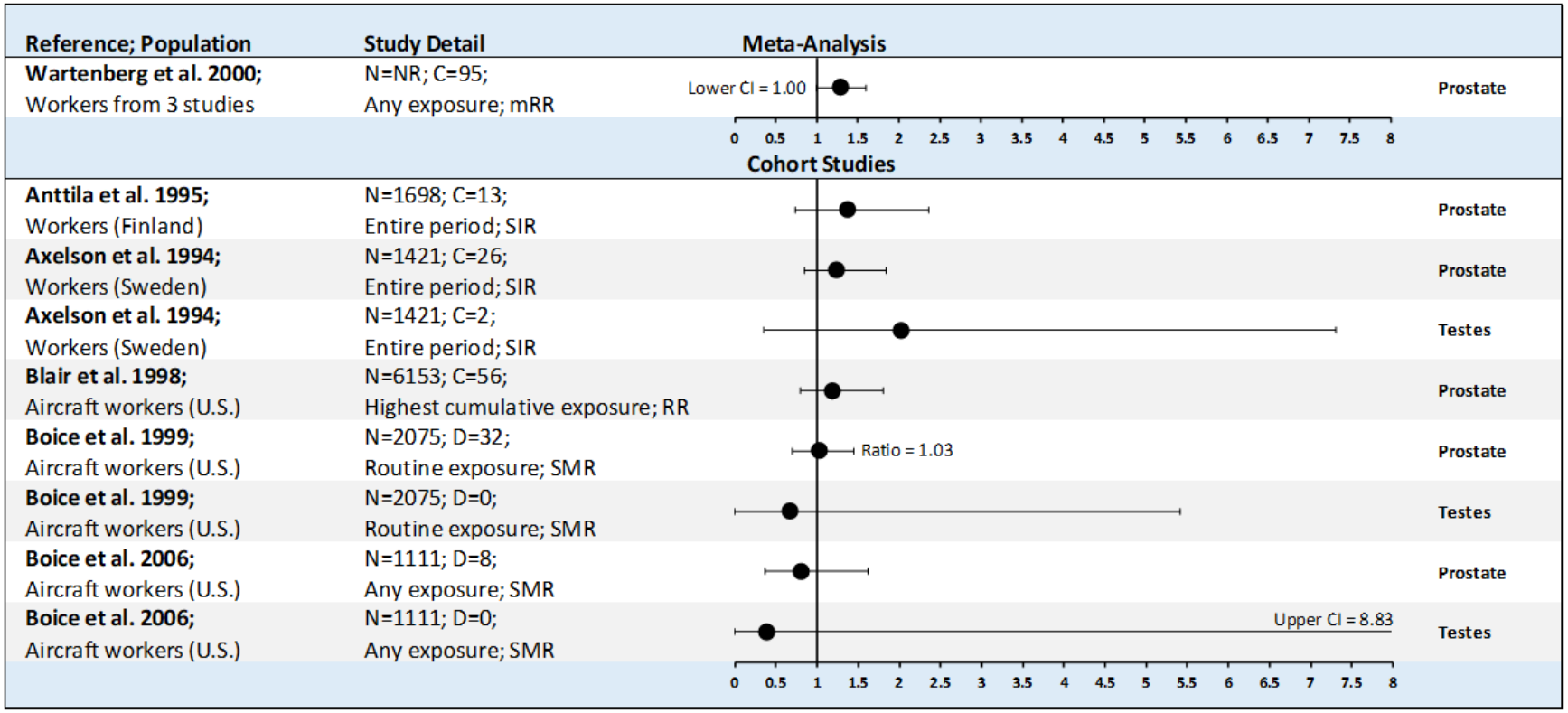
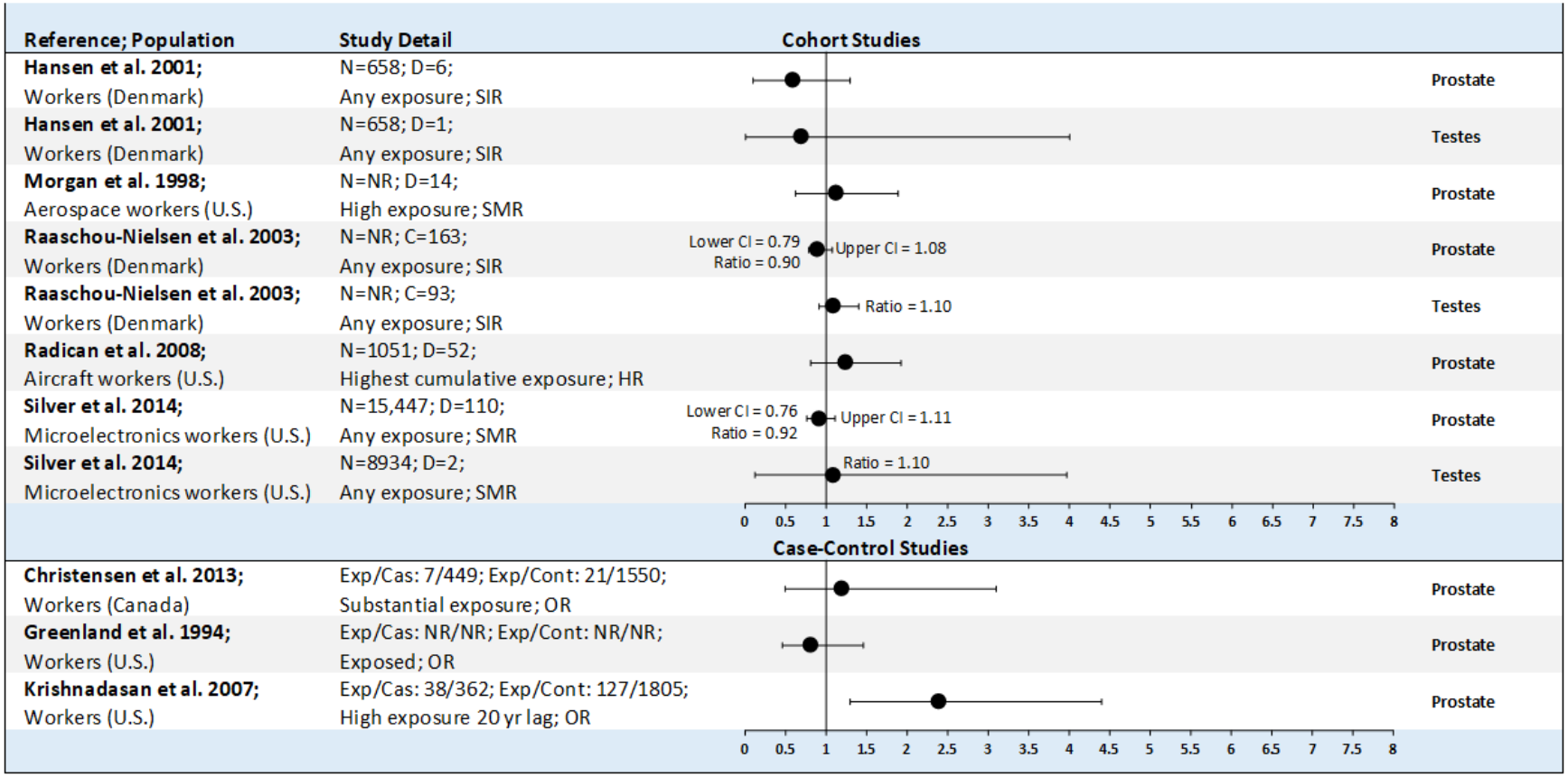


Figure 3-13 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Male Reproductive Cancer



= risk estimate and 95% CI

C = number with reproductive cancer; CI = confidence interval; D = number of deaths due to male reproductive cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; HR = hazard ratio; mRR = relative risk ratio; N = number of participants; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio; yr = year

Figure 3-14. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Central Nervous System Cancer

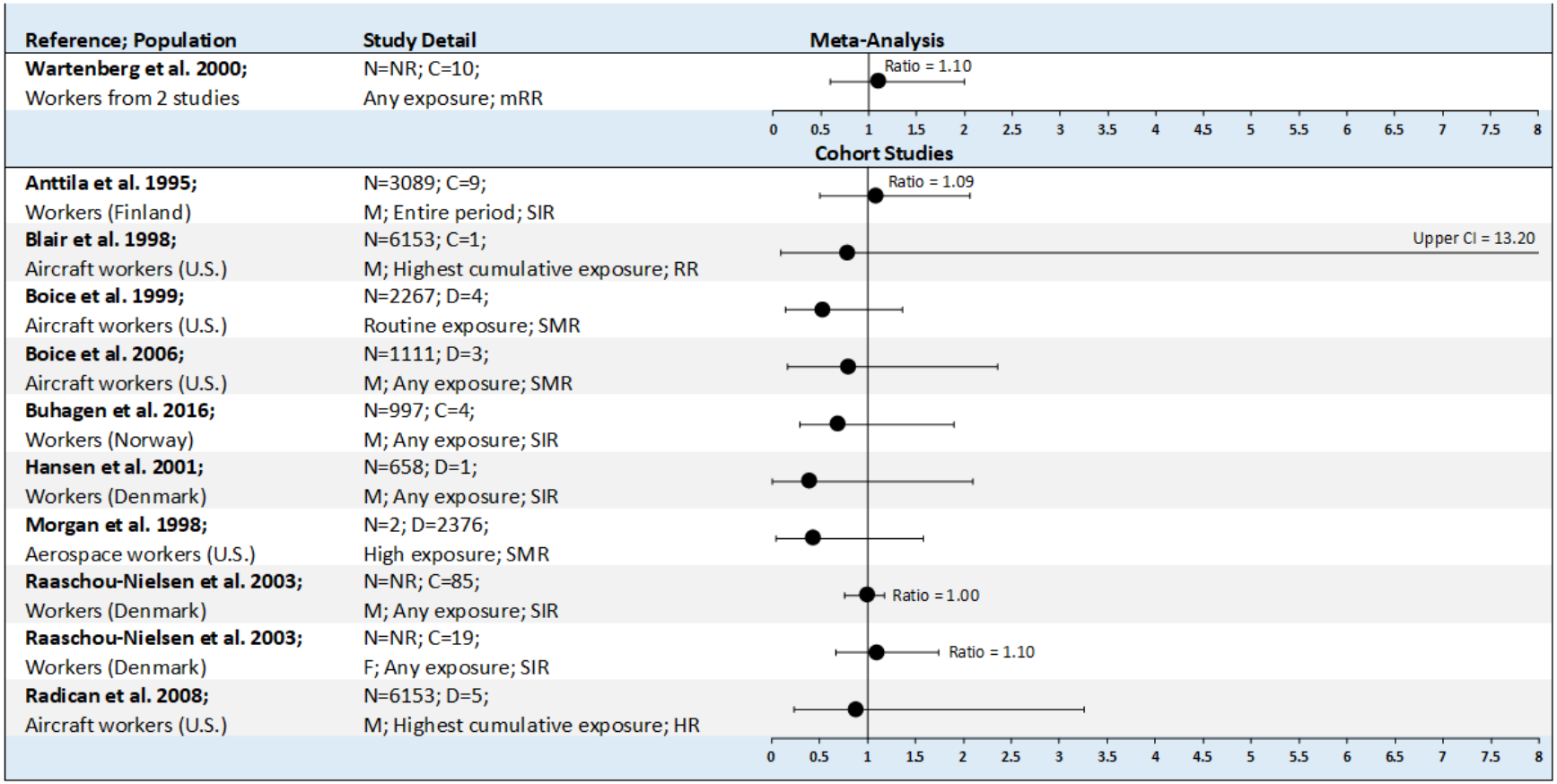
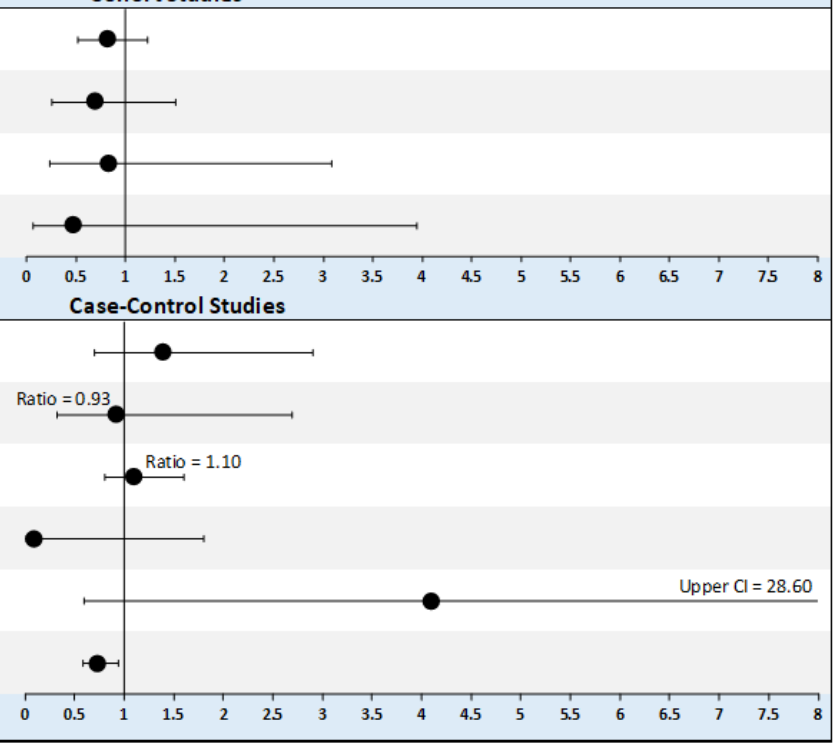


Figure 3-14 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Central Nervous System Cancer

Reference; Population	Study Detail
Cohort Studies	
Silver et al. 2014; Microelectronics (U.S.)	N=15,447; D=24; M; Any exposure; SMR
Silver et al. 2014; Microelectronics (U.S.)	N=8934; D=6; F; Any exposure; SMR
Zhao et al. 2005; Aerospace workers (U.S.)	N=2689; C=3; Highest exposure tertile; RR
Zhao et al. 2005; Aerospace workers (U.S.)	N=2227; C=1; Highest exposure tertile; RR
Case-Control Studies	
DeRoos et al. 2001; Children of male workers (U.S. and CAN)	Exp/Cas: 22/405; Exp/Cont: 12/302; Exposed; OR
Greenland et al. 1994; Workers (U.S.)	Exp/Cas: NR/NR; Exp/Cont: NR/NR; M; Exposed; OR
Heineman et al. 1994; Workers (U.S.)	Exp/Cas: 128/428; Exp/Cont: 125/445; M; Exposed; OR
Neta et al. 2012; Workers (U.S.)	Exp/Cas: 5/339; Exp/Cont: 13/541; Highest exposure; OR
Neta et al. 2012; Workers (U.S.)	Exp/Cas: 6/151; Exp/Cont: 27/555; Probable exposure; OR
Ruder et al. 2013; Workers (U.S.)	Exp/Cas: 172/438; Exp/Cont: 43/1141; Any exposure; OR



= risk estimate and 95% CI

C = number with central nervous system cancer; CAN = Canada; CI = confidence interval; CNS = central nervous system; D = number of deaths due to central nervous system cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; M = males; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SMR = standardized mortality ratio

Figure 3-15. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Multiple Myeloma

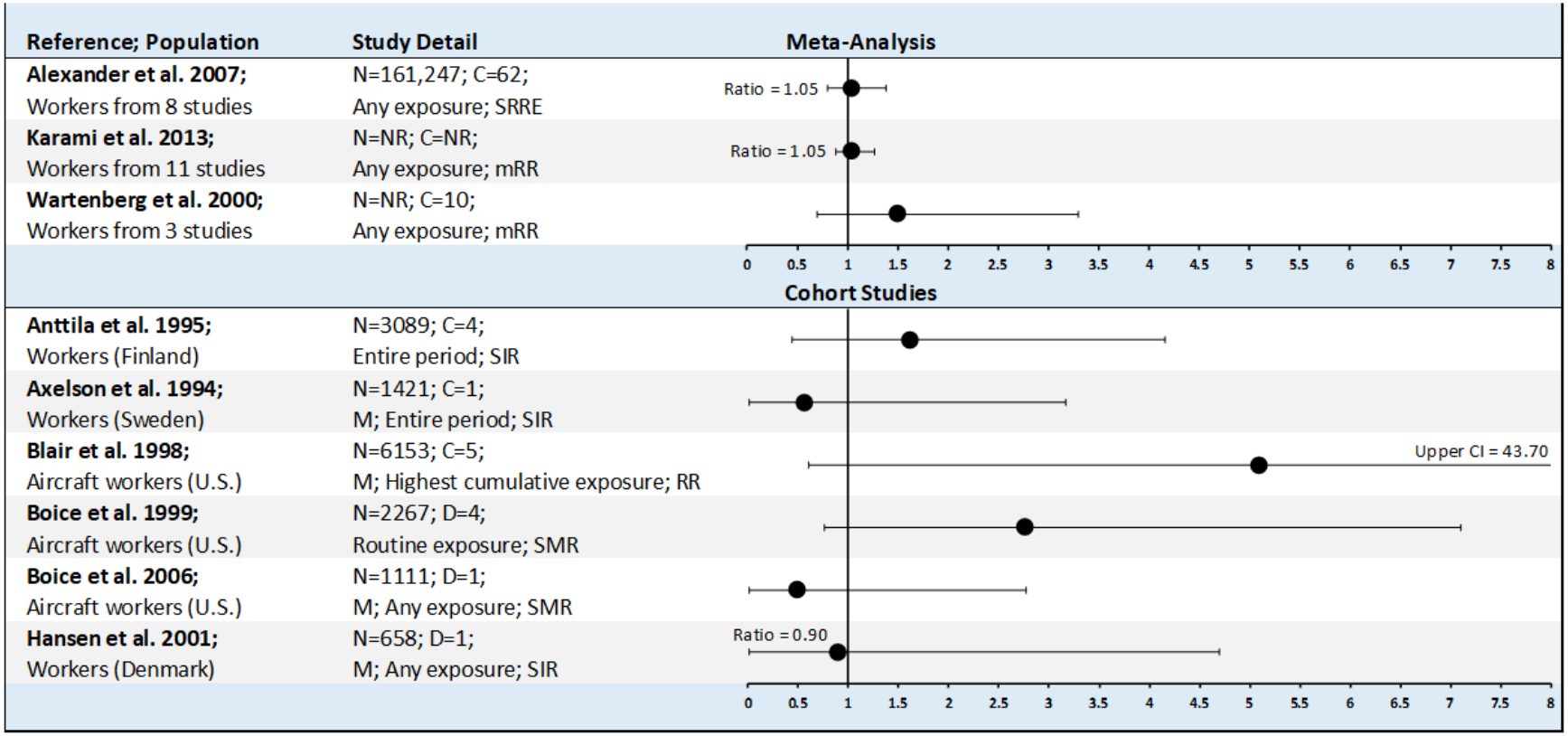
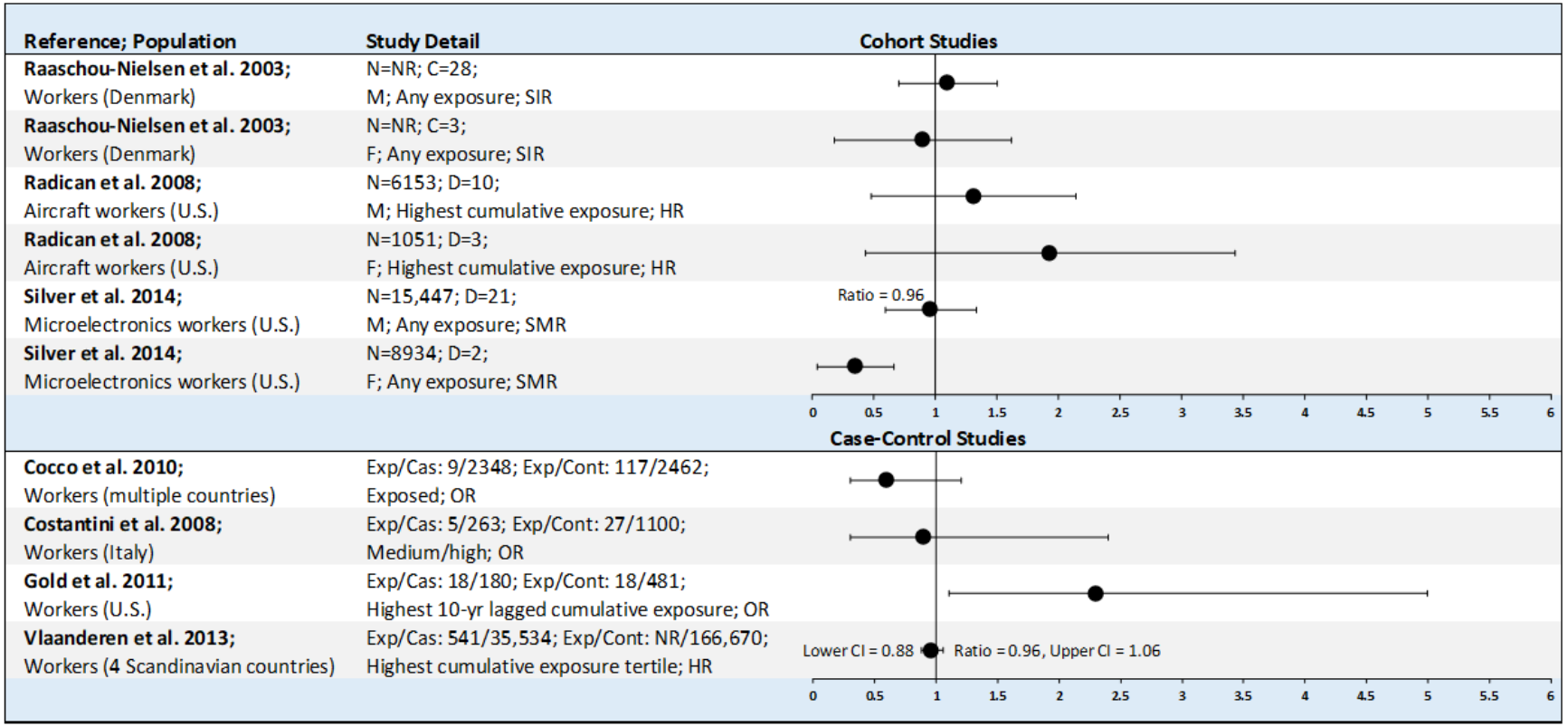


Figure 3-15 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Multiple Myeloma



⟝●⟞ = risk estimate and 95% CI

C = number with multiple myeloma; CI = confidence interval; D = number of deaths due to multiple myeloma; 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; mRR = relative risk ratio; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRRE = summary relative risk estimate; yr = year

Figure 3-16. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Leukemia

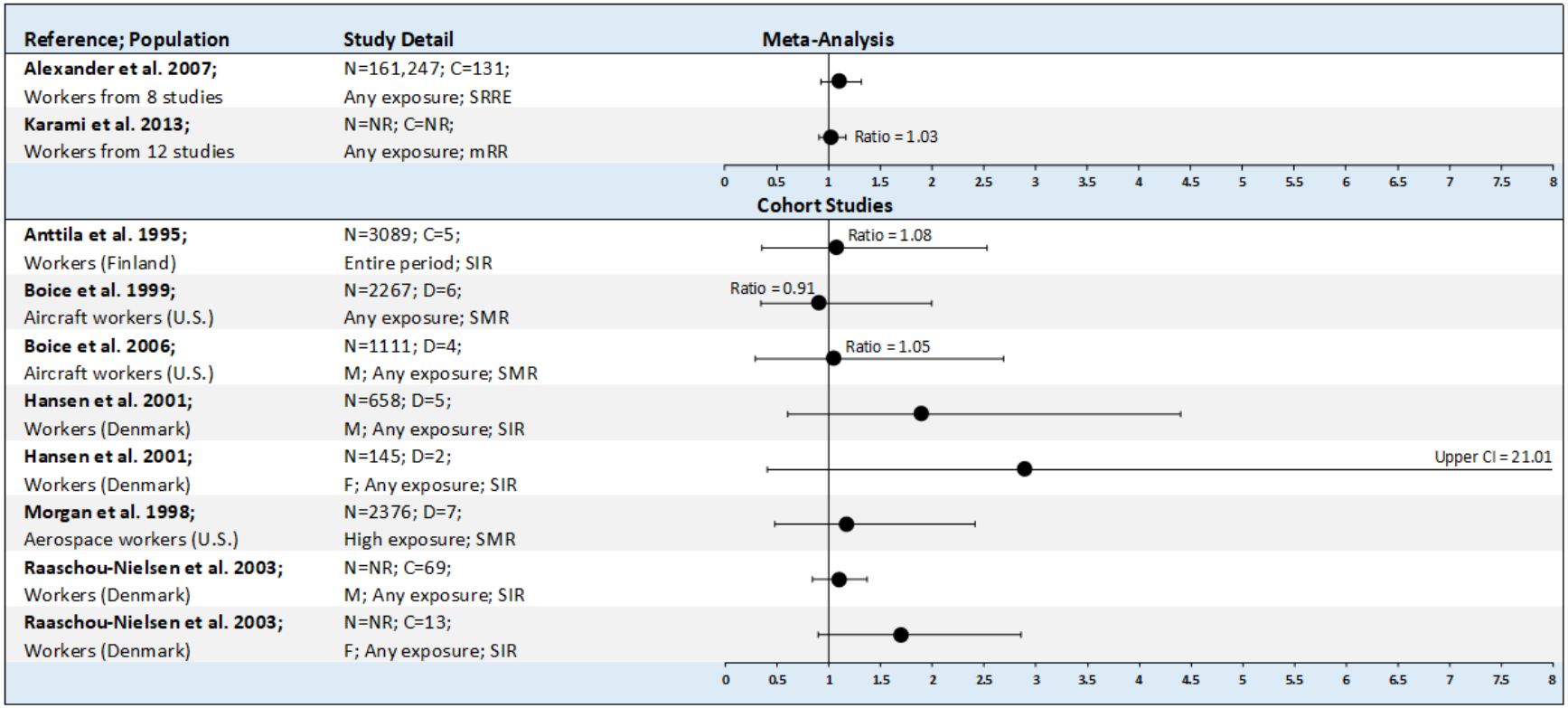
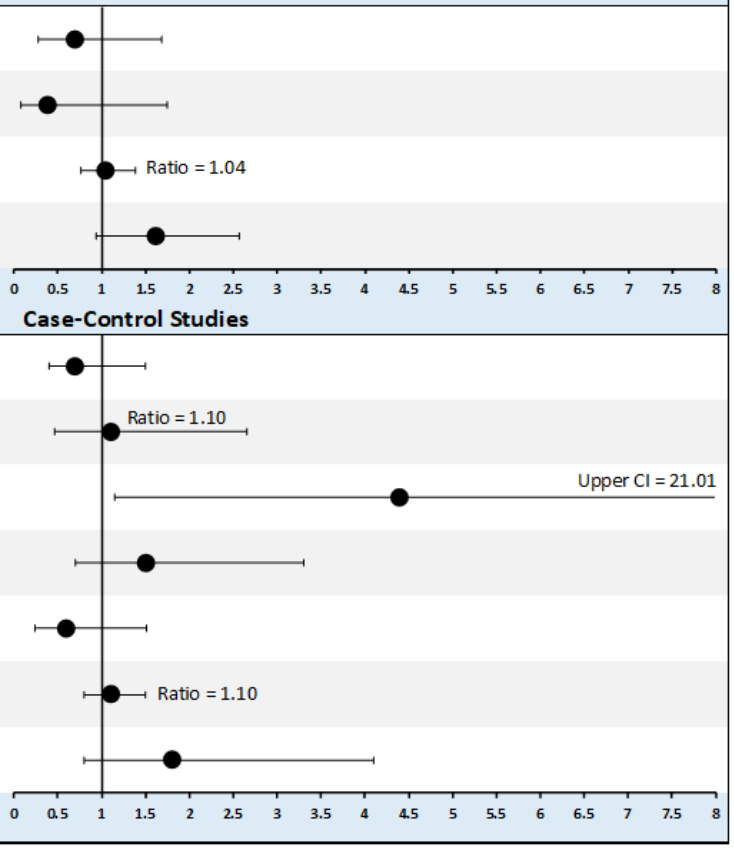


Figure 3-16 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Leukemia

Reference; Population	Study Detail
Cohort Studies	
Radican et al. 2008; Aircraft workers (U.S.)	N=6153; D=9; M; Highest cumulative exposure; HR
Radican et al. 2008; Aircraft workers (U.S.)	N=1051; D=2; F; Highest cumulative exposure; HR
Silver et al. 2014; Microelectronics workers (U.S.)	N=15,447; D=45; M; Any exposure; SMR
Silver et al. 2014; Microelectronics workers (U.S.)	N=8934; D=17; F; Any exposure; SMR
Case-Control Studies	
Costantini et al. 2008; Workers (Italy)	Exp/Cas: 11/586; Exp/Cont: 29/1278; Medium/high; OR
Greenland et al. 1994; Workers (U.S.)	Exp/Cas: NR/NR; Exp/Cont: NR/NR; Exposed; OR
McKinney et al. 1991; Children of workers (U.K.)	Exp/Cas: 7/109; Exp/Cont: 3/206; Exposure during periconception and gestation; OR
Nordstrom et al. 1998; Workers (Sweden)	Exp/Cas: 9/121; Exp/Cont: 26/484; M; Exposed; OR
Saberi Hosnijeh et al. 2013; Workers (Europe)	Exp/Cas: 5/109; Exp/Cont: 7865/137,084; High exposure; HR
Shu et al. 1999; Children of workers (U.S., CAN, and AUS)	Exp/Cas: 136/1018; Exp/Cont: 104/1076; Any paternal exposure; OR
Shu et al. 1999; Children of workers (U.S., CAN, and AUS)	Exp/Cas: 15/824; Exp/Cont: 9/910; Any maternal exposure; OR



= risk estimate and 95% CI

AUS = Australia; C = number with leukemia; CAN = Canada; CI = confidence interval; D = number of deaths due to leukemia; 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; mRR = relative risk ratio; N = number of participants; NR = not reported; OR = odds ratio; SMR = standardized mortality ratio; SRRE = summary relative risk estimate

Figures 3-2 through 3-16 include information on exposure type (e.g., specific industry or general occupational exposure), number of participants, 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 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.

Animal Studies. Statistically significant increases in the incidence of hepatomas (specific type of neoplasm not specified) occurred in male Swiss mice and in B6C3F1 mice of both sexes exposed to epoxide-free trichloroethylene (600 ppm) for 78 weeks. In contrast, a decrease in hepatomas was seen at 100 ppm in male Swiss mice; the statistical significance of this finding was not reported (Maltoni et al. 1986, 1988). In a retest with male B6C3F1 mice, a decrease in leukemias was seen (statistical significance not reported), with the percentage of hepatomas about the same for all dose levels and controls. There was also a significant increase in pulmonary tumors in male Swiss mice inhaling 600 ppm. Pulmonary tumors were also increased among treated female B6C3F1 mice but not among the males. Incidences were significantly increased over controls at 600 ppm for lung tumors in the female B6C3F1 mice and at 600 ppm for liver tumors in both sexes of B6C3F1 mice. Statistically significant, exposure concentration-related increased incidence of testicular Leydig cell tumors was reported in male Sprague-Dawley rats exposed to trichloroethylene at 0, 100, 300, or 600 ppm for 104 weeks (incidences of 5/95, 11/90, 24/90, and 22/90, respectively) (Maltoni et al. 1986, 1988).

The incidence of pulmonary adenocarcinomas was significantly increased over controls in female ICR mice exposed to 150 or 450 ppm reagent-grade trichloroethylene for 104 weeks, 5 days/week, 7 hours/day (Fukuda et al. 1983). There was no significant increase in other tumors in the mice or in similarly exposed female Sprague-Dawley rats. Henschler et al. (1980) reported statistically significant increases in the incidence and rate of development of malignant lymphomas in female NMRI mice (but not male NMRI mice or male or female Wistar rats or Syrian hamsters) exposed to trichloroethylene by inhalation at 100 or 500 ppm for 18 months. Incidences of malignant lymphomas in controls, 100 ppm, and 500 ppm groups were 9/29, 17/30, and 18/28, respectively. However, this type of tumor is historically common in unexposed female mice, possibly induced virally, and these investigators suggested that it may have resulted from immunosuppression.

The lowest concentrations resulting in cancer in reliable animal studies are indicated as CELs in Table 3-1 and Figure 3-1.

3.2.2 Oral Exposure

3.2.2.1 Death

Human studies have reported hepatorenal failure as the cause of death following accidental or intentional ingestion of trichloroethylene (De Baere et al. 1997; Kleinfeld and Tabershaw 1954; Liotier et al. 2008; Secchi et al. 1968; Vattemi et al. 2005). It was not possible to determine an accurate dose in these cases.

Acute oral LD_{50} values have been determined for mice (2,402 mg/kg) (Tucker et al. 1982) and rats (7,208 mg/kg) (Smyth et al. 1969). In a study in which pregnant rats were treated by gavage with trichloroethylene in corn oil on GDs 6–15, 2 of 13 died at 1,125 mg/kg/day, while all survived at 844 mg/kg/day (Narotsky et al. 1995). The lethality of trichloroethylene may be related to the delivery vehicle. Administration of trichloroethylene in an aqueous Emulphor vehicle proved to be more lethal but less hepatotoxic than similar administration of trichloroethylene in corn oil during a 4-week exposure period (Merrick et al. 1989). Further explanation of these study results is included in Section 3.2.2.2, under Hepatic Effects. Deaths of rats and mice have occurred following intermediate-duration exposure in range-finding studies and during chronic-duration cancer studies (Henschler et al. 1984; NCI 1976; NTP 1990). The premature deaths were the result of tumors or other conditions (body weight loss, respiratory infection, renal failure, and central nervous system depression) caused by very high daily doses. Further explanation of these studies is included in Section 3.2.2.7. LD_{50} values and the lowest doses causing death in rats and mice are recorded in Table 3-3 and plotted in Figure 3-17.

3.2.2.2 Systemic Effects

The highest NOAEL and all reliable LOAELs for each species, duration, and end point for systemic effects following oral exposure are recorded in Table 3-3 and plotted in Figure 3-17.

Respiratory Effects. Pulmonary congestion and edema were observed in a 43-year-old male who died following an oral overdose of trichloroethylene (De Baere et al. 1997). One study suggested increased respiratory disorders (asthma, bronchitis, pneumonia) in children with chronic exposure to a solvent-contaminated water supply (Byers et al. 1988). Two municipal wells in eastern Woburn, Massachusetts, were found to contain several solvents including trichloroethylene (267 ppb) and

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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 (Sprague-Dawley)	Gd 6-15 (GO)				1125 F (2/13 died)	Narotsky et al. 1995	
2	Rat (Fischer- 344)	2 wk ad libitum (F)		6618			NTP 1986	
3	Rat (NS)	once (G)				7208 (LD50)	Smyth et al. 1969	
4	Mouse (CD-1)	14 d ad libitum (F)		12180			NTP 1985	
5	Mouse (CD-1)	once (G)				2402 M (LD50) 2443 F (LD50)	Tucker et al. 1982	
Systemic								
6	Rat (Fischer- 344)	14 d (GO)	Hepatic	500 F	1500 F (increased liver weight, hepatocellular hypertrophy)		Berman et al. 1995	
			Renal		50 F (increased kidney weight)			
			Endocr	1500 F				

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
7	Rat (Wistar)	10 d 1 x/d (GO)	Hepatic	2000 M			Elcombe 1985	
8	Rat (Fischer- 344)	10 d 1 x/d (GO)	Hepatic		1000 M (22% increased liver weight, 1.8-fold greater palmitoyl CoA oxidation activity)		Goldsworthy and Popp 1987	
			Renal	1000 M				
			Bd Wt	1000 M				
9	Rat (Fischer- 344)	10 d 1 x/d (GO)	Renal	1000			Goldsworthy et al. 1988	
10	Rat (Fischer- 344)	Gd 6-19 (GO)	Resp	1125 F		1500 F (rales, dyspnea)	Narotsky and Kavlock 1995	
			Bd Wt			1125 F (maternal body weight gain 45% lower than controls)		
11	Rat (Sprague-Dawley)	Gd 6-15 (GO)	Bd Wt			475 F (31% decreased body weight gain)	Narotsky et al. 1995	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
12	Rat (Fischer- 344)	2 wk ad libitum (F)	Bd Wt	584	1358 (16% decreased body weight gain)		NTP 1986	
13	Rat (Sprague-Dawley)	7 d 1x/d (GO)	Hepatic		2000 M (12-16% increased absolute and relative liver weight)		Nunes et al. 2001	
			Bd Wt	2000 M				
14	Rat (Osborne-Mendel)	3 d 1 x/d (GO)	Hepatic	1100 M			Stott et al. 1982	
			Renal	1100 M				
15	Mouse (Swiss-Webster)	10 d 1 x/d (GO)	Hepatic	50 M	100 M (2-fold increase in palmitoyl CoA oxidation)		Elcombe 1985	
16	Mouse (B6C3F1)	10 d 1 x/d (GO)	Hepatic		1000 M (50% increased liver weight, 6.25-fold greater palmitoyl CoA oxidation activity)		Goldsworthy and Popp 1987	
			Renal	1000 M				
			Bd Wt	1000 M				

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
17	Mouse (CD-1)	14 d ad libitum (F)	Hepatic	1000	2479 (increased liver weight)		NTP 1985	
			Bd Wt	12180				
18	Mouse (B6C3F1)	3 d 1 x/d (GO)	Hepatic		2400 M (hepatic hypertrophy, centrilobular swelling)		Stott et al. 1982	
			Renal	2400 M				
19	Mouse (CD-1)	14 d 1 x/d (G)	Hemato	240 M			Tucker et al. 1982	
			Hepatic	240 M				
			Renal	240 M				
			Bd Wt	240 M				
Neurological								
20	Rat (Fischer- 344)	14 d (GO)		150 F	500 F (increased rearing)		Moser et al. 1995	
21	Rat (Sprague-Dawley)	Gd 6-15 (GO)		475 F		633 F (transient ataxia)	Narotsky et al. 1995	
22	Rat (Sprague-Dawley)	7 d 1x/d (GO)			2000 M (25% increased foot splay)		Nunes et al. 2001	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
Reproductive								
23	Rat (Sprague-Dawley)	14 d (W)			143 M (decreased in vitro fertilization capacity of sperm)		DuTeaux et al. 2004	
Developmental								
24	Rat (Sprague-Dawley)	Gd 6-15 (GO)		844		1125 (increased prenatal loss, micro- or anophthalmia)	Narotsky et al. 1995	
25	Mouse (B6D2F1)	Gd 1-5 Gd 6-10 Gd 1-15 1 x/d (GO)		240			Cosby and Dukelow 1992	
26	Mouse (NMRI)	7 d 1 x/d (GO)			50 M (reduced rearing rate at 60 days of age)		Fredriksson et al. 1993	
INTERMEDIATE EXPOSURE								
Death								
27	Rat (Long- Evans)	2 wk 5 d/wk Gd 0-21 7 d/wk (GO)				1000 (4/23 died)	Manson et al. 1984	
28	Rat (Osborne-Mendel)	6 wk 5 d/wk 1 x/d (GO)				5620 (10/10 died)	NCI 1976	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
29	Mouse (B6C3F1)	4 wk 5 d/wk 1 x/d (GW)				1200 M (2/12 deaths) 900 F (2/12 deaths)	Merrick et al. 1989	
30	Mouse (B6C3F1)	6 wk 5 d/wk 1 x/d (GO)				5620 M (4/5 deaths) 3160 F (2/5 deaths)	NCI 1976	
31	Mouse (B6C3F1)	13 wk 5 d/wk 1 x/d (GO)				1500 M (2/10 died) 3000 F (1/10 died)	NTP 1990	
Systemic								
32	Rat (Long- Evans)	2 wk 5 d/wk Gd 0-21 7 d/wk (GO)	Bd Wt			1000 (34% depressed body weight gain)	Manson et al. 1984	
33	Rat (Fischer- 344)	18 wk ad libitum (F)	Hepatic	316	632 (19-24% increased relative liver weight in F0 rats)		NTP 1986	
			Bd Wt		158 F (10% lower terminal body weight)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
34	Rat (Fischer- 344)	13 wk 5 d/wk 1 x/d (GO)	Resp		1000 F (pulmonary vasculitis involving small veins in 6/10)		NTP 1990	
			Cardio	2000 M				
			Gastro	2000 M				
			Musc/skel	2000 M				
			Hepatic	2000 M				
			Renal		1000 F (minimal or mild cytomegaly, karyomegaly of renal tubular epithelial cells in 5/10)			
			Endocr	2000 M				
			Dermal	2000 M				
			Bd Wt	1000 M		2000 M (body weights 24% less than controls)		
35	Rat (Osborne-Mendel)	3 wk 5 d/wk 1 x/d (GO)	Hepatic	1100 M			Stott et al. 1982	
			Renal	1100 M				
			Bd Wt	1100 M				
36	Rat (Wistar)	16 wk (W)	Bd Wt	206 M			Waseem et al. 2001	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
37	Mouse (Hybrid)	10-11 wk (W)	Bd Wt			122 (30% depressed terminal body weight)	Blossom and Doss 2007	
38	Mouse (Hybrid)	Up to 63 d (W)	Bd Wt	31			Blossom et al. 2008	
39	Mouse (Swiss- Cox)	6 wk 5 d/wk 1 x/d (GO)	Hepatic	100 M	400 M (enlarged hepatocytes)	1600 M (central lobular necrosis)	Buben and O'Flaherty 1985	
			Bd Wt	3200				
40	Mouse (Hybrid)	36 or 48 wk (W)	Bd Wt		60 F (26% decreased body weight gain after 11 weeks of treatment)		Cai et al. 2008	
41	Mouse (Hybrid)	Up to 22 wk (W)	Hepatic	734 F			Griffin et al. 2000a; Gilbert et al. 1999	
			Renal	734 F				
			Bd Wt	734 F				
42	Mouse (Hybrid)	4 or 32 wk (W)	Bd Wt	400 F			Griffin et al. 2000b	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
43	Mouse (B6C3F1)	30 wk (W)	Hepatic	3.5 F			Keil et al. 2009	
			Renal	3.5 F				
			Bd Wt	3.5 F				
44	Mouse (Hybrid)	30 wk (W)	Hepatic	2.2 F			Keil et al. 2009	
			Renal	2.2 F				
			Bd Wt	2.2 F				
45	Mouse (B6C3F1)	4 wk 5 d/wk 1 x/d (G)	Hepatic		450 F (117% increase in relative liver weight)	600 M (focal necrosis, 136% increase in relative liver weights)	Merrick et al. 1989	
			Bd Wt	2400 M				
46	Mouse (CD-1)	18 wk ad libitum (F)	Hepatic		737 (increased liver weight, hepatocellular hypertrophy)		NTP 1985	
			Renal		737 (tubular degeneration and karyomegaly of the corticomedullary renal tubular epithelium in F0 males and females)			
			Bd Wt	737				

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
47	Mouse (B6C3F1)	3 wk 5 d/wk 1 x/d (GO)	Hepatic	250 M	500 M (liver enlargement, increased DNA content per gram tissue)	1200 M (liver enlargement, increased DNA content, centrilobular hepatocyte swelling)	Stott et al. 1982	
			Renal	2400 M				
			Bd Wt	2400 M				
48	Mouse (CD-1)	6 mo ad libitum (W)	Gastro	18 M 793 F	217 M (gas pockets in the intestinal coating, blood in the intestines in 5)		Tucker et al. 1982	
			Hemato	393 M 793 F	660 M (red blood cell counts 16% lower than controls)			
			Hepatic	793 F				
			Renal	217 M 437 F	393 M (elevated urinary protein and ketones) 793 F (elevated urinary protein and ketones)			
			Bd Wt	393 M	660 M (body weights 11% lower than controls, associated with decreased water intake)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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								
49	Mouse (Hybrid)	10-11 wk (W)			122 (decreased splenic T- and B-lymphocytes)		Blossom and Doss 2007	
50	Mouse (Hybrid)	Up to 63 d (W)			31 (altered immunoregulation)		Blossom et al. 2008	
51	Mouse (Hybrid)	36 or 48 wk (W)			60 F (inflammation in liver, kidney, lungs, and pancreas)		Cai et al. 2008	
52	Mouse (Hybrid)	Up to 22 wk (W)			455 F (increased serum antinuclear antibodies and total serum immunoglobulins at 4 and 8 weeks indicative of accelerated autoimmune response)		Griffin et al. 2000a; Gilbert et al. 1999	
53	Mouse (Hybrid)	4 or 32 wk (W)			21 F (multiple indicators of autoimmune hepatitis)		Griffin et al. 2000b	
54	Mouse (B6C3F1)	30 wk (W)			0.35[b] F (30% decreased thymus weight, increased serum levels of IgG and selected autoantibodies)		Keil et al. 2009	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
55	Mouse (Hybrid)	30 wk (W)		2.2 F			Keil et al. 2009	
56	Mouse (B6C3F1)	Gd 0-21 and 3 or 8 wk PPD (W)			0.37[b] (decreased PFC response in male and female pups, increased hypersensitivity response in male pups)		Peden-Adams et al. 2006	
57	Mouse (CD-1)	4 or 6 mo ad libitum (W)			18 F (suppressed cell-mediated immune response, inhibited bone marrow stem cell colonization)		Sanders et al. 1982	Dose estimates from earlier study report (Tucker et al. 1982)
58	Mouse	48 wk (W)			1051 F (accelerated autoimune response in autoimmune-prone MRL+/+ mice)		Wang et al. 2007b	
Neurological								
59	Rat (Sprague-Dawley)	10 wk 5 d/wk 1 x/d (GO)			2500 F (altered myelin thickness of the trigeminal nerve)		Barret et al. 1991	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
60	Rat (Sprague-Dawley)	10 wk 5 d/wk 1 x/d (GO)			2500 F (altered trigeminal nerve morphometrics, fatty acid composition indicative of demyelination)		Barret et al. 1992	
61	Rat (Fischer- 344)	6 wk 5 d/wk 1 x/d (GO)				1000 M (decreased dopaminergic neurons in substantia nigra)	Gash et al. 2008	
62	Rat (Wistar)	16 wk (W)		206 M			Waseem et al. 2001	
Reproductive								
63	Rat (Fischer- 344)	18 wk ad libitum (F)		158			NTP 1986	
					316 (9% decrease in number of liveborn pups)			
64	Rat (Long- Evans)	6 wk 5 d/wk 1 x/d (GO)		100 M		1000 M (impaired copulatory behavior, mount/ ejaculation latency, intromissions)	Zenick et al. 1984	
65	Mouse (CD-1)	17 wk ad libitum (F)		375 M 750 F	750 M (18-45% decreased sperm motility)		NTP 1985	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
66	Mouse (CD-1)	18 wk ad libitum (F)		362 M	737 M (decreased sperm motility in F0 and F1 males)		NTP 1985	
Developmental								
67	Rat (Sprague-Dawley)	2-3 mo before mating and/or gestation ad libitum (W)				0.218 (increased fetal heart abnormalities)	Dawson et al. 1993; Johnson et al. 1998	
68	Rat (Sprague-Dawley)	14 d before mating Gd 0-21 -weaning ad libitum (W)				37 M (40% decrease in number of myelinated fibers in the hippocampus)	Isaacson and Taylor 1989	
69	Rat (Sprague-Dawley)	Throughout gestation (22 d) (W)		0.00045		0.048[b] (increased incidence of congenital heart abnormalities)	Johnson et al. 2003	
70	Rat (Long- Evans)	2 wk 5 d/wk Gd 0-21 7 d/wk (GO)		100		1000 (decreased neonatal survival)	Manson et al. 1984	Serious maternal toxicity at 1000 mg/kg/day (4/23 died, 34% depressed body weight gain)

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
71	Rat (Fischer- 344)	18 wk ad libitum (F)			158 (11-13% decreased pup body weight at PND 21		NTP 1986	
72	Rat (Sprague-Dawley)	14 d before mating Gd 0-21 -weaning ad libitum (W)			37 M (increased exploratory behavior)		Taylor et al. 1985	
73	Mouse (MRL +/+)	GD0-birth (W)			2.96 F (Increased locomotor activity in male pups tested on PND 42)		Blossom et al. 2017	
74	Mouse (CD-1)	17 wk ad libitum (F)		375 M		750 (increased perinatal mortality)	NTP 1985	
75	Mouse (CD-1)	18 wk ad libitum (F)		362		737 (increased perinatal mortality)	NTP 1985	
76	Mouse (B6C3F1)	Gd 0-21 and 3 or 8 wk PPD (W)			0.37 (18% decreased body weight in 3-week-old pups)		Peden-Adams et al. 2006	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
CHRONIC EXPOSURE								
Death								
77	Rat (Osborne-Mendel)	78 wk 5 d/wk 1 x/d (GO)				1097 M (47/50 died) 549 F (35/48 died)	NCI 1976	
78	Rat (Fischer- 344)	103 wk 5 d/wk 1 x/d (GO)				500 M (30/50 died) 500 F (17/50 died)	NTP 1990	
79	Mouse (B6C3F1)	78 wk 5 d/wk 1 x/d (GO)				869 F (8/50 died)	NCI 1976	
80	Mouse (B6C3F1)	103 wk 5 d/wk 1 x/d (GO)				1000 M (34/50 died)	NTP 1990	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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								
81	Rat (Sprague-Dawley)	52 wk 5 d/wk 1 x/d (GO)	Resp	250			Maltoni et al. 1986	
			Cardio	250				
			Gastro	250				
			Musc/skel	250				
			Hepatic	250				
			Renal	50 M	250 M			
			Endocr	250				
			Dermal	250				
			Ocular	250				
			Bd Wt	250				

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
82	Rat (Osborne-Mendel)	78 wk 5 d/wk 1 x/d (GO)	Resp	1097			NCI 1976	
			Cardio	1097				
			Gastro	1097				
			Musc/skel	1097				
			Hepatic	1097				
			Renal		549 (toxic nephrosis, proximal tubular epithelium alterations)			
			Endocr	1097				
			Dermal		549 (alopecia, roughening of hair coat, sores)			
			Ocular		549 (squinting, red discharge)			
			Bd Wt	549 M	1097 M (body weights 18% lower than controls at 78 weeks)			
					549 F (body weights 15% lower than controls at 78 weeks)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
83	Rat (August)	103 wk 5 d/wk 1 x/d (GO)	Resp	1000			NTP 1988	
			Cardio	1000				
			Gastro	1000				
			Musc/skel	1000				
			Hepatic	1000				
			Renal		500 (toxic nephrosis 20% of males and 17% of females, cytomegaly)			
			Endocr	1000				
			Dermal	1000				
			Ocular	1000				
			Bd Wt	500 M	1000 M (body weights 12.3% lower than controls)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
84	Rat (Marshall)	103 wk 5 d/wk 1 x/d (GO)	Resp	1000			NTP 1988	
			Cardio	1000				
			Gastro	1000				
			Musc/skel	1000				
			Hepatic	1000				
			Renal		500 (toxic nephrosis 36% of males and 63% of females, cytomegaly)			
			Endocr	1000				
			Dermal	1000				
			Ocular	1000				
			Bd Wt	500 F	1000 F (body weights 10.1% lower than controls)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
85	Rat (ACI)	103 wk 5 d/wk 1 x/d (GO)	Resp	1000			NTP 1988	
			Cardio	1000				
			Gastro	1000				
			Musc/skel	1000				
			Hepatic	1000				
			Renal		500 (toxic nephrosis 37% of males and 45% of females, cytomegaly)			
			Endocr	1000				
			Dermal	1000				
			Ocular	1000				
			Bd Wt		500 M (body weights 11% lower than controls)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
86	Rat (Osborne-Mendel)	103 wk 5 d/wk 1 x/d (GO)	Resp	1000			NTP 1988	
			Cardio	1000				
			Gastro	1000				
			Musc/skel	1000				
			Hepatic	1000				
			Renal		500 (toxic nephrosis 78% of males and 60% of females, cytomegaly)			
			Endocr	1000				
			Dermal	1000				
			Ocular	1000				
			Bd Wt	500 M	1000 M (body weights 11.6% lower than controls)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
87	Rat (Fischer- 344)	103 wk 5 d/wk 1 x/d (GO)	Resp	1000			NTP 1990	
			Cardio	1000				
			Gastro	1000				
			Hepatic	1000				
			Renal		500 (slight to well marked toxic nephrosis, cytomegaly)			
			Endocr	1000				
			Dermal	1000				
			Bd Wt	500 M	1000 M (body weights 13% lower than controls)			
					500 F (body weights 12% lower than controls)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
88	Mouse (B6C3F1)	78 wk 5 d/wk 1 x/d (GO)	Resp	2239 M			NCI 1976	
			Cardio	2239 M				
			Gastro	2339 M				
			Musc/skel	2239 M				
			Hepatic	2239 M				
			Renal		1160 M (toxic nephrosis)			
					869 F (toxic nephrosis)			
			Endocr	2239 M				
			Dermal		869 F (alopecia, skin sores)			
			Ocular	2239 M				
			Bd Wt	2239 M				

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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
89	Mouse (B6C3F1)	103 wk 5 d/wk 1 x/d (GO)	Resp	1000			NTP 1990	
			Cardio	1000				
			Gastro	1000				
			Hepatic	1000				
			Renal		1000 (slight to moderate toxic nephrosis, cytomegaly)			
			Endocr	1000				
			Dermal	1000				
			Bd Wt		1000 M (body weights 10% lower than controls)			
90	Mouse (Hybrid)	Gd 0 through 12 mo (W)	Bd Wt	0.33 M 3.4 F	3.3 M (12% depressed mean terminal body weight)		Peden-Adams et al. 2008	Estimated doses based on direct exposure of the offspring via their drinking water; they had also been exposed during gestation and lactation

Table 3-3. Levels of Significant Exposure to Trichloroethylene - 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								
91	Mouse (Hybrid)	Gd 0 through 12 mo (W)			0.33 M (29% decreased thymic cellularity)		Peden-Adams et al. 2008	Estimated doses based on direct exposure of the offspring via their drinking water; they had also been exposed during gestation and lactation
Cancer								
92	Rat (Fischer- 344)	103 wk 5 d/wk 1 x/d (GO)				1000 M (CEL: renal tubular cell adenocarcinomas)	NTP 1990	
93	Mouse (B6C3F1)	103 wk 5 d/wk 1 x/d (GO)				1000 (CEL: hepatocellular carcinomas)	NTP 1990	

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

b Study results used as support for the EPA (2011e) preferred chronic RfD of 0.0005 mg/kg/day for trichloroethylene and the ATSDR chronic-duration and intermediate-duration oral MRLs for trichloroethylene. The preferred chronic RfD of EPA is based on results of three critical studies for which individual candidate chronic RfDs were derived: A candidate chronic RfD of 0.00048 mg/kg/day for decreased thymus weight in female mice exposed to trichloroethylene in the drinking water for 30 weeks (Keil et al. 2009), a candidate chronic RfD of 0.00037 mg/kg/day for decreased plaque forming cell (PFC) response in 3- and 8-week-old pups and increased delayed-type hypersensitivity in 8-week-old pups exposed to trichloroethylene via the maternal drinking water throughout gestation and postnatally (until 3 or 8 weeks of age) via the drinking water (Peden-Adams et al. 2006), and a candidate chronic RfD of 0.00051 mg/kg/day for fetal heart malformations in rats exposed to trichloroethylene via the maternal drinking water during gestation (Johnson et al. 2003). Selected details regarding EPA's methodology for derivation of the preferred chronic RfD using results from the three critical studies are presented in Appendix A.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; IgG = Immunoglobulin G; Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; PFC = plaque-forming cell; PND = post-natal day; PPD = post-parturition day; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s)

Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral

Acute (≤14 days)

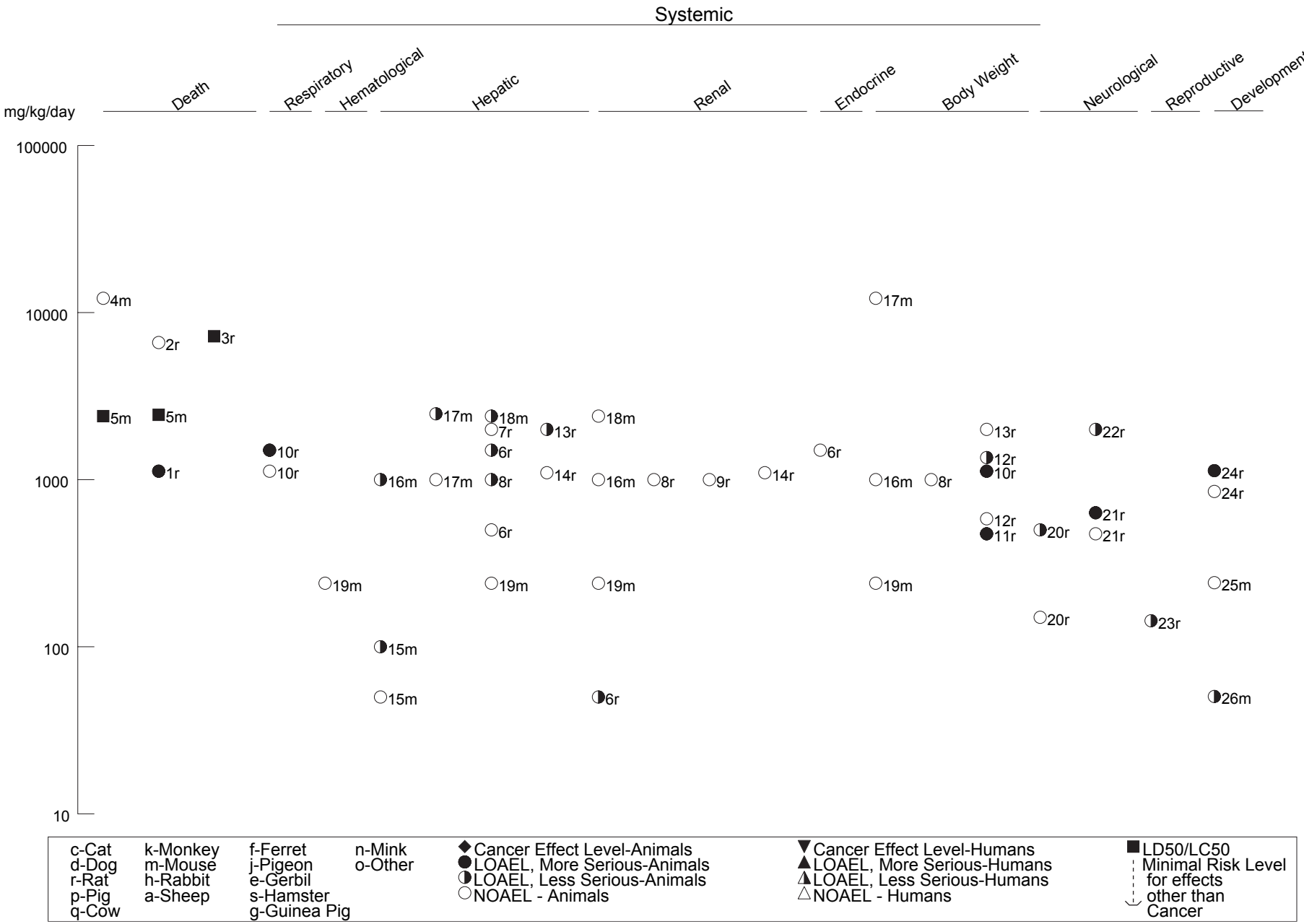


Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral *(Continued)*

Intermediate (15-364 days)

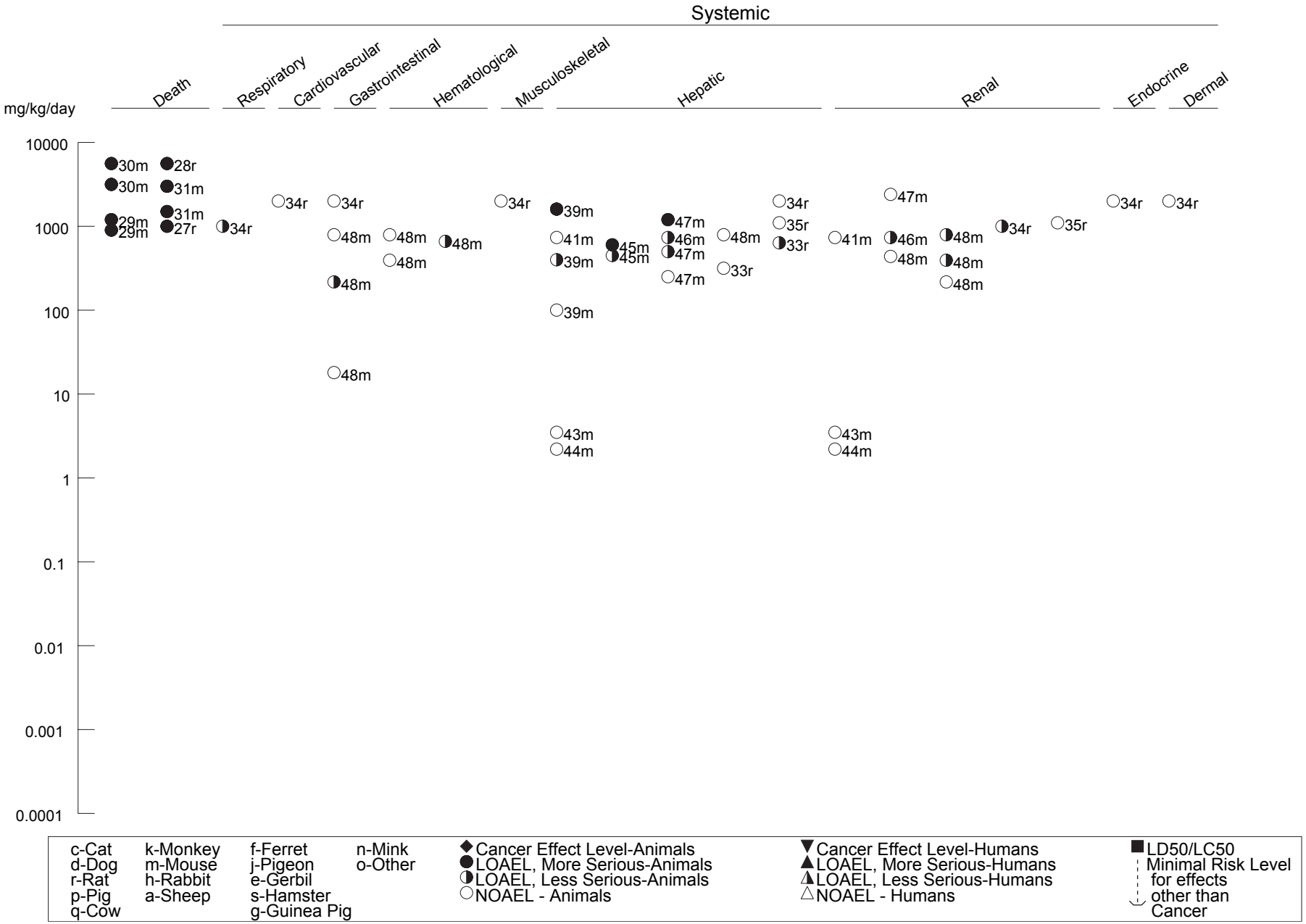


Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral *(Continued)*

Intermediate (15-364 days)

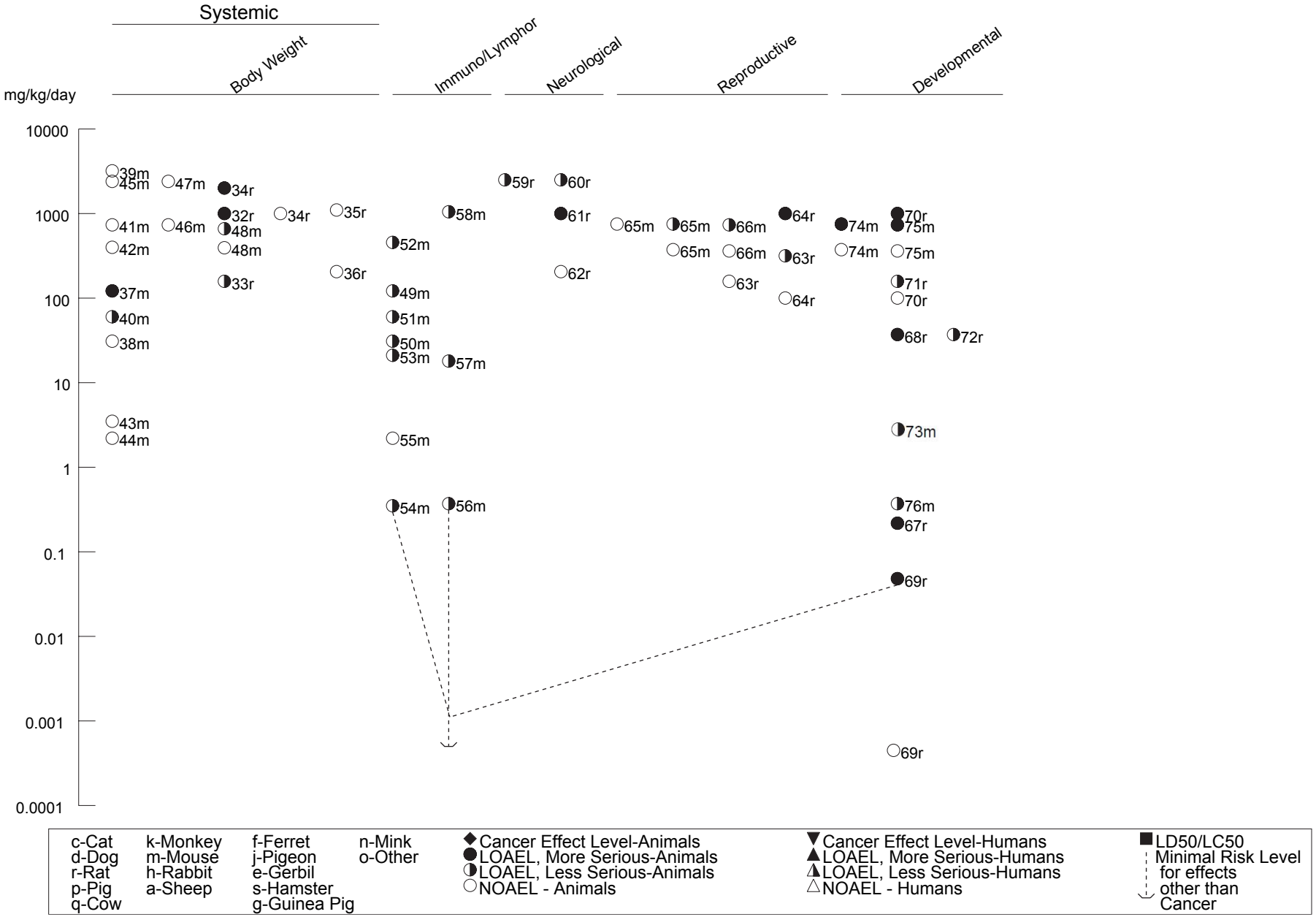


Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral *(Continued)*

Chronic (≥365 days)

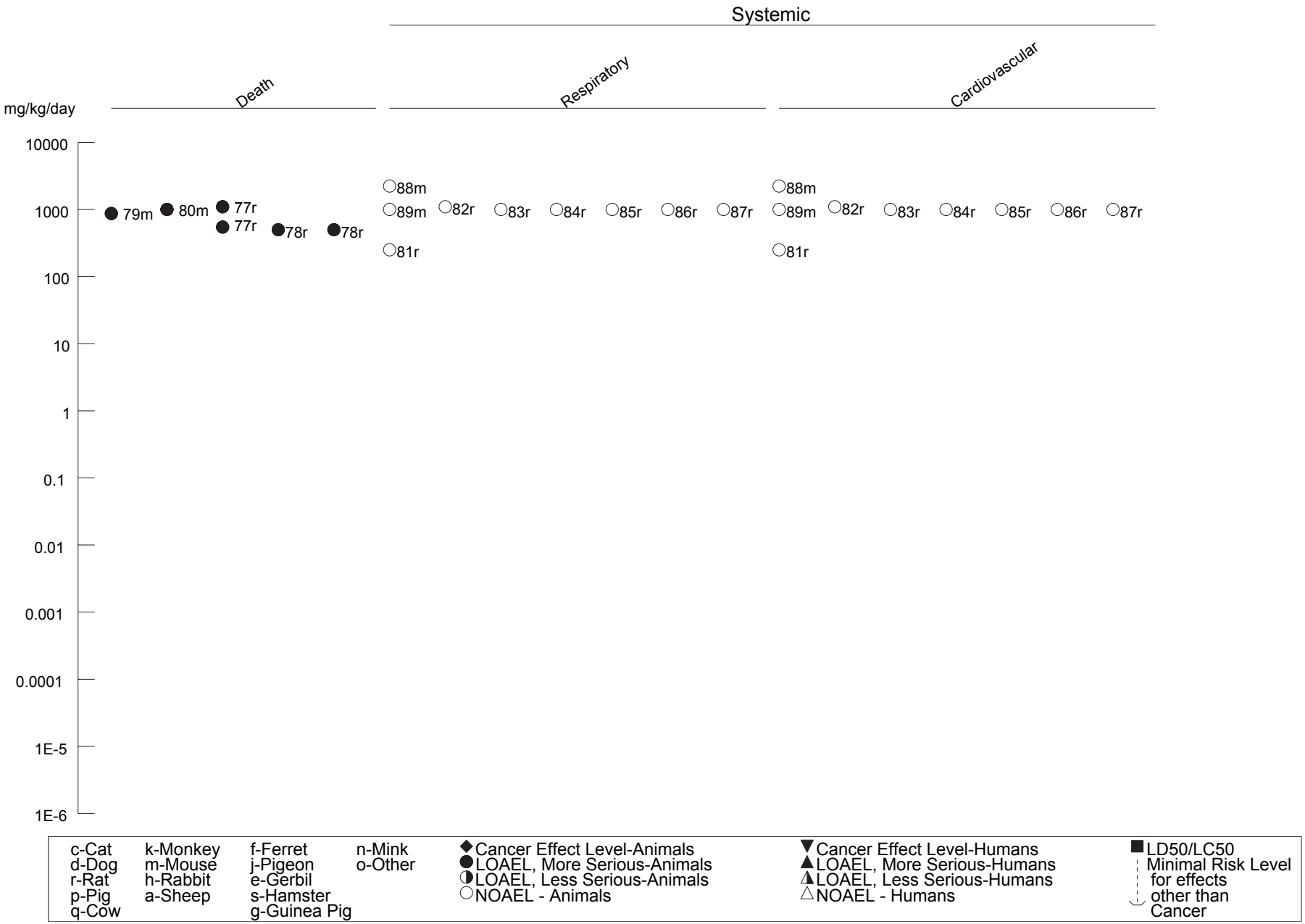


Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral *(Continued)*

Chronic (≥365 days)

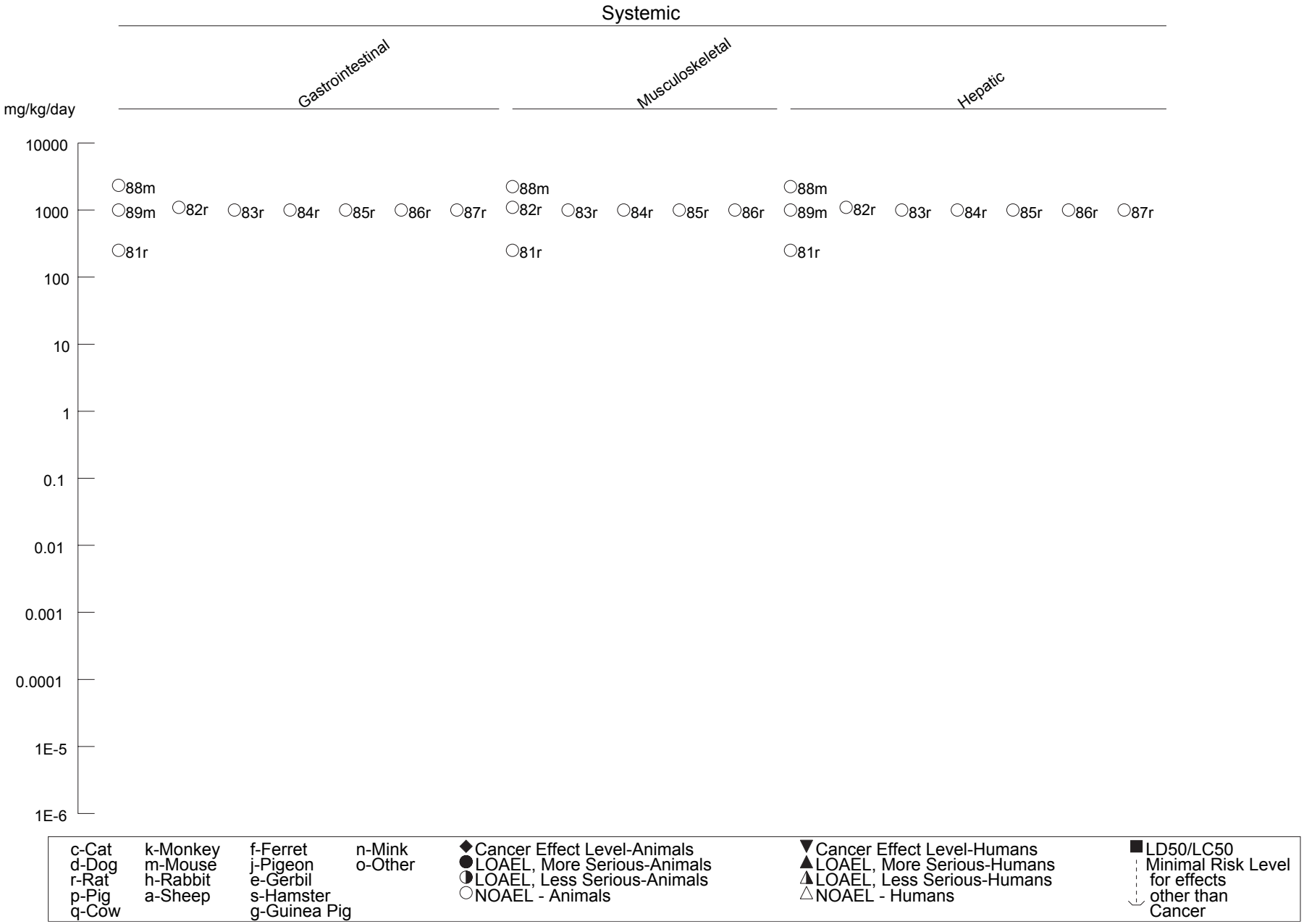


Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral *(Continued)*

Chronic (≥365 days)

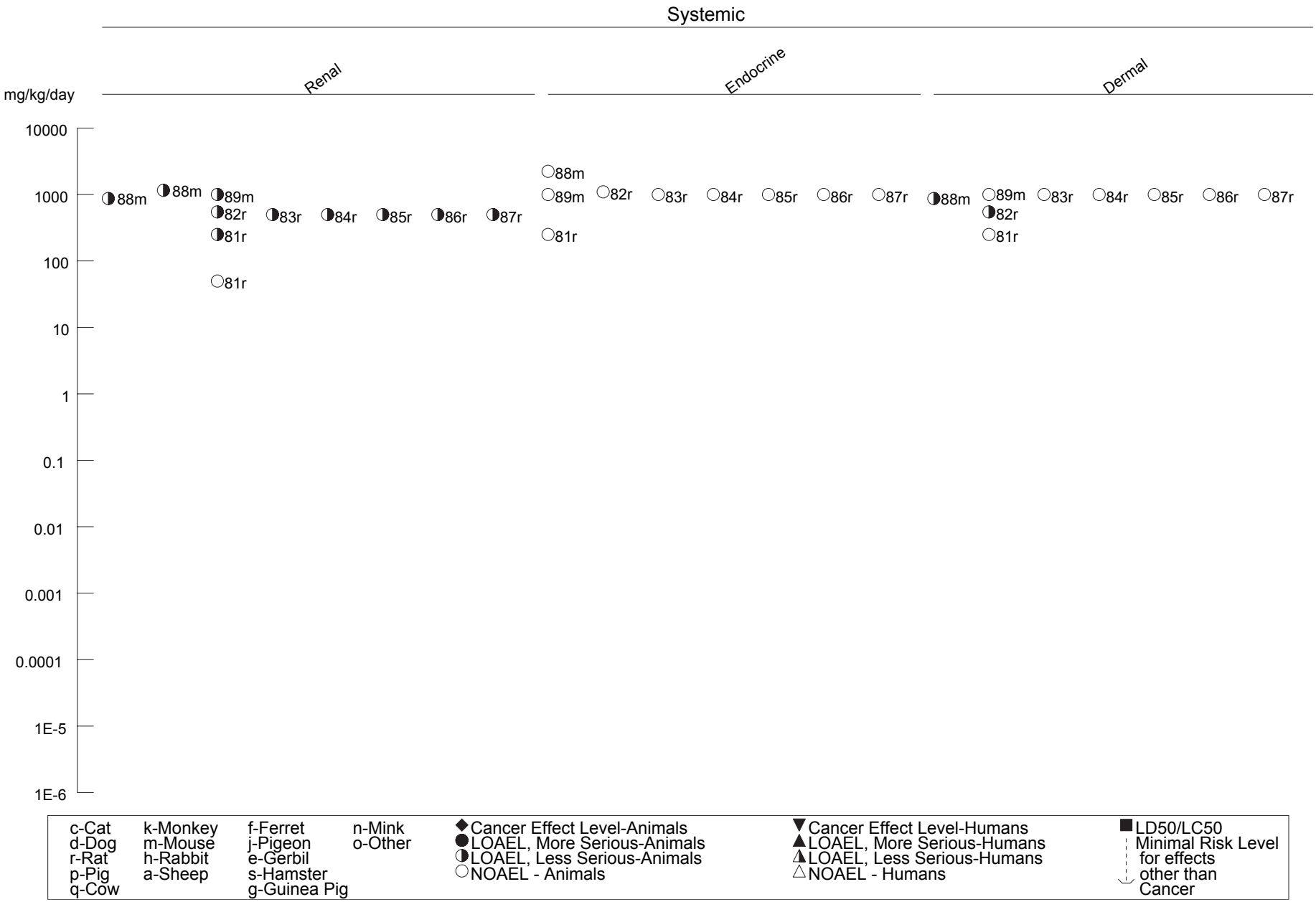
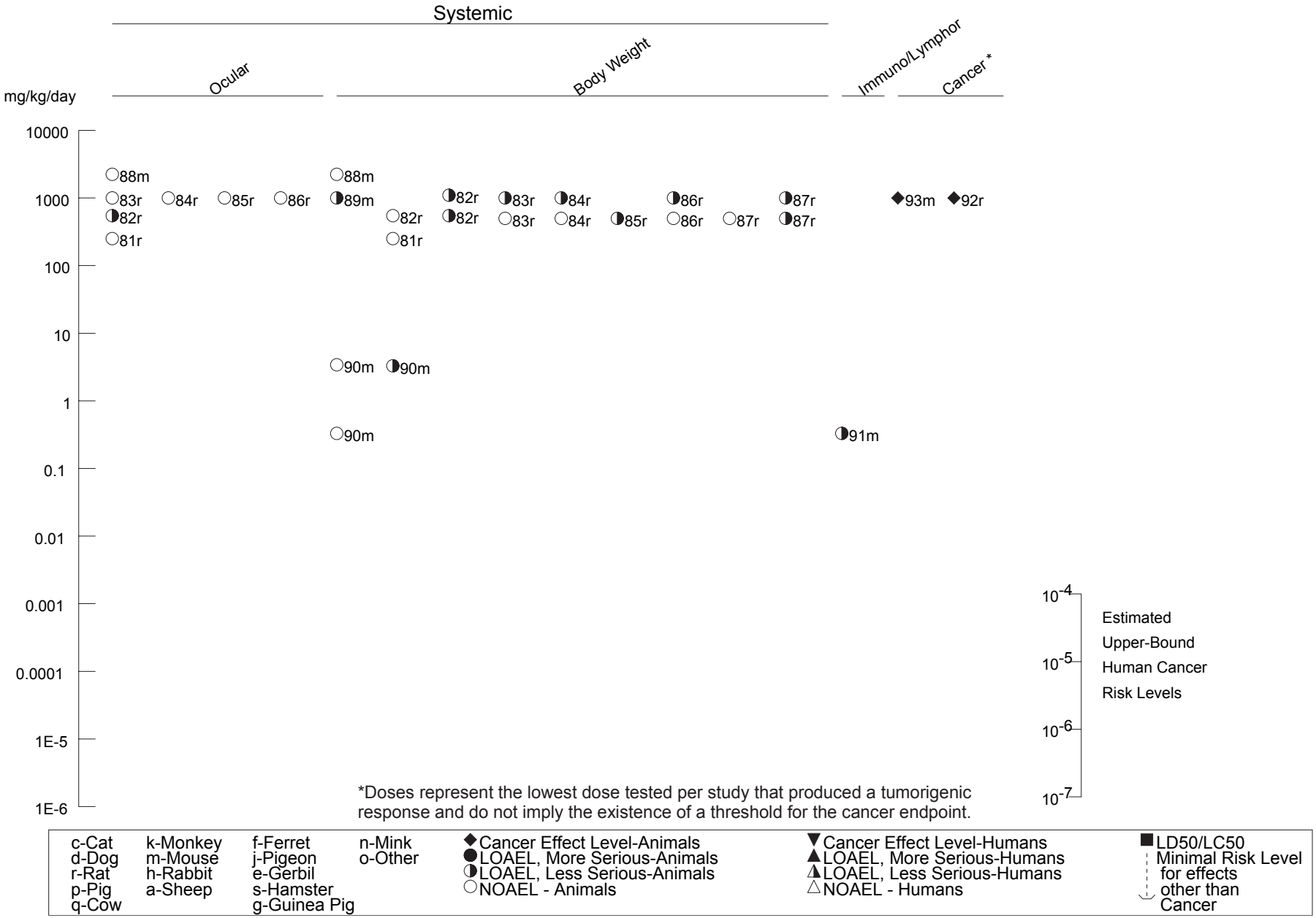


Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral *(Continued)*

Chronic (≥365 days)



tetrachloroethylene (21 ppb). The increased susceptibility to infection may be secondary to effects on the immune system. Accurate chemical-specific exposure levels for individuals could not be determined because the water distribution system was designed to use water from different wells at different rates and times. Other limitations of this study are described in Section 3.2.2.7.

Rales and dyspnea were observed in pregnant rats treated by gavage with 1,500 mg/kg/day trichloroethylene in corn oil on GDs 6–19 (Narotsky and Kavlock 1995). Respiratory effects were not observed at 1,125 mg/kg/day. Pulmonary vasculitis was observed in 6 of 10 female rats treated with 1,000 mg/kg/day (by gavage) and 6 of 10 male rats treated with 2,000 mg/kg/day (in corn oil) for 13 weeks (NTP 1990). This effect was also observed in 1 of 10 male and 1 of 10 female control rats. Histopathological examinations were not completed at the other doses in this study. Therefore, it is not possible to determine if this is a dose-related effect. Nonneoplastic histopathological changes in the lungs have not been observed in other intermediate- and chronic-duration studies of rats or mice orally exposed to trichloroethylene (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990). The maximum doses used in these studies were 3,000 mg/kg/day for an intermediate-duration study in mice (NTP 1990) and 1,097 mg/kg/day for a chronic-duration study in rats (NCI 1976).

Cardiovascular Effects. In one case study, a woman who had accidentally consumed about 20 mL of trichloroethylene was reported to have suffered a myocardial infarction within 2 hours of ingestion (Morreale 1976). In two other case studies, men who ingested 350 and 500 mL of trichloroethylene had ventricular arrhythmias that persisted for up to 3 days (Dhuner et al. 1957). The arrhythmias were described as ventricular tachycardia with extrasystoles from different ventricular foci. Cardiac arrhythmia was also reported in women who ingested unknown amounts of trichloroethylene (Moritz et al. 2000; Perbellini et al. 1991). Sinus tachycardia was observed in a man who ingested approximately 70 mL of trichloroethylene (Brüning et al. 1998) and another man who ingested an unknown amount of trichloroethylene (Vattemi et al. 2005).

Cardiovascular effects of trichloroethylene were investigated in families from Woburn, Massachusetts, that included at least one child with leukemia (Byers et al. 1988). Medical and laboratory tests were conducted on 25 family members who were included in the study. Of those family members who were adults at the time of assessment (apparently 23 of the 25), 14 complained of symptoms including unexplained rapid heart rate at rest, palpitations, or near syncope. Eleven of these adults were given resting and exercise tolerance electrocardiograms, 24-hour Holter monitoring tests, and echocardiograms. Of these 11, 8 had serious ventricular dysfunctions, 7 had multifocal premature ventricular beats, and

6 required cardiac medication. None of the subjects had clinically significant coronary artery disease. No rationale was given for the selection of the 11 adults given extensive testing. No background information on family history of heart disease, smoking habits, or occupational history was given on any of the 25 family members. Other details and limitations of this study are described in Section 3.2.2.7. When compared to a national sample population, statistically significant excess of stroke was consistently reported in the ATSDR Trichloroethylene Subregistry baseline and follow-up reports of persons environmentally exposed to trichloroethylene (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). However, inherent limitations in study design preclude establishment of a cause-and-effect relationship.

Histopathological changes in the heart have not been observed in intermediate- and chronic-duration studies of rats or mice orally exposed to trichloroethylene (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990). The maximum doses used in these studies were 2,000 mg/kg/day for rats and 3,000 mg/kg/day for mice (intermediate-duration studies) (NTP 1990).

Gastrointestinal Effects. Vomiting, diarrhea, hemorrhagic gastritis, and abdominal perforation and necrosis have been reported in people who ingested large amounts of trichloroethylene (De Baere et al. 1997; Liotier et al. 2008; Moritz et al. 2000; Vattemi et al. 2005). Some of the people exposed to trichloroethylene and other chlorinated hydrocarbons in the drinking water in Woburn, Massachusetts, complained of chronic nausea, episodic diarrhea, and constipation (Byers et al. 1988). Although 52% of the subjects had these complaints, these general signs could not be specifically attributed to the trichloroethylene. Study limitations are described in Section 3.2.2.7. Self-reported gastrointestinal problems were not increased among persons in the ATSDR Trichloroethylene Subregistry who were exposed to trichloroethylene in their drinking water (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005).

Gas pockets in the intestinal coating and blood in the intestines were observed in five male mice treated with trichloroethylene in drinking water at a dose of 660 mg/kg/day (Tucker et al. 1982). Similar effects were observed in five male mice at a dose of 217 mg/kg/day, with no mice affected at doses of 393 or 18 mg/kg/day. Unfortunately, the number of mice examined for this effect was not clearly stated. Although this effect was not dose-related, it is an interesting observation and appears to be consistent with the human cases of gas-filled cysts in the submucosa of the small intestine observed in persons occupationally exposed to trichloroethylene (Nakajima et al. 1990a) (see Section 3.2.1.2).

Histopathological changes in the gastrointestinal tract have not been observed in intermediate- or chronic-duration studies in which rats and mice were administered trichloroethylene by gavage in corn oil (NCI 1976; NTP 1988, 1990) or olive oil (Maltoni et al. 1986). The maximum doses used in these studies were 2,000 mg/kg/day for rats and 3,000 mg/kg/day for mice (intermediate-duration studies) (NTP 1990).

Hematological Effects. No effects on blood coagulation (Perbellini et al. 1991) or routine hematology tests (Todd 1954) were observed in persons accidently exposed to a single oral dose of trichloroethylene that resulted in coma. When compared to a national sample population, a statistically significant excess of anemia was consistently reported in the ATSDR Trichloroethylene Subregistry baseline and follow-up reports of persons environmentally exposed to trichloroethylene (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). However, inherent limitations in study design preclude establishment of a cause-and-effect relationship. For example, exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences. Self-reported symptoms of members of the trichloroethylene subregistry may have been influenced by knowledge of trichloroethylene exposure. Selected symptoms are common to trichloroethylene and other substances found in the water sources.

Hematological effects were not observed in mice treated by gavage with trichloroethylene in 1% aqueous Emulphor for 14 days at doses up to 240 mg/kg/day (Tucker et al. 1982).

ATSDR (2018) is a retrospective cohort study of 50,684 marines stationed at Camp Lejeune, North Carolina who were exposed to drinking water containing tetrachloroethylene, trichlorethylene, and benzene. A reference group consisted of 8,615 marines stationed at Camp Pendleton, California who were not exposed to contaminated drinking water. Trichloroethylene-exposure groups for Camp Lejeune marines were stratified by cumulative exposure tertiles in terms of ppb-months (low: <110; medium: ≤110–<11,030; high: ≥11,030); the number of marines in each tertile was not reported. The Camp Lejeune study population was exposed from 1975 to 1985. The odds of aplastic anemia (23 instances among 50,684 marines at Camp Lejeune; 5 instances among 8,615 marines at Camp Pendleton) were not increased in marines exposed to trichloroethylene in drinking water at Camp Lejeune, North Carolina for any cumulative exposure tertile (ATSDR 2018).

Mice that received 18–793 mg/kg/day trichloroethylene in the drinking water for 6 months showed minor hematological changes, including a 16% decrease in the red blood cell count in males exposed to 660 mg/kg, an increase in fibrinogen levels in males, a decrease in white blood cell counts in females, and

shortened prothrombin times in females (Tucker et al. 1982). These changes were not considered toxicologically significant because they were not dose related, and some effects were transient.

Musculoskeletal Effects. Vattemi et al. (2005) reported skeletal muscle damage in a man who had ingested an unknown amount of trichloroethylene. No other studies were located regarding musculoskeletal effects in humans following oral exposure to trichloroethylene.

No histopathological changes in muscle (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990) or bone (NTP 1988, 1990) have been observed in intermediate- and chronic-duration studies in which rats and mice were treated by gavage with trichloroethylene in corn oil (NCI 1976; NTP 1988, 1990) or olive oil (Maltoni et al. 1986). The maximum doses used in these studies were 2,000 mg/kg/day for rats and 3,000 mg/kg/day for mice (intermediate durations) (NTP 1990).

Hepatic Effects. Hepatic failure was reported in the case of an accidental ingestion of trichloroethylene that led to an acute overdose (Kleinfeld and Tabershaw 1954). In other case studies, blood analyses revealed no hepatic injury in a man who drank several tablespoons of trichloroethylene (Todd 1954) or in women who drank about 20 mL (Morreale 1976) or an unknown quantity (Perbellini et al. 1991). When compared to a national sample population, statistically significant excesses of liver problems were consistently reported in the ATSDR Trichloroethylene Subregistry baseline and follow-up reports of persons environmentally exposed to trichloroethylene (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). However, inherent limitations in study design preclude establishment of a cause-and-effect relationship. For example, exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences. Self-reported symptoms of members of the trichloroethylene subregistry may have been influenced by knowledge of trichloroethylene exposure. Selected symptoms are common to trichloroethylene and other substances found in the water sources.

In the retrospective cohort morbidity study of Camp Lejeune, North Carolina marines described in Section 3.2.1.2 (Hematological Effects), ORs for all liver disease were 1.19 (95% CI 0.86–1.64) for the low exposure group, based on 192 instances; 1.63 (95% CI 1.18–2.25) for the medium exposure group, based on 217 cases; and 1.36 (95% CI 0.89–2.07) for the high exposure group, based on 48 instances (ATSDR 2018). ORs for cirrhosis were 1.64 (95% CI 0.78–3.44) for the low exposure group, based on 34 instances; 2.17 (95% CI 1.04–4.53) for the medium exposure group, based on 36 instances; and 1.68 (95% CI 0.62–4.57) for the high exposure group, based on 7 instances. ORs for fatty liver were

1.32 (95% CI 0.91–1.91) for the low exposure group, based on 151 instances; 1.81 (95% CI 1.25–2.63) for the medium exposure group, based on 171 instances; and 1.53 (95% CI 0.95–2.46) for the high exposure group, based on 38 instances. There was no apparent association between exposure to trichloroethylene and risk of hepatomegaly or liver failure.

Substantial toxic effects in the liver have been seen in acute studies in animals. Prout et al. (1985) administered single doses of 10–2,000 mg/kg trichloroethylene to rats and mice. Blood level kinetics of trichloroethylene and its metabolites revealed that trichloroethylene was metabolized more quickly in the mouse, and thus, at high doses, the mouse was exposed to greater concentrations of trichloroethylene metabolites than the rat. Hepatic hypertrophy and centrilobular swelling were observed in mice treated with three daily gavage doses of 2,400 mg/kg trichloroethylene in corn oil; liver effects were not observed in rats similarly treated at 1,100 mg/kg (Stott et al. 1982). Increased relative liver weights and hepatocellular hypertrophy were observed in rats treated by gavage with 1,500 mg/kg/day trichloroethylene in corn oil for 14 days (Berman et al. 1995). A dose-related increase in peroxisomal β-oxidation activity was seen, beginning at 100 mg/kg/day, in mice given trichloroethylene by gavage in corn oil for 10 days, but not in similarly-treated rats at doses up to 2,000 mg/kg/day (Elcombe 1985). A second 10-day study in which rats and mice were treated by gavage with trichloroethylene in corn oil at a dose of 1,000 mg/kg/day has confirmed the observation that the increase in peroxisomal β-oxidation activity is much greater in mice than rats (Goldsworthy and Popp 1987). In rats, relative liver weights and palmitoyl CoA oxidation activity increased 122 and 180%, respectively, while in mice, relative liver weights and palmitoyl CoA oxidation activity increased 150 and 625%, respectively. A similar dosing regimen, up to 1,000 mg/kg/day, produced no change in hepatocyte DNA content in male and female mice, while incorporation of radiolabelled thymidine in whole cells and DNA extracted from mature hepatocytes increased with the dose, responses suggestive of cellular proliferation (Dees and Travis 1993). Peroxisomal beta oxidation and palmitoyl CoA oxidation are markers of peroxisome proliferation. The differences in responses between the rats and mice may reflect species differences in trichloroethylene metabolism.

Several studies showed hepatotoxicity in mice that received trichloroethylene for intermediate periods by gavage in corn oil, although the effects may be sex specific. Males exposed for 6 weeks showed a dose-related progression of hepatic alterations with increasing doses of trichloroethylene, beginning with an increase in the relative liver weight at 100 mg/kg/day and enlarged liver cells and decreased DNA concentration at ≥400 mg/kg/day (Buben and O'Flaherty 1985). This progressed to an increase in the glucose-6-phosphatase activity at 800 mg/kg/day, focal necrosis at 1,600 mg/kg/day, and an increase in

serum ALT activity at 2,400 mg/kg/day. In another study, a dose-related effect was seen in male mice treated with trichloroethylene for 3 weeks (Stott et al. 1982). At 250 and 500 mg/kg/day, there were slight increases in cytoplasmic eosinophilic staining indicative of changes in hepatocyte organelles, while at 1,200 and 2,400 mg/kg/day, there was centrilobular hepatocellular swelling, which included giant cell inflammation and mineralized cells at the highest dose. Trichloroethylene administered to mice at 600 mg/kg/day for 4 weeks produced dose-related hepatic inflammation and associated necrosis in males, but necrosis of the liver was not observed in females treated with doses up to 1,800 mg/kg/day (Merrick et al. 1989). Male mice that received trichloroethylene at 240 mg/kg/day by gavage in 10% Emulphor for 2 weeks, or that consumed drinking water containing as much as 5 mg/mL (equivalent to a dosage of approximately 660 mg/kg/day) for 6 months, showed no treatment-related hepatic effects other than increased liver weights without accompanying macroscopic lesions (Tucker et al. 1982). Although enlarged livers were reported for mice treated by gavage with trichloroethylene in corn oil for 18 months at doses of 1,978 and 1,483 mg/kg/day for males and females, respectively, there were no other indicators of treatment-related liver effects (Henschler et al. 1984). Hepatic effects were not reported in mice treated by gavage with trichloroethylene in corn oil at doses up to 1,739 mg/kg/day for 78 weeks (NCI 1976) or at 1,000 mg/kg/day for 103 weeks (NTP 1990). Liver weight was not increased in female mice administered trichloroethylene in the drinking water for 30 weeks; however, the highest dose tested was 3.5 mg/kg/day (Keil et al. 2009).

Rats appear to be less sensitive than mice to trichloroethylene hepatotoxicity. Daily gavage administration of trichloroethylene (in corn oil) to male rats at 2,000 mg/kg/day for 7 days resulted in 12–16% increased liver weight, but no evidence of treatment-related histopathologic liver lesions (Nunes et al. 2001). Male rats treated with trichloroethylene by corn oil gavage at 1,100 mg/kg/day for 3 weeks failed to exhibit histopathology in the liver, although enhanced hepatic DNA synthesis (175% of control) was detected (Stott et al. 1982). Hepatic effects were not observed in rats treated by gavage with 2,000 mg/kg/day trichloroethylene in corn oil for 13 weeks (NTP 1990). No treatment-related nonneoplastic lesions of the liver were described for male or female rats treated with 1,000 mg/kg/day trichloroethylene for 2 years (NTP 1988, 1990), with 1,097 mg/kg/day for 78 weeks (NCI 1976), or with 250 mg/kg/day for 52 weeks (Maltoni et al. 1986).

Renal Effects. Acute cases of accidental trichloroethylene ingestion revealed no appreciable effects on renal function (Morreale 1976; Perbellini et al. 1991; Todd 1954). One study suggests an association between long-term exposure to solvent-contaminated well water and increased urinary tract infections in children (Lagakos et al. 1986a). However, there was no indication that clinical chemistry testing of urine

samples had been done; such testing might have detected changes in renal function. There was no indication that the increased rates of infection were due to structural or functional renal anomalies. These children were exposed to a number of solvents including trichloroethylene. In another study involving well-water contamination, residents of three communities in Michigan who were exposed to trichloroethylene and other solvents in drinking water had no increase in kidney disease (Freni and Bloomer 1988).

In the retrospective cohort morbidity study of Camp Lejeune, North Carolina marines described in Section 3.2.1.2 (Hematological Effects), ORs for all kidney disease were 1.39 (95% CI 0.90–2.15) for the low exposure group, based on 115 instances; 1.86 (95% CI 1.20–2.87) for the medium exposure group, based on 127 cases; and 1.43 (95% CI 0.81–2.52) for the high exposure group, based on 26 instances (ATSDR 2018). ORs for nephrotic syndrome were 2.68 (95% CI 1.04–6.94) for the low exposure group, based on 31 instances; 2.71 (95% CI 1.03–7.11) for the medium exposure group, based on 25 instances; and 3.03 (95% CI 0.95–9.62) for the high exposure group, based on 7 instances. ORs for renal failure were 1.38 (95% CI 0.75–2.51) for the low exposure group, based on 56 instances; 2.03 (95% CI 1.12–3.68) for the medium exposure group, based on 68 instances; and 1.37 (95% CI 0.62–3.02) for the high exposure group, based on 12 instances.

There was no evidence of nephrotoxicity in mice treated by gavage with trichloroethylene in corn oil at 2,400 mg/kg/day or in rats treated by gavage with 1,100 mg/kg/day for 3 days or 3 weeks (Stott et al. 1982). A gavage dose of trichloroethylene in corn oil (1,000 mg/kg/day) administered to male rats and mice for 10 days resulted in elevated cyanide-insensitive palmitoyl CoA oxidase levels in the kidneys, which is indicative of peroxisomal proliferation but not of cytotoxic effects (Goldsworthy and Popp 1987). In a later report, there was a lack of proximal tubular changes and no increase in alpha-2u-globulin in the kidneys of male rats when 1,000 mg/kg/day trichloroethylene was similarly administered to male and female F344 rats for 10 days (Goldsworthy et al. 1988). Protein droplets and cell replication in males and females did not differ from controls. Kidney weight and urinalyses were normal in mice administered 240 mg/kg/day by gavage in an aqueous Elmuphor solution for 14 days (Tucker et al. 1982). Significantly increased kidney weights (10% higher than controls) and hepatocellular hypertrophy were observed in rats treated by gavage with 1,500 mg/kg/day trichloroethylene in corn oil; significantly increased kidney weights at 5–500 mg/kg/day were only 3–5% higher than controls (Berman et al. 1995). Increased kidney weight and elevated urinary protein and ketones, but no gross pathologic effects, were seen in male rats given 393 mg/kg/day and female rats given 793 mg/kg/day trichloroethylene via drinking water for 6 months (Tucker et al. 1982). Cytomegaly and karyomegaly of the renal tubular epithelial cells were

observed in high-dose rats (males: 2,000 mg/kg/day; females: 1,000 mg/kg/day) and high-dose mice (3,000 mg/kg/day) treated by gavage with trichloroethylene in corn oil for 13 weeks (NTP 1990). The effect was described as minimal to mild in rats and mild to moderate in mice. Because histopathological examinations were not completed at lower doses, this study does not identify a NOAEL for renal effects.

Daily administration of trichloroethylene in corn oil by gavage for 78 weeks to male and female Osborne-Mendel rats (approximately 550–1,100 mg/kg/day) and B6C3F1 mice (approximately 1,200–2,300 mg/kg/day) resulted in treatment-related chronic nephropathy, characterized by degenerative changes in the tubular epithelium (NCI 1976). In chronic (103-week) carcinogenicity studies of rats and/or mice, nonneoplastic renal effects included toxic nephrosis (characterized as cytomegaly) at daily gavage doses of 500 and 1,000 mg/kg (NTP 1990) and cytomegaly of the renal tubular cells coupled with toxic nephropathy (NTP 1988). The NTP (1988) study examined the effects of trichloroethylene in four strains of rats. Osborne-Mendel rats appeared to be the most sensitive to the renal effects of trichloroethylene. At a dose of 500 mg/kg/day, toxic nephrosis occurred in 78% of male and 60% of female Osborne-Mendel rats, 37% of male and 45% female ACI rats, 36% of male and 63% of female Marshall rats, and 20% of male and 17% female August rats. Another chronic study revealed renal tubular nucleocytosis in 50% of male rats exposed to 250 mg/kg/day trichloroethylene for 52 weeks by oil gavage (Maltoni et al. 1986). Further explanation of these studies is in Section 3.2.2.7.

Endocrine Effects. Among persons in the ATSDR Trichloroethylene Subregistry, statistically significant increased prevalence of diabetes was reported at some (but not all) timepoints compared to a national referent population (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). However, inherent limitations in study design preclude establishment of a cause- and-effect relationship. For example, exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences. Self-reported symptoms of members of the trichloroethylene subregistry may have been influenced by knowledge of trichloroethylene exposure. Selected symptoms are common to trichloroethylene and other substances found in the water sources.

Adrenal gland weights were not affected in rats treated by gavage with 1,500 mg/kg/day trichloroethylene in corn oil for 14 days (Berman et al. 1995). Histopathological changes in endocrine glands (thyroid, parathyroid, pancreas, adrenals, pituitary) have not been observed in rats or mice exposed by gavage to trichloroethylene in oil for intermediate or chronic durations (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990).

Dermal Effects. Some of the people in Woburn, Massachusetts, who had been chronically exposed to trace amounts of trichloroethylene and other substances in the drinking water reported skin lesions (Byers et al. 1988). These were maculopapular rashes that were said to occur approximately twice yearly and lasted 2–4 weeks. These skin conditions generally ceased 1–2 years after cessation of exposure to contaminated water. The limitations of this study are discussed in Section 3.2.2.7. A case study was published of a 63-year-old rural South Carolina woman exposed to trichloroethylene and other chlorinated hydrocarbons in her well water, who developed diffuse fasciitis, although her husband did not (Waller et al. 1994). The level of trichloroethylene measured in the well water was 19 mg/L. Substitution of bottled water for drinking resulted in improvement of symptoms. Significant excess prevalence of skin rashes, eczema, or other skin disorders was reported in the ATSDR Trichloroethylene Subregistry of people exposed to trichloroethylene from contaminated domestic water supplies at baseline and several follow-up timepoints (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). However, inherent limitations in study design preclude establishment of a cause-and-effect relationship. For example, exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences. Self-reported symptoms of members of the trichloroethylene subregistry may have been influenced by knowledge of trichloroethylene exposure. Selected symptoms are common to trichloroethylene and other substances found in the water sources.

Alopecia, roughening of the hair coat, and sores were reported in rats, and alopecia and skin sores were reported in mice treated by gavage with trichloroethylene in corn oil for 78 weeks (NCI 1976). The rats were treated with time-weighted average (TWA) doses of 549 and 1,097 mg/kg/day, and the mice were treated with doses of 1,169 and 2,339 mg/kg/day for males and 869 and 1,739 mg/kg/day for females. Histopathological changes in the skin have not been observed in rats or mice treated by gavage with trichloroethylene in oil for intermediate or chronic durations (Maltoni et al. 1986; NTP 1988, 1990).

Ocular Effects. No studies were located regarding ocular effects in humans following oral exposure to trichloroethylene.

Squinting and a red discharge from the eyes were reported with increasing frequency in rats treated by gavage with trichloroethylene in corn oil at TWA doses of 549 and 1,097 mg/kg/day for 78 weeks (NCI 1976). No histopathological changes were observed in the eyes of rats or mice following chronic-

duration oral treatment with trichloroethylene (Maltoni et al. 1986; NCI 1976; NTP 1988). The highest doses used in these studies were 1,097 mg/kg/day for rats and 2,239 mg/kg/day for mice (NCI 1976).

Body Weight Effects. Several animal studies found no treatment-related effects on body weight during repeated oral exposure to trichloroethylene at gavage doses in the range of 100–3,200 mg/kg/day (Buben and O'Flaherty 1985; Goldsworthy and Popp 1987; Merrick et al. 1989; Stott et al. 1982; Tucker et al. 1982) or through the drinking water at concentrations resulting in estimated doses as high as 206 and 734 mg/kg/day (Griffin et al. 2000a; Waseem et al. 2001).

Several studies reported body weight effects following oral exposure to trichloroethylene; most of these studies did not include information regarding food or water consumption. Mean body weight of a group of rats administered trichloroethylene by gavage at 2,000 mg/kg/day for 13 weeks was 24% lower than that of controls; the NOAEL was 1,000 mg/kg/day (NTP 1990). In pregnant rats treated by gavage at 1,125 mg/kg/day on GDs 6–19, body weight gain was 45% lower than controls (Narotsky and Kavlock 1995). Narotsky et al. (1995) reported 31% lower body weight gain in rats treated with 475 mg/kg/day on GDs 6–15. DuTeaux et al. (2004) reported mean body weight gains of only 18–19 g in groups of male rats receiving trichloroethylene from the drinking water for 14 days at 143 or 270 mg/kg/day; the control group exhibited a mean body weight gain of 78 g. However, nonstatistically significant differences in mean initial body weight may have influenced the weight gain (mean initial body weight of controls was only 553 g compared to 573 and 606 g for the low- and high-dose groups, respectively). Cai et al. (2008) reported 26% decreased body weight gain during the first 11 weeks of a 48-week study in which female mice were administered trichloroethylene in the drinking water at concentrations resulting in an author-estimated average trichloroethylene intake of 60 mg/kg/day; there was no apparent treatment-related effect on water consumption, but the report did not include information regarding food consumption. As much as 30% depressed mean body weight was noted in young mice that received trichloroethylene from the drinking water at 122 mg/kg/day during 4 weeks of postweaning treatment; the mice had also been exposed via their mothers during gestation and lactation (Blossom and Doss 2007). Water consumption was similar among controls and trichloroethylene-treated groups, but food consumption data were not included in the study report. There were no effects on body weight among similarly-treated mice that received trichloroethylene from the drinking water at 31 mg/kg/day (Blossom et al. 2008).

Following chronic exposure, body weights of rats were similar to controls or up to 18% lower than controls at doses of 500 or 1,000 mg/kg/day, respectively (NCI 1976; NTP 1988, 1990). Among the different rat strains tested (ACI, August, Marshall, Osborne-Mendel), one gender was not consistently

more sensitive to the effects of trichloroethylene on body weight than the other gender. Body weights were not affected in rats treated by gavage with trichloroethylene in olive oil at 250 mg/kg/day for 52 weeks (Maltoni et al. 1986). In mice treated by gavage with trichloroethylene in corn oil for 103 weeks, body weights of males were 10% less than controls at a dose of 1,000 mg/kg/day, with no effect on body weights of female mice (NTP 1990). No body weight effects were seen in mice of either sex treated by gavage with trichloroethylene in corn oil for 78 weeks at doses up to 2,339 mg/kg/day (NCI 1976). A 12% depression in mean terminal body weight was noted in a group of male mice administered trichloroethylene in the drinking water for 12 months at a concentration resulting in an estimated trichloroethylene dose of 3.3 mg/kg/day; there were no effects on terminal body weight of similarly-exposed female rats (Peden-Adams et al. 2008). However, these rats had also been exposed to trichloroethylene via their mothers during gestation.

3.2.2.3 Immunological and Lymphoreticular Effects

Immunological abnormalities were reported in 23 of 25 adults in Woburn, Massachusetts, who were exposed to contaminated well water and who were family members of children with leukemia (Byers et al. 1988). These immunological abnormalities, tested for 5 years after well closure, included persistent lymphocytosis, increased numbers of T-lymphocytes, and depressed helper:suppressor T-cell ratio. Auto-antibodies, particularly anti-nuclear antibodies, were detected in 11 of 23 adults tested. This study is limited by the possible bias in identifying risk factors for immunological abnormalities in a small, nonpopulation-based group identified by leukemia types. Other limitations of this study are described in Section 3.2.2.7. A study of 356 residents of Tucson, Arizona, who were exposed to trichloroethylene (6–500 ppb) and other chemicals in well water drawn from the Santa Cruz aquifer found increased frequencies of 10 systemic lupus erythematosus symptoms, 5 of which were statistically significant (arthritis, Raynaud's phenomenon, malar rash, skin lesions related to sun exposure, seizure or convulsions) (Kilburn and Warshaw 1992). Diffuse fasciitis with eosinophilia was reported in a woman who had used well water contaminated with trichloroethylene (14 mg/L) for 6 years (Waller et al. 1994).

In the retrospective cohort morbidity study of Camp Lejeune, North Carolina marines described in Section 3.2.1.2 (Hematological Effects), risks of lupus or scleroderma were not increased in any trichloroethylene cumulative exposure group (ATSDR 2018).

Limited information was located regarding the potential for orally-administered trichloroethylene to induce immunosuppression in laboratory animals. Sanders et al. (1982) administered trichloroethylene to

male and female CD-1 mice by gavage at doses of 24 or 240 mg/kg/day for 14 days and to other groups of mice via the drinking water for 4 or 6 months at concentrations resulting in doses ranging from 18 to 793 mg/kg/day. Significantly decreased cell-mediated immune response to SRBCs was reported in the gavage-treated male (but not female) mice (25–61% decreased relative to controls). All groups of female (but not male) mice exposed via the drinking water exhibited significantly decreased cell-mediated immunity after 4 months of treatment (33–43% decreased relative to controls); however, following 6 months of treatment, the decreased response was observed only in the high-dose (793 mg/kg/day) group of female mice. In the drinking water study, antibody-mediated immunity was significantly inhibited in females only at the two highest doses (437 and 793 mg/kg/day). Overall, females were more sensitive and the effects on the immune system were consistent with those of other chlorinated hydrocarbons. No effects were seen on bone marrow or macrophage function. However, limitations of this study included the lack of a clear dose-response in most of the assays and the transient nature of some of the responses.

The potential for trichloroethylene to accelerate autoimmune diseases has been investigated in several oral studies. The MRL+/+, MRL-*lpr*, and NZB x NZW mouse strains spontaneously develop conditions that resemble the human disease, systemic lupus erythematosus (SLE). The MRL-*lpr* and NZB x NZW strains exhibit a high degree of susceptibility with early disease development (6–8 months); the MRL+/+ strain is less severely affected and exhibits later disease development (12 months). The MRL+/+ strain has been used in most studies.

Keil et al. (2009) administered trichloroethylene in the drinking water to groups of female NZBWF1 mice (known to spontaneously develop autoimmune disease) and B6C3F1 mice (a commonly-used strain used in immunotoxicity testing and not genetically prone to develop autoimmune disease) for 27 or 30 weeks, respectively, at 1.4 or 14 ppm (estimated trichloroethylene doses of 0.35 and 3.5 mg/kg/day, respectively). The B6C3F1 mice exhibited 30–38% decreased thymus weight; this effect was not seen in the autoimmune disease-prone strain. Numbers of activated T-cells (CD4+/CD44+) were increased in the B6C3F1 mice, but not the autoimmune disease-prone strain. Serum levels of autoantibodies to double-stranded DNA (dsDNA) and single-stranded DNA (ssDNA) were increased at more time points in the B6C3F1 mice than the autoimmune disease-prone strain. As expected in the autoimmune disease-prone strain, control mice exhibited age-related steadily increasing levels of antiglomerular autoantibodies; however, significant increases in antiglomerular autoantibodies in the trichloroethylene-treated autoimmune disease-prone strain were observed only at 11 and 19 weeks of age. Trichloroethylene exposure did not affect serum levels of antiglomerular autoantibodies in the B6C3F1 strain. Total serum IgG levels were significantly increased in the autoimmune disease-prone strain at 11 and 36 weeks of age

(high-dose group only) and in the B6C3F1 strain at 26 weeks of age (high-dose group only) and 39 weeks of age (low- and high-dose groups). Trichloroethylene did not significantly alter splenic NK cell activity in either mouse strain. Under the conditions of this study, trichloroethylene did not appear to contribute to the progression of autoimmune disease in the autoimmune disease-prone strain, but may have increased expression of markers associated with autoimmune disease in the B6C3F1 strain. The effect of decreased thymus weight in the low-dose group of mice serves as partial basis for the chronic-duration inhalation and oral MRLs for trichloroethylene (see Appendix A); this immunological effect is considered relevant to humans in the absence of data to indicate otherwise.

Female MRL+/+ mice (Gilbert et al. 1999; Griffin et al. 2000a) were exposed to trichloroethylene in the drinking water for 4, 8, or 22 weeks at concentrations of 0, 2.5, or 5.0 mg/mL (estimated doses of 0, 455, and 734 mg/kg/day, respectively).

After 4 weeks of treatment with trichloroethylene, splenic CD4+ T-cells were found to exhibit a dose-dependent increase in the percentage of cells expressing high levels of CD44, and a corresponding decrease in the percentage of cells expressing low levels of CD45RB; total serum immunoglobulins were increased as well. These results are suggestive of a trichloroethylene-induced accelerated autoimmune response. A subsequent study (Griffin et al. 2000b) employed lower trichloroethylene concentrations (0, 0.1, 0.5, and 2.5 mg/mL; estimated doses of 0, 21, 100, and 400 mg/kg/day) for 4 or 32 weeks and reported significantly increased serum antinuclear antibody levels following 4 weeks of treatment at 0.1 and 0.5 mg trichloroethylene/kg/day, dose-related increased percentage of activated CD4+ T-cells at 32 weeks, and significantly increased hepatic mononuclear infiltration in the portal region (a type of hepatic infiltration consistent with autoimmune hepatitis). These results collectively suggest that trichloroethylene exposure at occupationally-relevant concentrations might accelerate an autoimmune response.

Cai et al. (2008) exposed female MRL+/+ mice to trichloroethylene in the drinking water at 0 or 0.5 mg/mL (estimated doses of 0 or 60 mg/kg/day) for up to 48 weeks and reported increased serum concentrations of antinuclear antibodies after 36 and 48 weeks, accompanied by histopathological evidence of lymphocyte infiltration in the liver at 36 and 48 weeks and in the pancreas, lung, and kidney at 48 weeks. Immunoglobulin deposits were detected in kidney glomeruli at 48 weeks as well. The results suggest that trichloroethylene promoted inflammation in these organs.

Evidence of trichloroethylene-induced enhancement of allergic or hypersensitivity reactions in animals includes results of several studies by Seo and coworkers (Kobayashi et al. 2010, 2012; Seo et al. 2008b, 2012). In these studies, male rats or mice were administered trichloroethylene in the drinking water for 2 or 4 weeks at concentrations resulting in ingested doses of 0.12 µg trichloroethylene/mouse/day (low dose),12 µg/mouse/day (high dose), 0.73 µg/rat/day (low dose), or 72.6 µg/rat/day (high dose). Based on default reference body weights (EPA 1988), estimated doses were 0.004 and 0.4 mg trichloroethylene/kg/day for the low- and high-dose mice, respectively, and 0.0024 and 0.24 mg/kg/day for the low- and high-dose rats, respectively. Treatment with trichloroethylene at the lowest doses tested was reported to enhance passive and active anaphylaxis reactions and antigen-stimulated allergic responses and increase splenocyte proliferation, including concentration-related increased percentage of CD8+ cells in ovalbumin-aluminum hydroxide-immunized mice. The low dose levels employed in these studies were ≥2 orders of magnitude lower than those employed in other oral animal studies.

It should be noted that histopathological changes in the spleen and thymus were not observed in rats following acute-duration oral exposure to trichloroethylene in corn oil (Berman et al. 1995) or in rats or mice exposed orally to trichloroethylene for intermediate or chronic durations (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990).

The highest NOAEL values and all LOAEL values from each reliable study for immunological/ lymphoreticular effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-17.

Developmental immunotoxicity end points are discussed in Section 3.2.2.6.

3.2.2.4 Neurological Effects

There are several case studies of acute accidental ingestion of varying amounts (2 tablespoons to 16 ounces) of trichloroethylene by humans. These people had muscle weakness, vomiting, and became unconscious or delirious but recovered within 2 weeks (Morreale 1976; Perbellini et al. 1991; Stephens 1945; Todd 1954). Tremor and coma have been observed in people who ingested large amounts (500–1,000 mL) of trichloroethylene (Liotier et al. 2008; Moritz et al. 2000).

The epidemiological studies of the people exposed to trichloroethylene, as well as other chemicals, from well water in Woburn, Massachusetts, did not reveal neurological complaints (study limitations described

in Section 3.2.2.7) (Byers et al. 1988; Lagakos et al. 1986a). Some of the people from this population showed residual damage to the facial and trigeminal nerves, measured by a decreased blink reflex (indicating damage to cranial nerves V and VII) 6 years post-exposure (Feldman et al. 1988). Testing of water supplied to this population over a 2-year period (1979–1981) revealed mean trichloroethylene levels of 256 ppb (range 184–400 ppb) in one well and 111 ppb (range 63–188 ppb) in another well. A limitation of this study is the lack of individual exposure data. A similar limitation was inherent in a study examining neurobehavioral (speed of sway, nonverbal non-arithmetical measure of aptitude, profile of mood states), neurophysiological (simple visual reaction time, body balance, eye closure, and blink), and neuropsychological (immediate recall tests from Wechsler's Memory Scale, pegboard test) test results in residents exposed to well water containing trichloroethylene (6 or 500 ppb) and other chemicals in Tucson, Arizona. In this population, significant decreases in blink reflex, eye closure, choice reaction time, and intelligence test scores, as well as increases in mood disorders, were noted in exposed individuals compared to a group of referents from Phoenix, Arizona (Kilburn and Warshaw 1993). Efforts were made to control for individual variables such as age, sex, income, education, medical and psychological condition, and native language. Further study of this population revealed impaired balance (Kilburn et al. 1994). Among persons in the ATSDR Trichloroethylene Subregistry, statistically significant increases in hearing and speech impairment were noted in children <10 years of age at baseline assessment compared to a national referent population; however, at several follow-up timepoints, significant excesses were not found (ATSDR 1994, 1999, 2002; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). The trichloroethylene subregistry study reported borderline statistically significant associations between exposure to trichloroethylene concentrations >15 ppb and signs of neurobehavioral deficits (poorer performance on a digit symbol and contrast sensitivity tests and higher mean scores for confusion, depression, and tension) (ATSDR 2001; Reif et al. 2003). However, there are limitations to the study design. For example, exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences. Also, self-reported symptoms may have been influenced by knowledge of trichloroethylene exposure. In a retrospective cohort mortality study of 4,647 full-time civilian workers at Camp Lejeune during 1973–1985 potentially exposed to trichloroethylene-contaminated drinking water (among other contaminants), Bove et al. (2014a) did not calculate SMRs for Parkinson’s disease because less than five cases were observed.

In the retrospective cohort morbidity study of Camp Lejeune, North Carolina marines described in Section 3.2.1.2 (Hematological Effects), there was no indication of increased risk of amyotrophic lateral

sclerosis (ALS), multiple sclerosis, or Parkinson's disease in any trichloroethylene cumulative exposure group (ATSDR 2018).

In animal studies, signs of neurotoxicity and neuropathology have been observed in response to oral doses of trichloroethylene. Note that studies on neurological effects in laboratory animals exposed only during gestation are discussed in Section 3.2.2.6 (Oral Exposure, Developmental Effects).

In acute studies, increased rearing activity was observed in rats treated by gavage with 500 mg/kg/day trichloroethylene in corn oil for 14 days (Moser et al. 1995). Effects on activity were not observed at 150 mg/kg/day. Transient ataxia, observed shortly after dosing, was reported in pregnant rats treated by gavage with 633 mg/kg/day trichloroethylene in corn oil on GDs 6–15 (Narotsky et al. 1995). Ataxia was not observed at 475 mg/kg/day. Adult male rats exposed to 312 mg/L trichloroethylene in their drinking water (approximate dose of 23.3 mg/kg/day) for 4 weeks, followed by 2 weeks of nonexposure, then 2 more weeks of exposure, showed increased performance in the Morris Swim Test and decreased brain myelination (Isaacson et al. 1990). Nunes et al. (2001) reported 25% increased foot splay in rats administered trichloroethylene by gavage (in corn oil) at 2,000 mg/kg/day for 7 days. Degenerative changes in dopaminergic neurons were observed in the substantia nigra from rats administered trichloroethylene by gavage at 1,000 mg/kg/day 5 days/week for 6 weeks; dopamine levels were significantly decreased in the substantia nigra, but not in the striatum (Gash et al. 2008).

Exposures of 10 weeks (5 days/week) to 2,500 mg/kg/day trichloroethylene in corn oil by gavage resulted in altered myelin thickness in the rat mental nerve, a branch of the trigeminal nerve (Barret et al. 1991). Effects of similar exposures on the rat trigeminal nerve included decreased fiber diameter and altered fatty acid composition in total lipid extracts, indicative of demyelination (Barret et al. 1992). Stronger effects were seen with the trichloroethylene decomposition product dichloroacetylene.

Central nervous system effects were also observed during two chronic studies of rats and mice. In the first study, rats exposed to 500 or 1,000 mg/kg/day trichloroethylene in corn oil by gavage for 103 weeks exhibited sporadic and generally transient effects that included ataxia, lethargy, convulsions, and hind limb paralysis (NTP 1988). Later in the study some rats convulsed before dosing and while they were being weighed, suggesting that the effect was more than just an acute effect occurring directly after dosing. In a 54-week carcinogenicity study using exposure levels of 2,400 mg/kg/day for males and 1,800 mg/kg/day for females, mice demonstrated central nervous system effects characterized by an initial period of excitation a few minutes after daily treatment by gavage with trichloroethylene in corn

oil, followed by a subanesthetic state (not characterized) lasting another 15–30 minutes (Henschler et al. 1984).

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-17.

3.2.2.5 Reproductive Effects

Adverse reproductive effects were not noted in a human population in Massachusetts that was exposed to trichloroethylene in drinking water (Byers et al. 1988; Lagakos et al. 1986a). There was no increase in adverse pregnancy outcomes within three communities in Michigan where residents were exposed to trichloroethylene and other solvents in drinking water (Freni and Bloomer 1988). Residents in communities surrounding the Rocky Mountain Arsenal in Colorado were assessed for health outcomes, including selected reproductive/developmental end points, after trichloroethylene was detected in the drinking water (ATSDR 2001). There were no statistically significant positive associations between exposure to trichloroethylene and outcomes that included parity, miscarriages, birth defects, and abnormal menstrual cycle, even within the group with highest estimated exposures to trichloroethylene (>10 ppb). This study is limited for the purpose of determining causal relationships between exposure to trichloroethylene and health outcomes because exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences, and self-reported symptoms of members of the trichloroethylene subregistry may have been influenced by knowledge of trichloroethylene exposure.

The retrospective cohort morbidity study of Camp Lejeune, North Carolina marines described in Section 3.2.1.2 (Hematological Effects) evaluated risk of adverse male and female reproductive effects associated with trichloroethylene cumulative exposure from contaminated drinking water sources (ATSDR 2018). ORs for risk of male infertility were 2.69 (95% CI 1.22–5.92) for the low exposure group, based on 64 instances; 2.83 (95% CI 1.28–6.29) for the medium exposure group, based on 54 instances; and 2.31 (95% CI 0.88–6.05) for the high exposure group, based on 11 instances. ORs for risk of low sperm count were 4.26 (95% CI 1.01–17.96) for the low exposure group, based on 29 instances; 4.59 (95% CI 1.08–19.50) for the medium exposure group, based on 25 instances; and 0.74 (95% CI 0.07–8.15) for the high exposure group, based on 1 instance. ORs for risk of female infertility were 1.58 (95% CI 1.05–2.37) for the low exposure group, based on 81 instances; 1.18 (95% CI

0.58–2.39) for the medium exposure group, based on 12 instances; and 1.73 (95% CI 0.83–3.60) for the high exposure group, based on 12 instances.

A continuous breeding fertility study was conducted in which male and female F344 rats were fed diets containing microencapsulated trichloroethylene that resulted in doses of approximately 0, 75, 150, or 300 mg/kg/day from 7 days before mating through birth of the F2 generation (NTP 1986). There was an increase in the relative left testis/epididymis weight in the F0 generation and a decrease in absolute left testis/epididymis weight in the F1 generation; however, the NTP staff concluded that these results were more likely due to generalized toxicity rather than a specific effect on the reproductive system. Furthermore, the testis/epididymis weight changes were not accompanied by histopathological changes in these or any other tissue examined. There was no effect on reproductive performance. A similarly designed fertility study was conducted with CD-1 mice using the same dietary concentrations of trichloroethylene (up to 750 mg/kg/day) (NTP 1985). There were no treatment-related effects on mating, fertility, and reproductive performance in either the F0 or F1 mice, but sperm motility was reduced by 45% in F0 males and 18% in F1 males. F1 males exhibited significantly increased mean relative left testis/epididymis and right epididymis weights (9–11% greater than controls).

No effects on female fertility were noted in rats treated by gavage with trichloroethylene in corn oil at 1,000 mg/kg/day for 2 weeks before mating through gestation and postnatal days 0–31 (Manson et al. 1984). Maternal body weight gain was about 9% lower than controls at 1,000 mg/kg/day. No treatment-related effects on fertility were seen in studies of female rats receiving trichloroethylene from the drinking water during premating and/or gestation at estimated doses as high as 129 mg/kg/day (Dawson et al. 1993; Johnson et al. 1998, 2003). DuTeaux et al. (2004) reported decreased *in vitro* fertilization capacity of sperm from male rats that had been exposed to trichloroethylene in the drinking water for 14 days at concentrations resulting in estimated doses of 143 and 270 mg/kg/day. There were no significant effects on reproductive organ weights, sperm concentration, or percentage of motile sperm, although histopathologic evaluations of testes revealed slight (unspecified) changes in efferent ductile epithelium. Zenick et al. (1984) reported impairment in copulatory behavior, mount/ejaculation latency, and intromissions in male rats administered trichloroethylene by gavage at 1,000 mg/kg/day, 5 days/week for 6 weeks.

Histopathological changes in reproductive organs were not observed in rats or mice treated by gavage with trichloroethylene in corn oil for chronic durations (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990).

The highest doses used in these studies were TWA doses of 1,097 mg/kg/day in rats, 2,239 mg/kg/day in male mice, and 1,739 mg/kg/day in female mice (NCI 1976).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-17.

3.2.2.6 Developmental Effects

Epidemiological data are typically limited by concomitant exposure to other potentially hazardous substances, and case-control studies are limited by small numbers of cases.

In a survey of 80,938 live births and 594 fetal deaths conducted in an area of New Jersey with contaminated public drinking water (average exposure of 55 ppb), Bove et al. (1995) reported ORs for trichloroethylene in the drinking water and risk of selected developmental end points. For exposure to trichloroethylene at levels >10 ppb, ORs were 1.68 (90% CI 0.76–3.52) for central nervous system defects based on six cases, 2.53 (90% CI 0.91–6.37) for neural tube defects based on four cases, 1.30 (90% CI 0.39–3.68) for oral cleft defects based on three cases, 1.24 (50% CI 0.75–1.94) for major cardiac defects based on an unspecified number of cases, and 1.30 (50% CI 0.88–1.87) for ventricular septal defects based on an unspecified number of cases. Uncertainty regarding exposure classification and small numbers of cases, in addition to the presence of other drinking water contaminants, were the main limitations of this study.

In a study of residents exposed to drinking water contaminated with solvents (including 267 ppb trichloroethylene) in Woburn, Massachusetts, there was a suggestion that the combination of eye and ear anomalies and the combination of central nervous system, chromosomal, and oral cleft anomalies in newborns were associated with contaminated water exposure (Lagakos et al. 1986a). However, several scientists have questioned the biological relevance of the unusual groupings of these anomalies for purposes of statistical analysis (MacMahon 1986; Prentice 1986). The grouping of central nervous system disorders, chromosomal disorders, and oral cleft anomalies is questionable because they are not linked in embryological development. Other disorders that the study authors classified as congenital are not so classified by the International Classification of Diseases (ICD). Because expected rates are generated from statistical databases that rely on the ICD classifications, this regrouping could affect the data analyses and the conclusions drawn from them. In addition, not enough demographic or medical background information was provided on the subjects in this study to indicate that other potential

contributing factors were being considered. The study was performed following considerable publicity about the well contamination and the possible health effects that could follow these exposures, thus potentially contributing to recall bias of the participants. Further limitations of this study are described in Section 3.2.2.7.

In a report of the Woburn population prepared by the Massachusetts Department of Public Health (MDPH 1996), it was indicated that there was an increased prevalence in choanal atresia (a rare respiratory effect) and hypospadias/congenital chordee, and a small increase in eye defects, but there was no association between trichloroethylene exposure and heart defects. There were no statistically significant associations between exposure concentrations and birth defects, although analyses were limited by the small number of cases observed. Birth weights tended to be lower in trichloroethylene-exposed infants compared to controls, but not statistically significantly lower. The rate of choanal atresia per 1,000 live births and fetal deaths was 0.88 in the trichloroethylene-exposed Woburn population (based on 4 cases), compared to rates of 0.11 in the Atlanta comparison population (based on 17 cases) and 0.13 in the California comparison population (based on 33 cases). In a prospective study completed after well closure, the rate of choanal atresia was 0.88 (based on 1 case) in Woburn, 0.11 (based on 1 case) in the surrounding communities, and 0.2 in Atlanta (based on 9 cases) and 0.13 in California (based on 33 cases) (MDPH 1996). The study authors cautioned that their study did not rule out moderate increases in rates of the less common adverse reproductive outcomes. For these outcomes only large increases would have been detected.

White et al. (1997) reported verbal naming/language impairment in 6/13 children from the Woburn, Massachusetts population and similar indicators of cognitive impairment in children from two other communities with reported high levels of trichloroethylene in the drinking water (from 3.3 ppb to as much as 2,440 ppb) for as long as 12–25 years. However, these results are based on clinical examination and diagnostic procedures performed on limited numbers of subjects.

In a Tucson, Arizona, population exposed to trichloroethylene (6–239 ppb) and other contaminants (dichloroethylene and chromium) in the drinking water from certain wells, an association was found between the elevated levels of trichloroethylene in drinking water and congenital heart disease in children whose parents were exposed during the month before conception and the first trimester of pregnancy (Goldberg et al. 1990). Among children whose mothers lived in the areas receiving trichloroethylene contaminated water during the first trimester of pregnancy, the rate of congenital heart defects was approximately 2.5 times higher than among children of mothers who were not exposed to trichloro-

ethylene during pregnancy. Moreover, the rate of congenital heart defects decreased in the previously exposed area after the contaminated wells were shut off. The cases of birth defects reported in this study were medically confirmed and all were derived from the same hospital clinic population. A significant limitation of this report is that the exposure was ill-defined. Exposures for individuals were not quantifiable, the areas that received trichloroethylene-contaminated water were not clearly delineated, the year when exposure began was unknown, and the amount of trichloroethylene in the water varied from year to year, though actual concentrations were measured in 1981. In addition, the population was exposed to other substances in the water (including dichloroethylene and chromium), although concentrations of trichloroethylene were highest. Rodenbeck et al. (2000) found no significant association between trichloroethylene in the drinking water and birth weight outcomes in a section of the Tucson, Arizona, area where the trichloroethylene contamination in the drinking water was estimated to have ranged from <5 to 107 µg/L during the period of 1978–1981. In this study, a comparison group without trichloroethylene-contaminated drinking water was selected to match the socioeconomic status of the trichloroethylene-exposed population.

Among persons in the ATSDR Trichloroethylene Subregistry, statistically significant increases in hearing and speech impairment were noted in children <10 years of age at baseline assessment compared to a national referent population; however, at several follow-up timepoints, significant excesses were not found (ATSDR 1994, 1999, 2002; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). There are inherent limitations to the ATSDR Trichloroethylene Subregistry study. For example, exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences. Self-reported symptoms of members of the trichloroethylene subregistry may have been influenced by knowledge of trichloroethylene exposure. Selected symptoms are common to trichloroethylene and other substances found in the water sources.

A small effect on birth weight was noted in a report on adverse birth outcomes for a population living at Camp Lejeune, North Carolina (ATSDR 1997, 1998). The women were exposed some time during gestation. Statistical significance ($p \leq 0.05$) was achieved for all births (n=31) within the trichloroethylene-exposed group (mean birth weight 3,361 kg; standard error [SE] 71.8) compared to 997 unexposed births (mean birth weight 3,469 kg; SE 16.9) and all male births (trichloroethylene-exposed mean birth weight 3,213 kg; SE 113.2; n=12 versus trichloroethylene-unexposed birth weight 3,527 kg; SE 25.2; n=497). The trichloroethylene-exposed female birth weight (n=19) was not significantly different from that of controls (n=500). The study authors cautioned that the small trichloroethylene-exposed group size weakens the causal association. In a case-control study of children

born to mothers exposed to trichloroethylene-contaminated drinking water at Camp Lejeune during pregnancy in the time period of 1968–1985, exposure to trichloroethylene at >5 ppb resulted in ORs of 2.4 (95% CI 0.6–9.6) for risk of neural tube defects based on 3 cases in the exposed group and 0.8 (95% CI 0.2–3.0) for risk of oral cleft defects based on three cases in the exposed group (Ruckart et al. 2013).

A case-control study examining maternal residential proximity to chlorinated solvent emissions was conducted using the Texas Birth Defects Registry for births occurring between 1996 and 2008 (Brender et al. 2014). For trichloroethylene adjusted ORs (95% CIs) for neural tube defect, anencephaly, and spina bifida were 0.95 (0.82, 1.08), 0.99 (0.76, 1.29), and 0.94 (0.79, 1.12), respectively. These risk estimates were not adjusted for exposure to other solvents.

A study of three Michigan communities exposed to chlorinated solvents including trichloroethylene (up to 14,890 ppb) in contaminated drinking water found no increase in congenital defects (Freni and Bloomer 1988). The size of the cohort, however, was smaller than that of other studies.

Gilboa et al. (2012) evaluated possible associations between estimated maternal occupational exposure to various solvents (including trichloroethylene) and congenital heart defects in offspring. The study population included mothers (n=2,047) of infants with simple isolated congenital heart defects and control mothers (n=2,951) who delivered between 1997 and 2002 and who participated in the National Birth Defects Prevention Study. Occupational solvent exposure was estimated based on self-reported information regarding job description and possible chemical exposures. There was no difference in prevalence of congenital heart defects among trichloroethylene-exposed mothers and control mothers (69/2047 or 3.4% among case mothers versus 94/2951 or 3.2% among control mothers; p=0.6). Major limitations of this study include the potential for misclassification of exposure and confounding by exposure to other solvents.

Bukowski (2014) reviewed available epidemiological data and noted that four studies reported associations between trichloroethylene exposure and congenital heart defects (Bove et al. 1995; Forand et al. 2012; Goldberg et al. 1990; Yauck et al. 2004). Bukowski (2014) stated that these studies contained inherent limitations in study design or analytical procedures, which may have influenced the findings. Bukowski (2014) also identified five studies that found no association between exposure to trichloroethylene and congenital heart defects (Gilboa et al. 2012; Lagakos et al. 1986a; MDPH 1996; Ruckart et al. 2013; Tola et al. 1980). Based on the available epidemiological data, Bukowski (2014)

contended that there is “no substantive or consistent evidence” for trichloroethylene-induced congenital heart defects.

Studies in animals indicate that trichloroethylene can act as a developmental toxicant, especially at doses high enough to result in maternal toxicity. Significant decreases in litter size have been reported in rats treated by gavage with 1,125 mg/kg/day trichloroethylene in corn oil on GDs 6–19 in F344 rats (Narotsky and Kavlock 1995) or GDs 6–15 in Sprague-Dawley rats (Narotsky et al. 1995). The deaths appeared to have occurred early in the dosing period. Maternal effects noted at 1,125 mg/kg/day included decreased body weight gain, transient ataxia, and decreased motor activity (Narotsky and Kavlock 1995; Narotsky et al. 1995). A dose-related increase in micro- or anophthalmia that was statistically significant at 1,125 mg/kg/day was also observed (Narotsky et al. 1995). Eye defects were observed in 1, 5.3, 9.2, 11.7, and 30% of pups from dams treated at 0, 475, 633, 844, and 1,125 mg/kg/day, respectively; doses ≥633 mg/kg/day resulted in overt maternal toxicity, including ataxia and significant weight loss (Narotsky et al. 1995). In a study in mice that did not use maternally toxic doses, no developmental effects were observed in the offspring of B6C3F1 mice treated by gavage with 240 mg/kg/day trichloroethylene in corn oil on GDs 1–5, 6–10, or 1–15 (Cosby and Dukelow 1992).

In a continuous breeding study in which trichloroethylene in microcapsules was added to the diet, there was a 61% perinatal mortality rate in F1 offspring of CD-1 mice exposed to 750 mg/kg/day from conception through weaning (NTP 1986). Decreased maternal body weight gain and reduced fetal body weights were also observed, but there were no skeletal or visceral anomalies. F344 rats similarly exposed to 300 mg/kg/day exhibited maternal toxicity manifested as decreased body weight, increased liver and kidney weights, and a slight reduction in litter size with no anomalies (NTP 1986).

Manson et al. (1984) administered trichloroethylene to female rats by gavage in corn oil at 0, 10, 100, or 1,000 mg/kg/day for 2 weeks prior to mating (5 days/week), during 1 week of mating (5 days of treatment), and throughout gestation. Significant treatment-related effects were limited to the 1,000-mg/kg/day group. Maternal effects included the death of 4/23 of the dams and 34% depression of body weight gain among the survivors. One high-dose dam had a completely resorbed litter. Developmental effects included increased numbers of stillborn pups (9/142 including 1/64 males and 8/78 females versus 2/181 controls including 1/87 males and 1/94 females). Significantly decreased neonatal survival postculling (postnatal days 3–18) was noted (24/110 deaths including 7 male and 17 female pups versus 14/128 controls including 7/62 males and 7/66 females). These effects on the pups

were likely the result of serious maternal toxicity rather than a direct developmental effect. There were no signs of treatment-related teratogenic effects.

Johnson and coworkers (Dawson et al. 1993; Johnson et al. 1998, 2003) reported increased incidences of cardiac malformations in fetuses of rat dams exposed to trichloroethylene in the drinking water during premating and gestation or gestation alone. Groups of 9–39 female rats were exposed to trichloroethylene in drinking water at 0, 1.5, or 1,100 ppm (estimated doses of 0.218 and 129 mg/kg/day, respectively) either before pregnancy (for 3 months prior to mating), before and during gestation (2 months prior to mating plus 21 days of gestation), or during gestation only (Dawson et al. 1993; Johnson et al. 1998). Maternal toxicity was not observed in any of the exposure groups. Fetal heart defects were not observed in fetuses from dams exposed only before pregnancy. Abnormal fetal heart development was observed at both concentrations in dams exposed before and during pregnancy (3% of 238 concurrent control fetuses; 8.6% or 22/255 of the low-dose fetuses; 9.2% or 40/434 of the high-dose fetuses). In dams exposed only during pregnancy, fetal heart defects were observed only at the higher dose (11/105 or 10.48% versus 3% of 238 concurrent controls).

Johnson et al. (2003) reported results from rat dams administered trichloroethylene in the drinking water at 0.0025, 0.25, 1.5, or 1,100 ppm during gestation (estimated doses of 0.00045, 0.048, 0.218, and 129 mg/kg/day, respectively). The study authors stated that there were no statistically significant differences between controls and trichloroethylene-treated groups regarding maternal and fetal variables other than congenital cardiac abnormalities. Control data were pooled from multiple studies; the study report did not include concurrent control data. Incidences of control fetuses with cardiac abnormalities were 13/606 (2.15%). Incidences of fetuses with cardiac abnormalities in the 0.0025, 0.25, 1.5, and 1,100 ppm groups were 0/144 (0%), 5/110 (4.5%), 9/181 (5.0%), and 11/105 (10.48%), respectively. Compared to the pooled controls, the incidences of fetuses with cardiac abnormalities were significantly increased only at the 1.5 and 1,100 ppm exposure levels ($p=0.044$ and $p<0.001$, respectively). The study authors also reported results on a per-litter basis (number of litters with at least one fetus that exhibited a cardiac malformation per number of litters). Nine of 55 control litters had one or more fetuses with a cardiac malformation; incidences in the 0.0025, 0.25, 1.5, and 1,100 ppm groups were 0/12 (0%), 4/9 (44%), 5/13 (38%), and 6/9 (67%), respectively. Limitations to the studies of Johnson and coworkers include statistical analyses of findings on a per-fetus basis and use of nonconcurrent control data in the analysis.

In comparing the study reports of Dawson et al. (1993) and Johnson et al. (2003), Hardin et al. (2004) noted that: (1) the data for the 1.5 and 1,100 ppm dose groups were common to both studies, (2) there was some variation between the two study reports regarding incidence data for selected cardiac defects, and (3) the report of Johnson et al. (2003) included an "uncharacteristically large control group" (55 dams) compared to 9–13 dams in trichloroethylene-treated groups. Johnson et al. (2004) acknowledged that the data for the 1.5 and 1,100 ppm dose groups were common to both study reports (Dawson et al. 1993; Johnson et al. 2003), and noted that additional dose groups (0.0025 and 0.25 ppm groups) were subsequently assessed in ongoing investigations and included in combination with the 1.5 and 1,100 ppm dose groups to avoid duplication and sacrifice of additional animals. In the Johnson et al. (2003) study report, reclassification of cardiac defects resulted in slight differences from the Dawson et al. (1993) report regarding terminology and incidences for cardiac defects. Ranges of study dates and numbers of animals used in control and trichloroethylene-treated groups were presented in a table published in the correspondence section of the January 2005 Environmental Health Perspectives [113(1):A18] along with explanation for combining results for multiple control groups (Anonymous 2005). In the correspondence section of the April 2014 Environmental Health Perspectives [122(4):A94], it was noted that: (1) exact exposure start dates for two trichloroethylene exposure groups and their concurrent controls in the table published in the correspondence section of the January 2005 Environmental Health Perspectives [113(1):A18] could not be confirmed but were in 1994 (not 1995); (2) all trichloroethylene exposures lasted throughout gestation; (3) all experiments were run with concurrent controls; and (4) rats were ordered on a 40-animal maximum capacity and were randomly assigned to study groups (Anonymous 2014). Critical review of the studies of Johnson and coworkers (Dawson et al. 1993; Johnson et al. 1998, 2003) has led some investigators to conclude that the weight of evidence from human and animal data does not support a role for trichloroethylene in congenital heart defects (e.g., Hardin et al. 2004, 2005; Watson et al. 2006). However, in the absence of convincing information to the contrary, the report of trichloroethylene-induced cardiac malformations in rat fetuses is considered valid and relevant to humans, based on available epidemiological and animal data, as well as mechanistic information (EPA 2011e). EPA (2014a) released results from a Toxic Substances Control Act (TSCA) Work Plan Chemical Risk Assessment for trichloroethylene that included a weight-of-evidence analysis for fetal cardiac malformations following trichloroethylene exposure (see Appendix N in EPA 2014a; see also EPA 2014b). EPA concluded that "while the Johnson et al. studies have limitations, there is insufficient reason to dismiss their findings, especially when the findings are analyzed in combination with the remaining body of human, animal and mechanistic evidence" (see p. 98 in EPA 2014a). An EPA executive panel (EPA 2016) reviewed EPA's position regarding the weight-of-evidence for trichloroethylene-induced fetal cardiac malformations in rats and concluded that the information

presented in the Toxicological Review of Trichloroethylene (EPA 2011e) is "consistent with EPA's IQG [Information Quality Guideline] standards of objectivity and utility." The increased incidences of fetuses with cardiac malformations from the rat dams administered trichloroethylene during gestation serve as partial basis for the chronic-duration inhalation and oral MRLs for trichloroethylene (see Appendix A).

Fisher et al. (2001) designed a study to assess the ability of trichloroethylene and two of its metabolites (TCA and dichloroacetic acid [DCA]) to induce cardiac defects in Sprague-Dawley rat fetuses. Rat dams were administered trichloroethylene by gavage (in soybean oil vehicle) on GDs 6–15 at doses of 0 or 500 mg/kg/day; a positive control group was administered retinoic acid. The metabolites, TCA and DCA, were administered at a 300 mg/kg/day dose level. Fetal hearts were examined on GD 21 by *in situ* cardiovascular stereomicroscope examination, followed by implementation of a special heart dissection and staining method to enhance microscopic visualization of heart morphology. The incidences of fetuses with heart malformations were 13/290 (4.5%) for the trichloroethylene-treated group and 24/367 (6.5%) for the controls. On a litter basis, 12 of 20 litters from the trichloroethylene-treated dams exhibited at least one cardiac malformation compared to 12 of 25 control litters. Incidences of fetuses with heart malformations in the groups administered TCA or DCA were similar to that of controls; the positive control group exhibited expected results (51/155 fetuses with malformations compared to 13/290 controls; 92% of litters with a malformation compared to 60% in controls).

Blossom and Doss (2007) assessed the effects of trichloroethylene on the immune system of young MRL+/+ mice that had been exposed via their mothers during gestation and lactation (maternal doses of 123 and 684 mg/kg/day) and for an additional 4 weeks via their drinking water (offspring doses of 122 and 553 mg/kg/day). Significantly increased cytokine IFN-γ production by splenic CD4+ cells, decreased splenic CD8+ and B220+ lymphocytes, increased IgG2a and histone, and altered thymocyte profiles were observed at the low-dose level. At the high dose, increased IFN-γ production by splenic CD4+ cells; decreased splenic CD+4, CD8+, and B220+ lymphocytes; and altered thymocyte profiles were noted. In a subsequent study that employed a single trichloroethylene exposure level (0.1 mg/mL) resulting in a 25.7 mg/kg/day maternal dose and a 31 mg/kg/day dose to the offspring, trichloroethylene treatment resulted in altered immunoregulation as evidenced by increased thymocyte cellularity associated with increased thymocyte subset distribution, increased reactive oxygen species generation in total thymocytes, and increased splenic CD4+ T-cell production of cytokines IFN-γ and IL-2 in females and TNF-α in males (Blossom et al. 2008).

Peden-Adams et al. (2006) administered trichloroethylene to male and female B6C3F1 mice (not prone to autoimmune disease) via the drinking water at 0, 1.4, or 14 ppm during mating, gestation, and lactation (estimated doses to the dams of 0, 0.37, and 3.7 mg/kg/day). Selected pups were assessed at 3 weeks of age for effects on the immune system (thymus and spleen weights, splenic lymphocyte proliferation, NK cell activity, plaque-forming cell [PFC] response to SRBC, numbers of splenic B220+ cells, and thymic and splenic T-cell immunophenotypes). Other pups were similarly assessed at 8 weeks of age with additional assessments of autoantibodies to dsDNA and delayed-type hypersensitivity response (indicated by foot pad swelling following subcutaneous injection of SRBC). Thymus weights were not affected by trichloroethylene exposure. Spleen weight was depressed by 15% in the 1.4-ppm exposure group of pups 3 weeks of age. Splenic lymphocyte proliferation and NK cell activity were not affected in pups at either tested time point. The PFC response was significantly decreased in male and female pups at both trichloroethylene exposure levels. Splenic numbers of B220+ cells were decreased only in 3-week-old pups of the 14 ppm treatment level. Delayed-type hypersensitivity response was significantly increased in 8-week-old female pups of low- and high-dose groups and in high-dose male pups; there was no significant effect on autoantibodies to dsDNA in the 8-week-old male or female pups. The decreased PFC response in the male and female pups serves as partial basis for the chronic-duration oral MRL for trichloroethylene (see Appendix A); this effect is considered relevant to humans in the absence of data to indicate otherwise.

Postnatal exposure of male mice to 50 or 290 mg/kg/day trichloroethylene between the ages of 10 and 16 days resulted in a significant reduction in rearing (raising front legs, resting on haunches) rate at both doses when they were tested at age 60 days; the effect did not appear to be dose-dependent and there was no treatment-related effect on locomotion or total activity (Fredriksson et al. 1993). The results of this study indicate that trichloroethylene may affect brain maturation.

Results of several animal studies implicate the hippocampal brain region (a region involved in spatial memory and navigation) as a target of trichloroethylene developmental toxicity following gestational and/or early postnatal exposure. A 40% decrease in the number of myelinated fibers was observed in the hippocampus of 21-day-old offspring of rats receiving trichloroethylene from the drinking water at approximately 37 or 75 mg/kg/day from premating throughout gestation and lactation (Isaacson and Taylor 1989). Decreased numbers of myelinated fibers were noted in the hippocampus of young rats receiving trichloroethylene from the drinking water at 5.5 mg/kg/day for 4 weeks (Isaacson et al. 1990); in those rats exposed for 2 additional weeks (following a 2-week non-treatment period) at an effective dose level of 8 mg/kg/day, increased level of performance of spatial navigational tasks and decreased

amount of hippocampal myelin were observed. Decreases in myelinated fibers represent a serious adverse effect. The study authors suggested that the reduction in hippocampal myelin may be related to the increased level of performance of spatial navigational tasks. Blossom et al. (2012) reported altered glutathione redox homeostasis (indicating a more oxidized state) and dose-related increased levels of glutathione precursors within the hippocampus of male mice receiving trichloroethylene via their mothers during lactation and directly from the drinking water for 3 weeks postweaning at estimated doses as low as 2.7 mg/kg/day (postweaning dose); neurobehavioral end points were not assessed. A significant dose-related trend for increased time required for grid traversal was noted in 21-day-old rats that had been exposed to trichloroethylene via their mothers during gestation and lactation at maternal doses ranging from approximately 75 to 300 mg/kg/day (NTP 1986); effects on other measures of open-field locomotor activity or miscellaneous behavior were not observed and evaluation of the F1 rats at 45 days of age was unremarkable, suggesting that trichloroethylene had a transient effect. In contrast, 6-week-old offspring of mice exposed throughout gestation to trichloroethylene in drinking water had increased motor activity, based on the distance traveled in 20 minutes (Blossom et al. 2017). The distance traveled by offspring of dams exposed to a daily dose of 2.96 mg/kg/day was increased by approximately 31% (p=0.01), relative to controls. For dams exposed to 26.56 mg/kg/day, the distance traveled was increased by 21% relative to control; however, this increase did not reach statistical significance (p-0.06). Distance traveled at 2-minute epoch during the 20-minute testing period was significantly increased in offspring of both treatment groups. Results suggest that neurotoxic effects may be sustained in offspring following prenatal-only exposure.

Glucose uptake by the brain was reduced in 21-day-old offspring of rats provided with 312 mg/L trichloroethylene (about 37 mg/kg/day) (Noland-Gerbec et al. 1986). Activity measurements showed increases in the 60-day-old offspring of rats provided with trichloroethylene in the drinking water at 312 mg/L (about 37 mg/kg/day) (Taylor et al. 1985).

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-17.

3.2.2.7 Cancer

Cancer Classifications. Cancer classifications for trichloroethylene by the HHS (NTP 2016), IARC (2014), and EPA (2011e) are reviewed in Section 3.2.1.7 (Inhalation, Cancer). Conclusions made in

comprehensive reviews (EPA 2011e; IARC 2014; NTP 2016) regarding associations between trichloroethylene exposure and specific cancer types also are summarized.

Epidemiological Studies. Epidemiological studies on the potential carcinogenic effects of oral exposure to trichloroethane are of populations exposed to drinking water contaminated with trichloroethylene and other solvents and chemicals, including tetrachloroethylene, benzene, chloroform, arsenic, and other halogenated solvents. The epidemiological data for oral exposure to trichloroethylene are much more limited than the inhalation data due to small numbers of studies and small cohort sizes, as well as potential confounding by co-exposure to other chlorinated solvents. Table 3-4 provides an overview of selected epidemiological studies, including study populations, exposure assessments (qualitative versus semi-quantitative, assessment methods), consideration of confounders, and study strengths and limitations.

Studies were selected for inclusion based on the following considerations:

- studies meeting the following criteria as listed in EPA (2011e): cohort or case-control study design; evaluation of incidence or mortality; adequate selection in cohort studies of exposure and control groups and of cases and controls in case-control studies; trichloroethylene exposure potential inferred to each subject and quantitative assessment of trichloroethylene exposure assessment for each subject by reference to industrial hygiene records indicating a high probability of trichloroethylene use, individual biomarkers, job-exposure matrices, or obtained from subjects using questionnaire (case-control studies);
- studies meeting the EPA (2011e) criteria that were published after 2011; and
- studies reporting risk estimates specific for trichloroethylene.

Five studies met these criteria (Table 3-4): three cohort studies (Bove et al. 2014a, 2014b; Cohn et al. 1994) and two case-control studies (Ruckart et al. 2013, 2015). Military personnel and civilians from the Marine Corps Base at Camp Lejeune, North Carolina were evaluated by ATSDR (2018), Bove et al. (2014a, 2014b), and Ruckart et al. (2013, 2015). The Ruckart et al. (2013) study examined childhood hemopoietic cancers in children exposed prenatally and in early childhood. One study examined a population of adults from New Jersey (Cohn et al. 1994). Several other studies evaluated the carcinogenic potential of drinking water contaminated with trichloroethylene; however, risk estimates specific for trichloroethylene were not reported (Costas et al. 2002; Davis 2005; Fagliano et al. 1990; Freni and Bloomer 1988; Lagakos et al. 1986b; MDPH 1997; Parker and Rosen 1981; Vartiainen et al. 1993). Therefore, these studies were not selected for review. For additional details and reviews of

Table 3-4. Overview of Epidemiological Studies Evaluating Associations between Oral Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Cohort studies			
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 of marines (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]: number of participants in each exposure category was 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
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 confidence intervals; 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 reported Limitations: lack of adjustment for possible confounders; potential misclassification of exposure; lack of information on individual exposure potential

Table 3-4. Overview of Epidemiological Studies Evaluating Associations between Oral Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Case-control studies			
Ruckart et al. 2013; Camp Lejeune, North Carolina; childhood cancer	Historical reconstruction of drinking water levels using groundwater fate and transport and water-distribution system models	Maternal age and education; use of prenatal vitamins; working; smoking; alcohol use; 1st trimester fever; child's sex; paternal occupational exposure to solvents	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 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 confidence intervals for the estimated risk estimates; due to small numbers of cases, could not distinguish effects of one chemical independent of the others

[a]Unless otherwise noted, study strengths and limitations were noted by EPA (2011e).
[b]Study strengths and limitations were noted by the study authors.

epidemiological studies assessing the potential carcinogenicity of oral trichloroethylene, the EPA IRIS Toxicological Review for Trichloroethylene (EPA 2011e), IARC (2014), and NTP (2016) may be consulted.

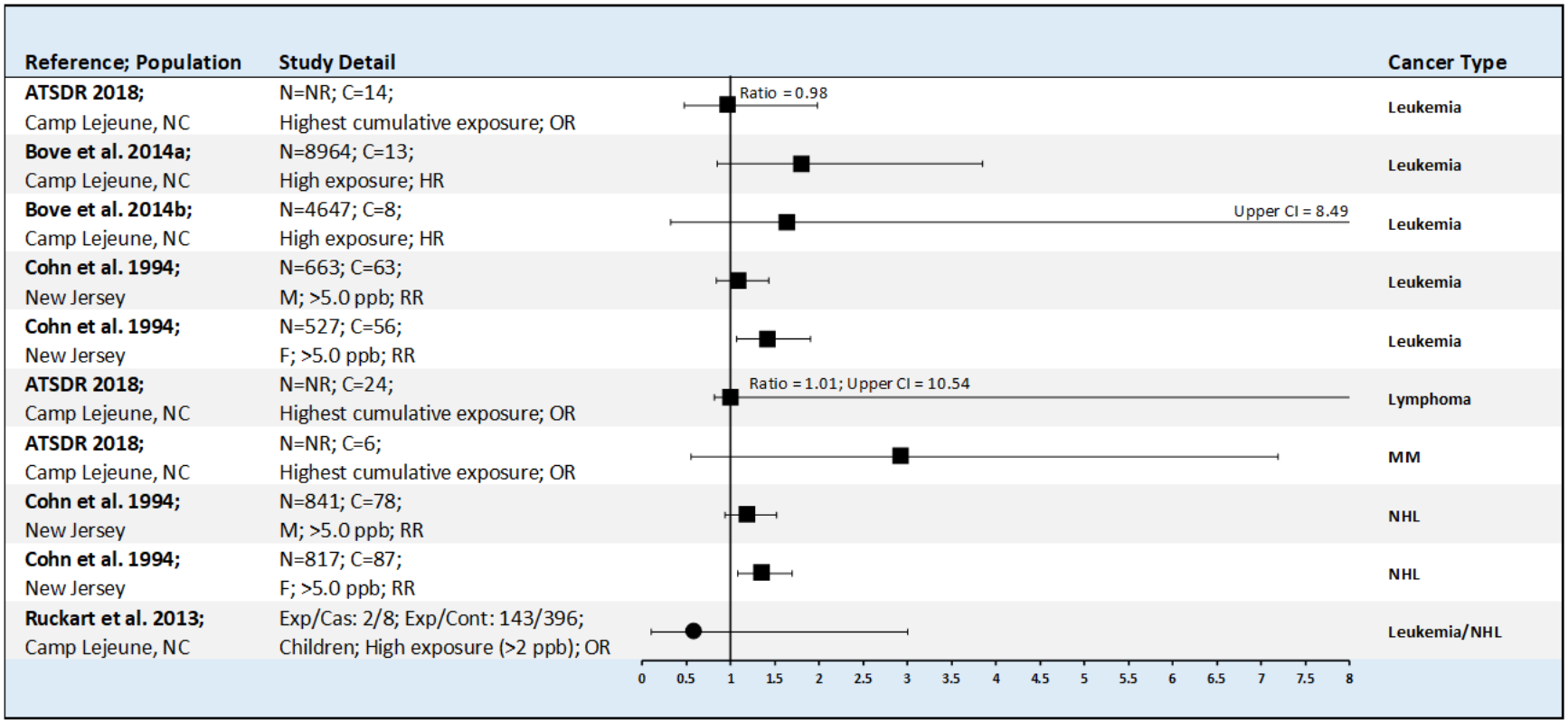
Exposure assessment methods are listed in Table 3-4. It is important to note that none of the exposure assessments included individual monitoring data or rigorous monitoring to determine individual trichloroethylene intake. Most studies provided a semi-quantitative estimate of oral exposure based on exposure and leaching models. Exposure misclassification is possible from use of these models because they do not estimate individual trichloroethylene intakes, and modeled exposure of trichloroethylene may not reflect long-term drinking water exposure concentrations or tetrachloroethylene intakes.

The potential influence of confounding factors is an important consideration in the interpretation of these epidemiological studies. As summarized in Table 3-4, consideration of confounders was not consistent across studies. The Ruckart et al. (2013) study included several confounders; however, other studies evaluated few confounders. Lack of consideration of confounding factors may add uncertainty to interpretation of study results. For assessments of the carcinogenic potential of oral trichloroethylene, 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 Camp Lejeune was contaminated with trichloroethylene, tetrachloroethylene, benzene, vinyl chloride, and trans-1,2-dichloroethylene (Ruckart et al. 2013). None of the studies considered co-contaminants in water as a confounding factor; therefore, it is difficult to rule out potential contributions of other chemicals. One study considered paternal occupational exposure to solvents (Ruckart et al. 2013).

Study results for hematopoietic cancers are shown in Figure 3-18; results for all other cancer endpoints are shown in Figure 3-19. These figures include information on geographic location of the population, number of participants/cases, cancer incidence, and study statistics (e.g., risk values and CIs) as reported by the study authors. Exposure classifications (e.g., qualitative or semiquantitative exposure) for presented risk values also are included. Selected studies evaluated non-Hodgkin's lymphoma, leukemia, breast cancer, and prostate cancer.

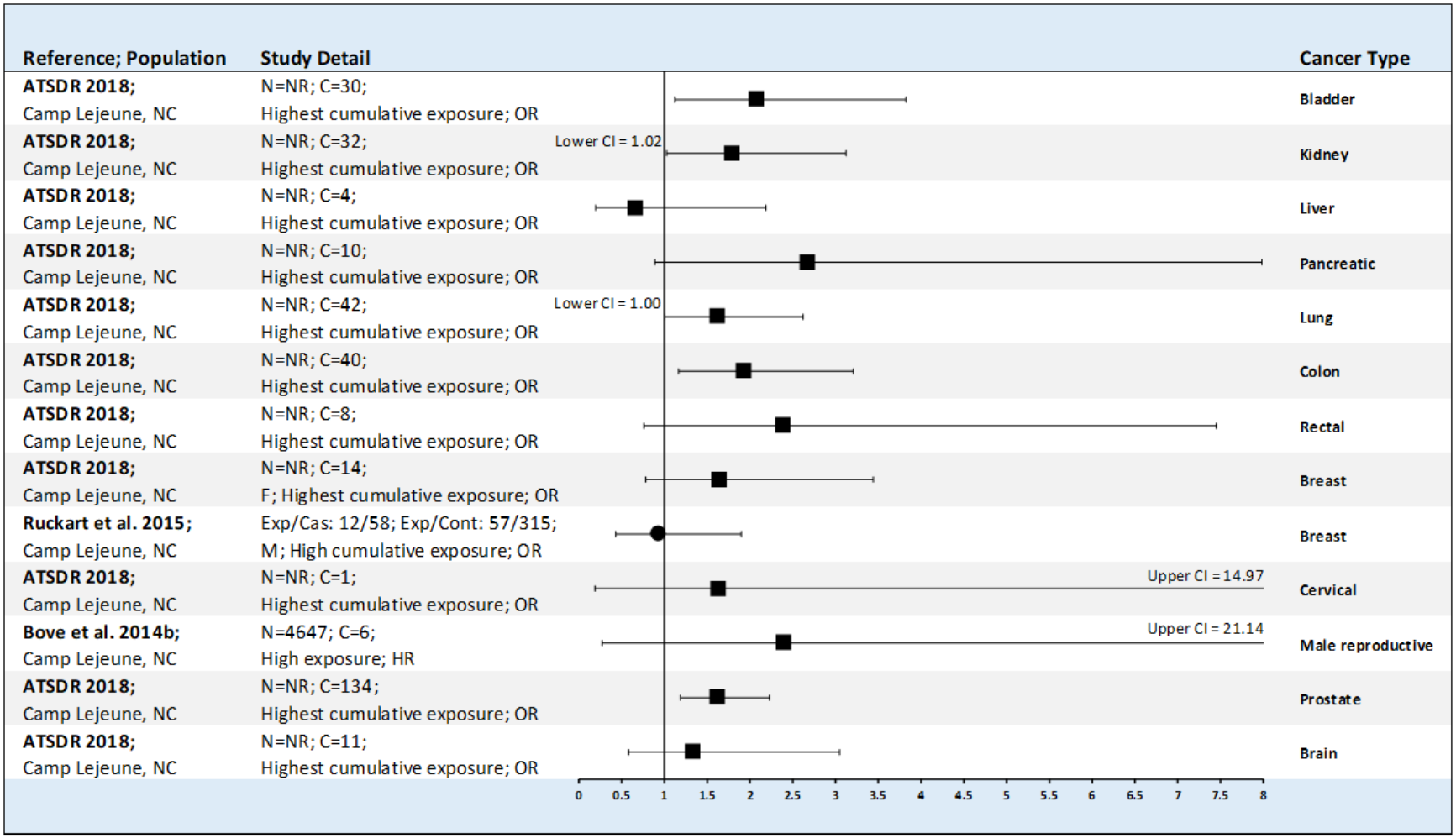
Animal Studies. Various types of cancers have been found in animals after trichloroethylene exposure by the oral route. It should be noted that the rodent bioassays employed relatively high (maximally-tolerated) chronic exposure levels. Other study design issues add to the uncertainty in interpreting the results of animal carcinogenicity studies. For example, epoxides are often used to stabilize

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



= risk estimate and 95% CI for cohort studies; = risk estimate and 95% CI for case-control studies; C = number with specific 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 = number of participants; OR = odds ratio; RR = rate ratio

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



= risk estimate and 95% CI for cohort studies; = risk estimate and 95% CI for case-control studies; C = number with specific 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 = number of participants; OR = odds ratio

trichloroethylene, which degrades rapidly when exposed to light. Some epoxides are known to form reactive radicals, which may be tumor initiators themselves. In one study, B6C3F1 mice exposed by oil gavage to industrial-grade trichloroethylene (in corn oil) containing small amounts of stabilizers such as epichlorohydrin and other epoxides had significant increases in hepatocellular carcinomas in male and female mice at the low- and high-dose levels (NCI 1976). ICR/Ha Swiss mice treated by gavage with trichloroethylene-containing epoxide stabilizers had increases in forestomach tumors, which were not observed in the group receiving trichloroethylene without stabilizers (Henschler et al. 1984). The forestomach tumors were believed to be induced by the direct alkylating epoxides. Liver and lung tumors were not observed in significant numbers.

Another difficulty with some of the chronic carcinogenicity studies in animals is the poor survival rate of the rodents. No compound-related carcinogenic effects were seen in rats exposed by gavage to trichloroethylene with stabilizers in corn oil (NCI 1976), but the high mortality in all groups of rats (due to toxicity) significantly detracted from the reliability of the conclusions in this study. Survival rate also affected the evaluation of a carcinogenic response in F344 rats (NTP 1990). In this study, using epoxide-free trichloroethylene, toxic nephrosis significantly reduced survival. A small but statistically significant increase in renal tubular cell adenocarcinomas occurred in the male rats, but there was no treatment-related increase of tumors in the female rats. The findings were judged to be equivocal by the investigators. When male and female Sprague-Dawley rats were dosed by gavage with epoxide-free trichloroethylene in olive oil, there was an increase in leukemia in males but not in females (Maltoni et al. 1986). However, limitations of this study include a relatively short treatment period (52 weeks) and failure to indicate the number of surviving animals. In a study of four strains of rats, increases were found in renal tubular cell adenomas in the low-dose male Osborne-Mendel rats and in interstitial cell tumors of the testis in the high-dose Marshall rats (NTP 1988). In addition, male and female ACI and August rats showed a slight (not statistically significant) increase in proliferative tubular cell lesions. However, this study was also considered to be inadequate for evaluating carcinogenicity by the NTP Peer Review Panel because of low survival rate and conduct flaws; the test material contained an amine stabilizer at a concentration of 8 ppm, but no epichlorohydrin or 1,2-epoxybutane.

In contrast to rats, B6C3F1 mice developed hepatocellular carcinomas and hepatocellular adenomas following exposure to epoxide-free trichloroethylene (NTP 1990). The evidence that trichloroethylene is a hepatic carcinogen in mice but not rats was supported by results of a study in which rats and mice were given trichloroethylene at 500 mg/kg/day by oil gavage for up to 14 days, and then assayed for site-specific cell proliferation in various organs (Klaunig et al. 1991). Thymidine labelling of isolated

hepatocytes showed increased DNA synthesis in exposed mice but not exposed rats, while renal DNA synthesis was unchanged in both species. The human relevance of trichloroethylene-induced hepatocarcinogenicity in mice has been questioned, in part, because relatively high exposure levels were required to induce hepatocarcinogenicity in mice, trichloroethylene did not induce liver tumors in rats, mice metabolize trichloroethylene more rapidly than rats and metabolism of trichloroethylene in humans is thought to be more comparable to that of rats than mice, and a peroxisome proliferator-activated receptor alpha (PPARα) mode of action for a major trichloroethylene metabolite (trichloroacetate) that induces liver tumors in mice is of questionable relevance to humans (Corton 2008; EPA 2011e; Klaunig et al. 2003; NRC 2009; and others).

CELs from all reliable studies are recorded in Table 3-3 and plotted in Figure 3-17.

The EPA concluded that trichloroethylene is carcinogenic to humans by all routes of exposure based on convincing evidence of a causal association between trichloroethylene exposure in humans and kidney cancer (EPA 2011e). EPA calculated an adult-based oral slope factor of $4.6x10^{-2}$ per mg/kg/day (rounded to $5x10^{-2}$ per mg/kg/day) resulting from PBPK model-based route-to-route extrapolation of the inhalation unit risk estimate based on human kidney cancer risks reported by Charbotel et al. (2006) and adjusted for potential risk for tumors at multiple sites using human epidemiologic data (EPA 2011e; IRIS 2011). EPA stated that the oral slope factor for trichloroethylene should not be used with exposures exceeding 10 mg/kg/day because above this level, the route-to-route extrapolation relationship is no longer linear (EPA 2011e; IRIS 2011). EPA also stated that the oral slope factor of $4.6x10^{-2}$ per mg/kg/day, calculated from adult exposure data, does not reflect presumed increased early-life susceptibility to trichloroethylene-induced kidney tumors (EPA 2011e; IRIS 2011). For risk assessments based on specific exposure scenarios, EPA (2011e; IRIS 2011) recommends the application of ADAFs: 10 for <2 years of age, 3 for 2 to <16 years of age, and 1 for ≥16 years of age (EPA 2005a). Based on exposure from age 0 to 70 years with age-specific 90^{th} percentile water consumption rates, the lower bound estimates (lower 95% confidence limits) on the drinking water concentrations associated with risk of $1x10^{-4}$, $1x10^{-5}$, and $1x10^{-6}$ are 50, 5, and 0.5 µg/L, respectively (EPA 2011e; IRIS 2011). Doses (in mg/kg/day) associated with risk of $1x10^{-4}$, $1x10^{-5}$, $1x10^{-6}$, and $1x10^{-7}$ are presented in Figure 3-17.

3.2.3 Dermal Exposure

Occupational exposure to trichloroethylene may involve dermal as well as inhalation exposure routes; however, no occupational studies were located that address dermal exposures.

3.2.3.1 Death

No studies were located regarding death of humans after dermal exposure to trichloroethylene.

One group of investigators reported that the dermal LD_{50} for trichloroethylene in rabbits is >29 g/kg, but did not report any other details (Smyth et al. 1969). No other dermal lethality data studies were available.

3.2.3.2 Systemic Effects

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

Hepatic Effects. Jaundice and abnormal liver function tests including increases in serum transaminase levels have been noted in individuals occupationally exposed to trichloroethylene by both dermal and inhalation exposure (Bauer and Rabens 1974; Phoon et al. 1984).

In one set of modified guinea pig maximization tests, guinea pigs were treated by intradermal injections of trichloroethylene in the induction phase followed by challenge dermal application (Tang et al. 2002, 2008). Among the guinea pigs that exhibited dermal sensitization reactions (>60% of the treated animals), mean relative liver weight was significantly increased (18% greater than controls) and serum ALT and AST levels were significantly increased (1.6- and 3.2-fold, respectively, greater than controls). Liver effects were not seen in those guinea pigs that did not exhibit evidence of trichloroethylene-induced dermal sensitization reactions. No studies were located regarding hepatic effects in animals after dermal exposure to trichloroethylene.

Renal Effects. No studies were located regarding renal effects in humans following dermal exposure to trichloroethylene.

In a modified guinea pig maximization test, 38 female guinea pigs were treated by intradermal injection of trichloroethylene followed by sensitizing dermal application at 7 days postinjection and challenge

dermal application at 14 days postinjection (Yu et al. 2012). Histopathological evidence of trichloroethylene-induced renal effects (swelling of tubular epithelial cell mitochondria, vacuolar degeneration, and atrophy of microvilli) and markedly elevated urease and urinary protein were noted in the group of trichloroethylene-sensitized animals.

Dermal Effects. Because of the high volatility of trichloroethylene, human occupational exposure by dermal routes usually includes some unspecified amount of inhalation exposure. Severe exfoliative dermatitis was reported in a man exposed to unspecified levels of 90–98% pure trichloroethylene for 3 hours in an unventilated room (Nakayama et al. 1988). A patch test using both trichloroethylene and trichloroethanol, a metabolite, yielded positive results for this man and negative results for 10 control subjects. This suggests that the patient had an allergic reaction to trichloroethylene. Skin irritations, burns, and rashes, such as generalized dermatitis, have resulted from occupational exposure to trichloroethylene (Bauer and Rabens 1974; Conde-Salazar et al. 1983; Phoon et al. 1984; Waller et al. 1994). The dermal effects are usually the consequence of direct skin contact with concentrated solutions, which results in desiccation due to the defatting action of the solvent. It is also possible that adverse dermatological conditions may also be mediated by immunological responses in some persons.

A study using skin samples from healthy humans revealed that trichloroethylene extracts lipids from the stratum corneum (Goldsmith et al. 1988). The study indicates that lipid extraction is the reason for whitened skin following exposure to organic solvents such as trichloroethylene.

Only one animal study was located. In this investigation, guinea pigs exhibited considerable erythema, edema, and increased epidermal thickness following an uncovered dermal exposure to undiluted trichloroethylene 3 times/day for 3 days (Anderson et al. 1986).

3.2.3.3 Immunological and Lymphoreticular Effects

Information regarding immunological effects in humans exposed to trichloroethylene derives mainly from occupational scenarios that involve inhalation and dermal exposure routes; refer to Section 3.2.1.3 for a discussion of immunological effects following occupational exposure to trichloroethylene.

In one set of modified guinea pig maximization tests, strong dermal sensitization reactions (erythema and edema) were elicited in guinea pigs treated by intradermal injections of trichloroethylene in the induction phase followed by challenge dermal application; dermal sensitization rates were on the order of 66–71%

(Tang et al. 2002, 2008). In another modified guinea pig maximization test in which 38 female guinea pigs were treated by intradermal injection of trichloroethylene followed by sensitizing dermal application at 7 days postinjection and challenge dermal application at 14 days postinjection, 24 animals (63%) exhibited dermal allergenic reactions (Yu et al. 2012).

3.2.3.4 Neurological Effects

In studies designed to examine dermal absorption of trichloroethylene, emersion of the hand (Sato and Nakajima 1978) or thumb (Stewart and Dodd 1964) for 30 minutes was reported to be painful. The pain was described as excruciating in one study (Sato and Nakajima 1978), and in another study, it was described as mild by one subject and moderately severe by two subjects (Stewart and Dodd 1964). Occupational exposure to trichloroethylene that involved both dermal and inhalation exposure has been reported to result in dizziness, headache, insomnia, lethargy, forgetfulness, and loss of feeling in the hands and feet (Bauer and Rabens 1974; Kohlmuller and Kochen 1994).

No studies were located regarding neurological effects in animals following dermal exposure to trichloroethylene.

3.2.3.5 Reproductive Effects

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

3.2.3.6 Developmental Effects

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

3.2.3.7 Cancer

Percutaneous absorption of trichloroethylene through intact human skin is quite limited, relative to absorption following ingestion or inhalation exposure. However, dermal exposure can significantly contribute to total systemic exposure when there is prolonged or repeated contact with concentrated trichloroethylene solutions.

The combined incidence of stomach, liver, prostate, and lymphohematopoietic cancers was increased among 2,050 male and 1,924 female Finnish workers occupationally exposed primarily to trichloroethylene (Anttila et al. 1995). The workers were exposed principally by inhalation, although there was some dermal contact. The statistical power of this study was low.

Experiments were conducted in which purified trichloroethylene (1 mg in acetone) was applied to the shaved backs of female ICR/Ha Swiss mice (Van Duuren et al. 1979). In an initiation-promotion study, a single application of trichloroethylene was followed by repeated application of phorbol myristate acetate (PMA) promoter. In a second study, mice were treated with trichloroethylene 3 times/week without a promoter. No significant tumor incidences were observed in these studies. Doses used in these studies were well below the maximum tolerated dose, which is often not reached in dermal studies.

3.3 GENOTOXICITY

The potential genotoxicity of trichloroethylene has been assessed to a small extent in humans and to a much greater degree in mammalian and nonmammalian test systems. Genotoxic effects produced by tetrachloroethylene are thought to be the result of reactive metabolic intermediates of metabolism of tetrachloroethylene (Cichoki et al. 2016; EPA 2011e; IARC 2014). Results of *in vivo* and *in vitro* genotoxicity testing of trichloroethylene are summarized in Tables 3-5 and 3-6, respectively. Human data provide inconclusive evidence for the genotoxicity of trichloroethylene. Results of testing in mammalian and nonmammalian test system indicate a potential for trichloroethylene to induce chromosomal damage. The weight of evidence suggests that trichloroethylene does not act directly as a mutagenic agent, but that the observed mutagenic responses are likely due to production of mutagenic metabolites and/or the presence of mutagenic epoxide stabilizers in commercial-grade trichloroethylene. The evidence for these findings is discussed below.

A marked increase in the incidence of chromosomal abnormalities, such as gaps, breaks, translocations, deletions, inversions, and hyperdiploidy, was detected in the lymphocytes of occupationally exposed workers (Rasmussen et al. 1988). The same researchers also looked at the frequency of nondisjunction for the Y chromosome in sperm; the result was negative. One problem with this investigation is that information regarding exposure to other potentially mutagenic factors, such as x-rays, viral infections, alcohol, and workplace chemicals, was unavailable for the control group (Rasmussen et al. 1988). An increase in hypodiploid cells was detected in an earlier study of trichloroethylene exposed workers, but

Table 3-5. Genotoxicity of Trichloroethylene *In Vivo*

Species/test system	End point	Results	Reference
Drosophila melanogaster	Chromosomal aberrations	–	Beliles et al. 1980
Human (occupational exposure)	Chromosomal aberrations	+	Rasmussen et al. 1988
Mouse	Chromosomal aberrations	–	Kligerman et al. 1994
Rat	Chromosomal aberrations	–	Kligerman et al. 1994
Rat	Chromosomal aberrations	–	Sujatha and Hegde 1998
Mouse	Micronucleus formation	+/–	Duprat and Gradiski 1980
Mouse	Micronucleus formation	–	Allen et al. 1994
Mouse	Micronucleus formation	–	Kligerman et al. 1994
Rat	Micronucleus formation	–	Kligerman et al. 1994
Rat	Micronucleus formation	+	Robbiano et al. 1998; 2004
Rat	Micronucleus formation	+	Sujatha and Hegde 1998
Human (occupational exposure)	Sister chromatid exchange	(+)	Gu et al. 1981a
Human (smokers, occupational exposure)	Sister chromatid exchange	+	Seiji et al. 1990
Human (nonsmokers, occupational exposure)	Sister chromatid exchange	–	Seiji et al. 1990
Human (smokers, nonsmokers, occupational exposure)	Sister chromatid exchange	–	Nagaya et al. 1989a
Mouse	Sister chromatid exchange	+	Kligerman et al. 1994
Rat	Sister chromatid exchange	–	Kligerman et al. 1994
Rat	C-mitotic changes	+	Sujatha and Hegde 1998
Mouse (spot test)	Gene mutation	(+)	Fahrig 1977
Mouse	Dominant lethal mutation	–	Slacik-Erben et al. 1980
Mouse	DNA-protein cross-links	–	Keller and Heck 1988[a]
Human (occupational exposure)	Nondisjunction of Y chromosome in sperm	–	Rasmussen et al. 1988
Rat (DNA damage)	Single-strand breaks	(+)	Nelson and Bull 1988
Rat (DNA damage)	Single-strand breaks	–	Parchman and Magee 1982
Rat (DNA damage)	Single-strand breaks	+	Nelson and Bull 1988
Mouse (DNA damage)	Single-strand breaks	+	Walles 1986
Mouse (DNA damage)	Single-strand breaks	+	Nelson and Bull 1988
Rat (DNA damage)	Single-strand breaks	+	McLaren et al. 1994
Rat (DNA damage)	Single-strand breaks	+	Robbiano et al. 2004
Rat (hepatocyte UDS)	Unspecified DNA damage	–	Mirsalis et al. 1989
Mouse (hepatocyte UDS)	Unspecified DNA damage	–	Mirsalis et al. 1989
Mouse (hepatocyte UDS)	Unspecified DNA damage	–	Doolittle et al. 1987
Rat (hepatocyte DNA damage)	Oxidative DNA damage	+	Toraason et al. 1999

Table 3-5. Genotoxicity of Trichloroethylene *In Vivo*

Species/test system	End point	Results	Reference
Rat (comet assay)	DNA breakage	–	Clay 2008
Mouse	DNA adducts	+	Kautiainen et al. 1997
Mouse	DNA adducts	+	Mazzullo et al. 1992
Rat	DNA adducts	+	Mazzullo et al. 1992
Mouse	Protein adducts	+	Kautiainen et al. 1997
Rat	Protein adducts	+	Halmes et al. 1997
Mouse host-mediated assays:			
Schizosaccharomyces pombe	Gene mutation	–	Rossi et al. 1983
Saccharomyces cerevisiae	Gene mutation	+	Bronzetti et al. 1978

– = negative result; + = positive result; (+) = weakly positive result; +/– = inconclusive result; DNA = deoxyribonucleic acid; UDS = unscheduled DNA synthesis

Table 3-6. Genotoxicity of Trichloroethylene *In Vitro*

Species/test system	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Mortelmans et al. 1986
S. *typhimurium* TA98, TA100	Gene mutation	–	–	Waskell 1978
S. *typhimurium* TA100	Gene mutation	–	–	Henschler et al. 1977
S. *typhimurium* TA1535	Gene mutation	–	–	Shimada et al. 1985
S. *typhimurium* TA100	Gene mutation	(+)	–	Baden et al. 1979
S. *typhimurium* TA100	Gene mutation	(+)	–	Bartsch et al. 1979
S. *typhimurium* TA100	Gene mutation	(+)	–	Crebelli et al. 1982
S. *typhimurium* TA100	Gene mutation	(+)	–	Simmon et al. 1977
S. *typhimurium* TA1535	Gene mutation	+/–	+/–	Baden et al. 1979
S. typhimurium TA98, TA100 (stabilized TCE, preincubation assay)	Gene mutation	–	–	McGregor et al. 1989
S. *typhimurium* (unstabilized TCE, vapor assay)	Gene mutation	–	No data	McGregor et al. 1989
S. *typhimurium* (stabilized TCE, vapor assay)	Gene mutation	+ (TA1535) +/– (TA100) – (TA98)	+ (TA1535) +/– (TA100) – (TA98)	McGregor et al. 1989
S. *typhimurium* YG7108pin3ERb$_5$	Gene mutation	No data	–	Emmert et al. 2006
Escherichia coli E12	Gene mutation	+/–	–	Greim et al. 1975
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae D7	Gene mutation	–	–	Koch et at 1988
S. cerevisiae	Gene mutation	+	–	Bronzetti et al. 1978
Schizosaccharomyces pombe	Gene mutation	–	–	Rossi et al. 1983
Aspergillus nidulans	Gene mutation	No data	(+)	Crebelli et al. 1985
S. cerevisiae D7	Recombination	No data	+	Callen et al. 1980
S. cerevisiae D4	Recombination	No data	–	Callen et al. 1980
S. cerevisiae	Recombination	+	–	Bronzetti et al. 1978
A. nidulans	Recombination	No data	(+)	Crebelli et al. 1985
S. cerevisiae D7	Gene conversion	–	–	Koch et al. 1988
S. cerevisiae D61.M	Mitotic aneuploidy	+	+	Koch et al. 1988

Table 3-6. Genotoxicity of Trichloroethylene *In Vitro*

Species/test system	End point	Results		Reference
		With activation	Without activation	
Mammalian cells:				
Rat primary hepatocytes (UDS)	DNA damage	No data	–	Shimada et al. 1985
Rat hepatocytes	DNA single-strand breaks	No data	+	Robbiano et al. 2004
Human hepatocytes	DNA single-strand breaks	No data	+	Robbiano et al. 2004
Human lymphocytes (UDS)	DNA damage	+/–	+/–	Perocco and Prodi 1981
Human WI-38 (UDS)	DNA damage	(+)	(+)	Beliles et al. 1980
Rat hepatocytes	Micronucleus formation	No data	+	Robbiano et al. 2004
Human hepatocytes	Micronucleus formation	No data	+	Robbiano et al. 2004
C3T3 mouse cells	Cell transformation	No data	(+)	Tu et al. 1985
Rat embryo cells	Cell transformation	No data	+	Price et al. 1978
Syrian hamster embryo cells	Cell transformation	No data	–	Amacher and Zelljadt 1983
Rat hepatocytes	Protein adducts	No data	+	Griffin et al. 1998
Human hepatocytes	Protein adducts	No data	+	Griffin et al. 1998

– = negative result; + = positive result; +/– = inconclusive result; (+) = weakly positive result;
DNA = deoxyribonucleic acid; TCE = trichloroethylene; UDS = unscheduled DNA synthesis

chromosomal breakage was not observed (Konietzko et al. 1978). Results from this study were considered inconclusive because of a lack of matched controls, the possible exposure of workers to other potentially mutagenic chemicals, and the possibility that the incidence of hypodiploid cells was the result of the chromosome preparation technique (EPA 1985c).

Cigarette smoking and trichloroethylene exposure may act synergistically to increase the rate of sister chromatid exchange (Seiji et al. 1990). Because cigarette smoking is a well-recognized factor in increased sister chromatid exchange, this study included comparisons of trichloroethylene-exposed and nonexposed individuals, who were smokers or nonsmokers. The only group with an increased frequency of sister chromatid exchange consisted of individuals who smoked and were exposed to trichloroethylene. However, this study had several limitations. The lack of an increase in unexposed smokers compared to nonsmokers may be due to the small number of smokers (n=7) or to the fact that they smoked no more than 5–10 cigarettes/day. In addition, concomitant exposure to other solvents occurred. In a similar investigation of sister chromatid exchange, negative results were obtained for both smokers and nonsmokers exposed to trichloroethylene (Nagaya et al. 1989a). As expected, the average frequency for sister chromatid exchange appeared to be higher among smokers than nonsmokers regardless of trichloroethylene exposure; unfortunately, statistical testing regarding increased sister chromatid exchange frequency among smokers was not performed. An earlier study did suggest a positive effect of trichloroethylene on increased sister chromatid exchange, but exposure to other chemicals may have confounded these results (Gu et al. 1981b).

The results from *in vivo* animal studies provide some evidence for the genotoxicity of trichloroethylene. High oral doses of trichloroethylene resulted in single-strand breaks in liver cells of B6C3F1 mice and Sprague-Dawley rats (Nelson and Bull 1988). The mice were much more sensitive to trichloroethylene than the rats. Nelson and Bull (1988) pretreated other groups of rats with small doses of trichloroethylene, phenobarbital, and ethanol (inducers of metabolism) to determine the importance of trichloroethylene metabolism in the production of single-strand breaks. Both phenobarbital and trichloroethylene pretreatments significantly increased single-strand breaks by trichloroethylene; ethanol did not. This suggests not only that trichloroethylene metabolites are important, but also that phenobarbital, not ethanol, can induce metabolic pathways involving the formation of the active metabolites of trichloroethylene. Treating the rodents with trichloroethylene metabolites (TCA, DCA, and chloral hydrate) produced strand breaks at lower doses than trichloroethylene. This implies that one or more of these metabolites is involved in strand breakage (Nelson and Bull 1988). An increase in strand breaks may reflect an effect on the DNA repair process rather than an increase in break formation.

Single-strand breaks in DNA of kidney and liver cells were observed in mice following a single intraperitoneal injection of trichloroethylene (Walles 1986). The breaks were repaired within 24 hours. It has been suggested that the single-strand breaks may be the result of repair of alkylated bases, the influence of oxygen radicals formed during the biotransformation of the substances, or the destruction of DNA by the autolysis of cells at toxic doses (Walles 1986). Oxidative DNA damage was reported in liver cells from rats administered a single intraperitoneal injection of trichloroethylene (Toraason et al. 1999). Increased incidences of micronuclei and DNA single-strand breaks were observed in kidney cells of rats given a single oral dose of trichloroethylene (Robbiano et al. 1998). Sujatha and Hegde (1998) reported increased micronucleus formation and C-mitotic changes (increased mitotic index, decreased frequencies of anaphases) in bone marrow cells from mice administered trichloroethylene intraperitoneally, but no effect on incidence of chromosomal aberrations. Covalent binding to DNA, RNA, and/or proteins from various organs in rats and mice after intraperitoneal injection has been observed (Halmes et al. 1997; Kautiainen et al. 1997; Mazzullo et al. 1992).

Other investigators found no evidence for DNA damage in trichloroethylene-treated rats or mice (Doolittle et al. 1987; Mirsalis et al. 1989; Parchman and Magee 1982). There was, however, evidence for an increased rate of DNA synthesis in mice (Doolittle et al. 1987; Mirsalis et al. 1989). Trichloroethylene gave a clearly negative response in a comet assay designed to assess whether trichloroethylene was involved in DNA breakage in the proximal tubules of rat kidneys (Clay 2008).

In a dominant lethal study, male mice were exposed to trichloroethylene concentrations ranging from 50 to 450 ppm for 24 hours and mated to unexposed females; the results were negative (Slacik-Erben et al. 1980). The splenocytes of mice exposed to up to 5,000 ppm trichloroethylene for 6 hours exhibited no aberrations in sister chromatid exchange or cell cycle progression and no increase in the number of micronuclei in cytochalasin B-blocked binucleated cells or bone marrow polynucleated erythrocytes (Kligerman et al. 1994). In the same study, however, rats under the same exposure regime showed a dose-related increase in bone marrow micronuclei, as well as a reduction in polychromatic erythrocytes at 5,000 ppm, indicating the possibility of aneuploidy. These results are contrary to those expected since mice are generally more susceptible to cellular injury and tumor induction by trichloroethylene than rats because trichloroethylene is more readily activated to reactive metabolites in mice than rats (or humans). A possible explanation is that chloral hydrate, a metabolite of trichloroethylene, is known to induce aneuploidy in the predominant pathways in rats, whereas in mice, the chloral hydrate pathway becomes saturated.

The results from *in vitro* studies do not provide strong support for the genotoxicity of trichloroethylene (Table 3-3). Assessments of trichloroethylene for mutagenic potential in various strains of *Salmonella typhimurium* have provided negative or at most weakly positive results (Baden et al. 1979; Bartsch et al. 1979; Henschler et al. 1977; McGregor et al. 1989; Mortelmans et al. 1986; Shimada et al. 1985; Waskell et al. 1978). Baden et al. (1979) reported a weakly positive result for strain TA1535 in the presence and absence of exogenous metabolic activation. Weakly positive results were reported for strain TA100 in the presence, but not the absence of exogenous metabolic activation (Baden et al. 1979; Bartsch et al. 1979; Crebelli et al. 1982; Simmon et al. 1977); the response was stronger using S-9 mix from mouse liver compared to rat liver (Simmon et al. 1977). McGregor et al. (1989) assessed whether oxirane compounds used to stabilize trichloroethylene influenced the outcome of gene mutation assays. Unstabilized trichloroethylene did not induce gene mutations in strains TA 98 or TA100 in a preincubation assay (with or without exogenous metabolic activation) or a vapor assay (with exogenous metabolic activation). Vapors of stabilized trichloroethylene induced a mutagenic response in strain TA1535 both with and without exogenous metabolic activation, an apparently weak mutagenic response in strain TA100, and no mutagenic response in strains TA98 or TA100. Assays of epoxybutane and epichlorohydrin, two common stabilizers used for trichloroethylene, resulted in positive responses in strains TA100 and TA1535 in the absence of exogenous metabolic activation. These results indicate that the mutagenic response observed for stabilized trichloroethylene is likely a response to stabilizers rather than to trichloroethylene itself. Henschler et al. (1977) found no evidence of mutagenicity in strain TA100 exposed to technical-grade trichloroethylene that included 0.22% epichlorohydrin and 0.2% epoxybutane; both epichlorohydrin and epoxybutane elicited a mutagenic response when tested separately. Trichloroethylene was not mutagenic to the *S. typhimurium* strain YG7108pin3ERb$_5$ (a strain expressing cytochrome P450) in the absence of exogenous metabolic activation (Emmert et al. 2006). Greim et al. (1975) reported a weakly positive mutagenic response in *Escherichia coli* strain E12 in the presence, but not in the absence, of exogenous metabolic activation.

The potential for epoxide-free trichloroethylene to induce gene mutations and mitotic segregation (recombination) in the fungus *Aspergillus nidulans* was assessed by Crebelli et al. (1985). No increase in mutation frequency was observed when colonies were plated onto selected media and then exposed to trichloroethylene vapors; however, a weakly positive response was elicited when colonies were grown in the presence of trichloroethylene and then plated onto selected media. Significantly increased numbers of colonies with haploids and non-disjunctional diploids (measures of mitotic segregation) were observed in trichloroethylene-exposed colonies and in colonies exposed to trichloroethanol or chloral hydrate

(trichloroethylene metabolites) compared to unexposed controls. These results indicate that trichloroethylene metabolism may have played a role in the mutagenic and mitotic segregation responses.

Significantly increased frequencies of mitotic gene conversion and recombination were observed in an assay of the D7 strain of the yeast *Saccharomyces cerevisiae* exposed to trichloroethylene, but there was no significant effect on the D4 strain that expresses 5 times lower cytochrome P450 concentration than strain D7 (Callen et al. 1980). Bronzetti et al. (1978) reported significantly increased frequencies of gene mutations and recombination in *S. cerevisiae* strain D7 in the presence, but not in the absence, of exogenous metabolic activation. Koch et al. (1988) found no significant effect of trichloroethylene on frequencies of gene mutations or recombination in *S. cerevisiae* strain D7 in the presence or absence of exogenous metabolic activation, but noted trichloroethylene-induced mitotic aneuploidy in *S. cerevisiae* strain D61.M in the presence and absence of exogenous metabolic activation.

An unscheduled DNA synthesis (UDS) assay with human lymphocytes was indeterminate for DNA damage when tested with and without exogenous metabolic activation (Perocco and Prodi 1981). An *in vitro* UDS assay with human WI-38 lung cells was only weakly positive (Beliles et al. 1980). A UDS assay for rat hepatocytes was negative for DNA damage (Shimada et al. 1985). Studies using mammalian cells *in vitro* have reported positive results for cell transformation in C3T3 cells (Tu et al. 1985) and rat embryo cells (Price et al. 1978), with negative results in a cell transformation assay in Syrian hamster embryo cells (Amacher and Zelljadt 1983). Robbiano et al. (2004) reported increased incidences of micronuclei and DNA single-strand breaks in primary cultures of rat and human kidney cells exposed to trichloroethylene. Covalent binding of trichloroethylene to proteins was observed in hepatocytes from rats and humans (Griffin et al. 1998).

The genotoxicity of selected trichloroethylene metabolites has been extensively reviewed (EPA 2011e); it was concluded that there is relatively strong evidence for the genotoxicity of chloral/chloral hydrate and some evidence for the genotoxicity of other trichloroethylene metabolites, including DCA, dichlorovinyl cysteine, and dichlorovinyl glutathione.

3.4 TOXICOKINETICS

Inhalation, oral, and dermal studies in animals and humans indicate that trichloroethylene is rapidly absorbed into the bloodstream, regardless of the route, where it is then widely distributed to its target organs, which include the liver, kidneys, and cardiovascular and nervous systems. Due to its lipophilic

nature, trichloroethylene can accumulate in fat. Metabolism occurs fairly rapidly, and resulting metabolites are responsible for much of the toxic effects of trichloroethylene. Metabolic products are excreted primarily in the urine, and unabsorbed or unmetabolized trichloroethylene is exhaled in the breath. Physiologically based pharmacokinetic (PBPK) modeling has been performed for both animal and human systems (see Section 3.4.5), and the models' predictions regarding target organ dosimetry have been accurate. However, physiological and metabolic differences between humans and other animals generally complicate extrapolation of effects from one species to another (see Section 3.5.3).

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Absorption of trichloroethylene in humans is very rapid upon inhalation exposure. Trichloroethylene has a blood/gas partition coefficient that is comparable to some other anesthetic gases (i.e., chloroform, diethylether, and methoxyfluorene), but it is more lipophilic than these gases. As a consequence of these properties, the initial rate of uptake of inhaled trichloroethylene in humans is quite high, with the rate leveling off after a few hours of exposure (Fernandez et al. 1977). The absorbed dose is proportional to the inhaled trichloroethylene concentration, duration of exposure, and alveolar ventilation rate at a given inhaled air concentration (Astrand and Ovrum 1976). Several studies indicate that 37–64% of inhaled trichloroethylene is taken up from the lungs (Astrand and Ovrum 1976; Bartonicek 1962; Monster et al. 1976).

Absorption kinetics of trichloroethylene are often monitored by measuring levels in the blood during and after exposure. Volunteers who inhaled 100 ppm for 6 hours showed a peak blood trichloroethylene level of approximately 1 μg/L after 2 hours (Müller et al. 1974). These levels fell rapidly when exposure ceased. Trichloroethylene levels in blood and breath increased rapidly in another study after initiation of a 4-hour exposure to 100 ppm, reaching near steady-state within an hour from the start of the exposure (Sato and Nakajima 1978). Three men accidentally exposed to trichloroethylene vapors (unspecified levels) for <30 minutes were hospitalized with acute symptoms and had venous blood levels ranging from 380 to 700 μg/L 4.5 hours after exposure (Kostrzewski et al. 1993).

When rats were exposed by inhalation to 50 or 500 ppm trichloroethylene for 2 hours, trichloroethylene was readily absorbed from the lungs into the circulation (Dallas et al. 1991). Uptake exceeded 90% during the first 5 minutes in both exposure groups, but decreased rapidly over the next 30 minutes to relatively constant (near steady-state) levels of 69 and 71% for the 50- and 500-ppm groups, respectively. The total

cumulative uptakes were 8.4 mg/kg in the 50-ppm group and 73.3 mg/kg in the 500-ppm group. Percentage systemic uptake of trichloroethylene was time dependent but not concentration dependent. Levels of trichloroethylene in exhaled breath reached near steady-state soon after the beginning of exposure and were then directly proportional to the inhaled concentrations. Other inhalation studies with rats exposed to as much as 8,000 ppm seemed to follow mixed uptake kinetics, with an initial slow first-order process followed by a saturable uptake process (Andersen et al. 1980). The kinetic constant, K_m was estimated as 463 ppm and maximum velocity, V_{max} was estimated as 146 ppm/kg/hour (24.3 mg/kg/hour).

Because most of the systemic absorption of inhaled trichloroethylene and other volatile organic compounds (VOCs) occurs in the alveoli, the extent of absorption of inhaled trichloroethylene depends upon the blood:air partition coefficient, the alveolar ventilation rate, and the cardiac output. Solubility in blood is a major factor determining the trichloroethylene concentration in blood leaving the lungs during inhalation exposure, as indicated by the blood:air partition coefficient. The higher the blood:air partition coefficient, the more soluble a substance in blood compared to air, and the more it binds to lipids and proteins in the blood. The blood:air partition coefficient has been reported to be 8.1–11.7 in humans, 13.3–25.82 in rats, and 13.4–15.91 in mice (EPA 2011e), which indicates that trichloroethylene is more readily absorbed by the blood of rats and mice than humans. Mean resting alveolar ventilation rates for humans, rats, and mice were reported to be 5.0, 52.9, and 116.5 mL/minute/100 g body weight, respectively; cardiac outputs of rats and mice are approximately 6 and 10 times greater, respectively, than that of humans (Brown et al. 1997). Therefore, for equivalent airborne exposure concentrations of trichloroethylene, internal doses are substantially higher in rodents than humans.

3.4.1.2 Oral Exposure

Although no actual rates of absorption have been measured in humans, cases of poisoning following ingestion indicate that absorption of trichloroethylene across the gastrointestinal mucosa is extensive (Brüning et al. 1998; DeFalque 1961; Kleinfeld and Tabershaw 1954; Stephens 1945). In one case, a woman hospitalized in a coma after drinking an unknown amount of trichloroethylene had a measured blood level of 4,500 mg/L 18 hours after ingestion, and the half-life was 20 hours (Perbellini et al. 1991). Trichloroethylene would be expected to be readily absorbed across the gastrointestinal mucosal barrier in humans because it is a small, nonpolar, and highly lipophilic compound.

Oral absorption of trichloroethylene in animals is rapid but can be influenced by fasting and the dosing vehicle. Trichloroethylene doses of 5, 10, and 25 mg/kg in 50% aqueous polyethylene glycol 400 were

administered to nonfasted rats, and a 10-mg/kg dose was administered to rats that were fasted for 8–10 hours (D'Souza et al. 1985). Trichloroethylene was rapidly and completely absorbed in the fasted rats, with peak blood concentrations seen 6–10 minutes after dosing. In nonfasted animals, peak blood trichloroethylene concentrations occurred at the same time, but peak blood levels were 2–3 times lower than those observed in fasted animals. Absorption of the compound from the gastrointestinal tract was also extended to periods of ≤9 hours after dosing of nonfasted animals. Furthermore, systemic absorption of trichloroethylene is about three times slower when administered in corn oil than when administered in water because corn oil acts as a reservoir for lipophilic chemicals such as trichloroethylene in the gut (Withey et al. 1983). Nonetheless, absorption of up to 90% of the administered dose has been observed in rats dosed by this method (Prout et al. 1985). A study of F344 rats that were fasted for 8 hours prior to oral dosing by gavage found a rapid appearance of trichloroethylene in the blood, which peaked after 0.75 hours (Templin et al. 1995). The same investigators also dosed beagle dogs and found that blood concentrations of trichloroethylene peaked after 1 hour. Absorption kinetic studies of fasted rats dosed by lipid-emulsion gavage revealed rapid appearance of trichloroethylene in the blood (typically peaking at 15 minutes post-exposure) followed by rapid disappearance (Templin et al. 1993). Rats similarly dosed with radiolabelled trichloroethylene showed rapid serum albumin adduction which peaked at 4–8 hours, then decayed with a half-life consistent with that of albumin itself (Stevens et al. 1992). However, some of the detected radioactivity may was likely due to trichloroethylene metabolites rather than the parent compound.

3.4.1.3 Dermal Exposure

Dermal absorption of trichloroethylene occurs following exposure to the vapor as well as direct contract with the liquid. Exposure of the forearm and hand of volunteers to 1.3 mmol/L ($3.18x10^4$ ppm) of trichloroethylene in a dynamic exposure cylinder for 20 minutes resulted in peak concentrations of trichloroethylene in the exhaled air at about 30 minutes after the initiation of exposure (Kezic et al. 2000). The calculated average dermal penetration rate was 0.049 cm/hour for trichloroethylene vapor. Rapid dermal absorption of trichloroethylene is evident from a study in which peak blood and exhaled air concentrations occurred within 5 minutes after a human subject immersed one hand in liquid trichloroethylene for 30 minutes (Sato and Nakajima 1978). Similarly, maximum penetration rates for 1 minute exposure of the volar forearm to liquid trichloroethylene occurred within 5 minutes of the start of exposure (modeled based on the time course of trichloroethylene in expired air following dermal versus inhalation exposure) (Kezic et al. 2001). The estimated dermal flux was 430 nmol/cm^2/minute.

Studies on dermal absorption of trichloroethylene in humans, as well as animals, are complicated by the fact that exposure in these studies is usually by direct contact of the skin with the undiluted chemical. Trichloroethylene is a lipophilic solvent that defats the skin and disrupts the stratum corneum, thereby enhancing its own absorption. Thus, the rate of absorption probably increases in a nonlinear fashion with greater epidermal disruption. Although the extent of absorption through the skin may be relatively modest with normal industrial use (Sato and Nakajima 1978; Stewart and Dodd 1964), there is insufficient information to evaluate the effects of chronic, low-level exposure in humans, especially when multiple routes may be involved.

To simulate environmental exposures, studies of absorption of trichloroethylene from water and soil were performed in two to four volunteers per exposure scenario (Poet et al. 2000). The estimated dermal permeability coefficients for trichloroethylene in water for 2-hour exposures were 0.015 cm/hour for immersion of the hand (exposed area in the range of 418–581 cm^2) in 4 L of 810–1,300 mg/L of trichloroethylene solution and 0.019 cm/hour for application of a total of 80 mL of 850–1,000 mg/L trichloroethylene solution in occluded patches (exposed area of 50.2 cm^2). The estimated dermal permeability coefficients for trichloroethylene in soil for 2-hour exposures were 0.0074 cm/hour for immersion of the hand in 4 kg of the 4,000–4,200 mg/kg trichloroethylene/soil mixture and 0.0043 cm/hour for application of a total of 80 g of the 3,200–21,000 mg/kg trichloroethylene/soil mixture in occluded patches. The total amounts of trichloroethylene absorbed were estimated at 27–56 g for the hand immersion in water, 2.8–3.4 g for the water patches, 19–21 g for the hand immersion in soil, and 1.2–11 g for the soil patches. The high level for the soil patches was for the highest trichloroethylene concentration in soil.

Similar experiments with rats indicated that rat skin was significantly more permeable to trichloroethylene in water and soil than was human skin (Poet et al. 2000). Permeability coefficients for rats were estimated at 0.31 cm/hour for exposure to 5 mL of 600–1,600 mg/L solution of trichloroethylene in water for 5 hours in an occluded patch (exposed area of 2.5 cm^2), 0.086 cm/hour for exposure to 1 g of a 5,000–40,600 mg/kg mixture of trichloroethylene in soil for 3 hours in a non-occluded patch (exposed area of 8 cm^2), and 0.09 cm/hour for exposure to 5 g of a 5,300–15,600 mg/kg mixture of trichloroethylene in soil for 5 hours in an occluded patch (exposed area of 8 cm^2). Total amounts of trichloroethylene absorbed were estimated at 2.7–7.5 mg for the occluded water patches, 1.7–15 mg for the non-occluded soil patches, and 14–40 mg for the occluded soil patches, with the higher amounts corresponding to the higher exposure concentrations.

Studies of undiluted liquid trichloroethylene also reported that significant amounts of trichloroethylene can be absorbed through the skin of animals. The percutaneous trichloroethylene absorption rate in mice was reported to be 7.82 μg/minute/cm^2 when 0.5 mL of liquid trichloroethylene was applied to clipped abdominal skin for 15 minutes (Tsuruta 1978). However, this may be lower than the actual rate since all metabolites resulting from the biotransformation of trichloroethylene were not determined. In guinea pigs, the blood concentration of trichloroethylene (reflecting absorption rate) during occluded patch exposure to 1 mL liquid trichloroethylene increased rapidly, peaking at 0.5 hours (0.8 μg/mL blood), and then decreased despite continuing dermal exposure for 6 hours (0.46 μg/mL blood) (Jakobson et al. 1982). This pattern is characteristic of hydrocarbon solvents with relatively high lipid solubility and low water solubility (≤100 mg/100 μL).

Percutaneous absorption was measured in female hairless guinea pigs exposed to dilute aqueous concentrations of trichloroethylene ranging from ≈0.020 to 0.110 ppm and also to a higher concentration of 100 ppm aqueous trichloroethylene (Bogen et al. 1992). The guinea pigs were exposed over a majority of their surface area for 70 minutes. The mean permeability coefficients obtained using low (0.23 mL/cm^2/hour) versus high (0.21 mL/cm^2/hour) concentrations of trichloroethylene were not significantly different, which indicates that dermal uptake of trichloroethylene from water is linear over the concentrations studied. The guinea pig may provide a reasonable model for assessing human percutaneous absorption of trichloroethylene. If the mean permeability constants obtained in the Bogen et al. (1992) study were applied to a 70-kg human with 18,000 cm^2 of dermal surface area 80% immersed during a 20-minute bath, the estimated dermal uptake is equal to the amount of trichloroethylene present in 1 L of the water used for bathing. Thus, dermal absorption may be a significant route of human exposure to trichloroethylene from water-related sources.

Studies with male and female rats given various levels of testosterone have implicated this hormone in determining the degree of dermal penetration of trichloroethylene (McCormick and Abdel-Rahman 1991). Dermal uptake of trichloroethylene in control female rats was twice that of control male rats. Male rats deprived of testosterone exhibited dermal uptake similar to that of control female rats; administration of testosterone to female rats resulted in dermal uptake similar to that of control male rats. The mechanism behind this effect is unclear.

3.4.2 Distribution

Trichloroethylene readily crosses biological membranes, resulting in rapid distribution to tissues regardless of route of exposure (EPA 2011e; NRC 2006). Route of exposure may result in greater initial distribution to portal-of-entry and first-pass organs, and higher distribution of trichloroethylene and its metabolites has been noted to organs involved in metabolism and excretion (liver, kidney, lung). Another important factor in determining distribution is the solubility of trichloroethylene in each organ, as indicated by the partition coefficient (EPA 2011e). In humans, the organ having the highest tissue:blood partition coefficient is fat (63.8–70.2) and the organ having the lowest is lung (0.48–1.7). Although adipose tissue also has the highest partition coefficient in rodents, it is smaller (22.7–36.1 in rats and 36.4 in mice) than in humans, indicating lower potential for storage of trichloroethylene in rodent fat than in human fat. A compilation of partition coefficients in these three species is available (EPA 2011e). Tissue:blood partition coefficients for brain were 2.62 for humans and 0.71–1.29 for rats; for liver were 3.6–5.9 for humans and 1.03–2.43 for rats; and for kidney were 1.3–1.8 for humans, 1.0–1.55 for rats, and 2.1 for mice.

3.4.2.1 Inhalation Exposure

Several studies of tissue distribution in humans after inhalation exposure to trichloroethylene report levels in the blood (Astrand and Ovrum 1976; Monster et al. 1976; Müller et al. 1974). In these studies, volunteers were exposed to trichloroethylene at concentrations in the range of 75–150 ppm for periods of 30 minutes to 6 hours. Once in the bloodstream, trichloroethylene is transported rapidly to various tissues, where most of it will be metabolized. Trichloroethylene was detected in the blood of neonates after the mothers had received trichloroethylene anesthesia (Laham 1970), and detectable levels (concentrations not reported) have been found in the breast milk of mothers living in urban areas (Pellizzari et al. 1982). Postmortem analyses of human tissue from persons with unspecified exposure revealed detectable levels of trichloroethylene (<1–32 μg/kg wet tissue) in most organs (McConnell et al. 1975). The relative proportions varied among individuals, but the major sites of distribution appeared to be body fat and the liver. Higher tissue concentrations of trichloroethylene were found in accidental occupational inhalation fatalities (12, 21, and 72 mg/kg in kidney, lung, and liver; 40–84 mg/L in blood [Coopman et al. 2003]; 174 mg/L in blood and 809 mg/kg in brain [Ford et al. 1995]).

In mice, the compound is cleared from the blood within 1 hour of a 100-mg/kg gavage dose (Templin et al. 1993), although binding to proteins such as hemoglobin or albumin likely influences the circulation time of trichloroethylene and its metabolites (Stevens et al. 1992). Blain et al. (1992) suggest that such

binding of trichloroethanol may allow distant structures like the visual cortex to be exposed, resulting in the changes in visual evoked potentials that they observed in rabbits inhaling trichloroethylene. Limited data also suggest that trichloroethylene can accumulate in fat following inhalation exposure in animals. There were relatively high levels of trichloroethylene in the perirenal fat (0.23 nmol/g) and the blood (0.35 nmol/g) of rats 17 hours after a 6-hour/day, 4-day exposure to 200 ppm, but virtually no trichloroethylene was found in the other tissues examined (Savolainen et al. 1977). Additional inhalation studies in mice and rats were performed to provide time course tissue distribution data for use in the development and validation of PBPK models (Greenberg et al. 1999; Keys et al. 2003; Simmons et al. 2002).

Placental transfer of trichloroethylene occurs in animals. Trichloroethylene inhaled by pregnant sheep and goats, at levels used to induce analgesia and anesthesia, is rapidly distributed into the fetal circulation, with peak levels occurring approximately 40–50 minutes after maternal exposure (Helliwell and Hutton 1950). The concentration of trichloroethylene in umbilical vein blood was comparable to that found in the maternal carotid artery.

3.4.2.2 Oral Exposure

The distribution of trichloroethylene in humans after oral exposure is poorly characterized. Case studies of oral exposure have found measurable levels in the blood (Perbellini et al. 1991; Yoshida et al. 1996) and 9.25, 78.3, and 747 μg/g in lung, kidney, and liver, and 210 μg/mL in blood (De Baere et al. 1997).

Limited data on tissue distribution following oral exposure in animals indicate that trichloroethylene is metabolized in the liver, although a portion of an absorbed dose may exceed the capacity of the liver to metabolize it during the initial pass through the liver. Trichloroethylene and its breakdown products that leave or bypass the liver are taken up by other tissues to some extent, particularly fat (Pfaffenberger et al. 1980). Rats were dosed by gavage with 1 or 10 mg trichloroethylene/rat/day for 25 days, and blood serum and adipose tissue levels of trichloroethylene and one of its breakdown products (chloroform) were determined at nine intervals during the exposure period and twice after cessation of dosing. Blood serum trichloroethylene levels were not detectable (i.e., <5 ng/mL serum) during the dosing period. Adipose tissue levels during the 25-day exposure averaged 280 and 20,000 ng trichloroethylene/g hexane-extractable fat for the 1- and 10-mg/rat/day groups, respectively. Average serum levels of chloroform (a metabolite of trichloroethylene) during the 25-day treatment period were 1,600 and 9,300 ng/mL, respectively, and average chloroform levels in fat were 100 and 480 ng/g fat, respectively. At 3–6 days

following cessation of trichloroethylene exposures, trichloroethylene and chloroform were rapidly eliminated from the fat; trichloroethylene was detected at only 1 ng/g fat at both dose levels and chloroform measured 6 ng/g fat at the low dose (1 mg/day) and was not detected at the high dose (10 mg/day). Additional studies were performed in rats and mice to provide time course tissue distribution data for use in the development and validation of PBPK models (Abbas and Fisher 1997; Keys et al. 2003).

3.4.2.3 Dermal Exposure

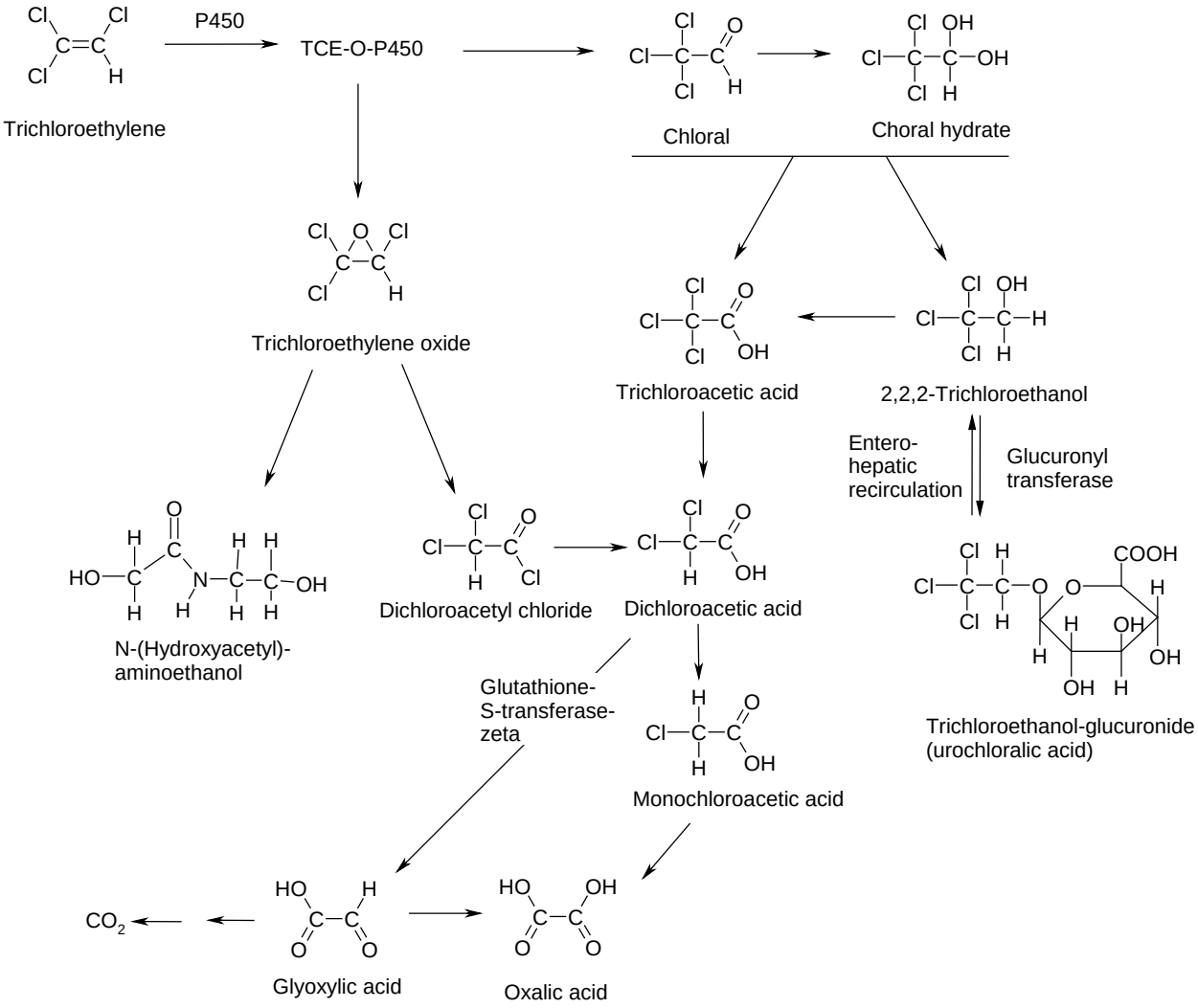
Following dermal exposure, trichloroethylene has been detected in blood and expired breath in human studies (Sato and Nakajima 1978). Studies of distribution among other tissues after dermal exposure in humans and animals were not located in the available literature.

3.4.3 Metabolism

Inhaled doses of trichloroethylene are metabolized extensively in humans. The percentage of the dose metabolized has been reported to be between 40 and 75% of the retained dose following single or repeated exposure to trichloroethylene vapors for periods of 3–8 hours at concentrations generally ranging from 50 to 350 ppm (Bartonicek 1962; Ertle et al. 1972; Fernandez et al. 1977; Kimmerle and Eben 1973a; Monster et al. 1976, 1979; Müller et al. 1972, 1974, 1975; Nomiyama and Nomiyama 1971, 1974a, 1974b, 1977; Ogata et al. 1971; Sato et al. 1977; Soucek and Vlachova 1960; Vesterberg and Astrand 1976). None of these studies provided evidence of saturation of trichloroethylene metabolism in humans, although there is some evidence of saturation of the oxidative pathway in experimental animals. The data of Nomiyama and Nomiyama (1977) and of Ikeda (1977) indicated that the liver's capacity for metabolizing inhaled doses of trichloroethylene is nonsaturable, at least for 3-hour exposures to trichloroethylene vapor at concentrations of up to 315 ppm. These investigators have suggested that at these relatively low concentrations of inhaled trichloroethylene, the parent compound was completely removed from the blood after a single pass through the liver. Saturation of trichloroethylene metabolism in humans has, however, been predicted by mathematical simulation models to occur at the relatively high exposure concentrations used in the past for anesthesia (i.e., 2,000 ppm) (Feingold and Holaday 1977).

Trichloroethylene metabolism in humans and animals occurs by cytochrome P450-dependent oxidation and glutathione (GSH)-dependent conjugation pathways (Figures 3-20 and 3-21, respectively). The major urinary metabolites of trichloroethylene in humans are the oxidative metabolites trichloroethanol,

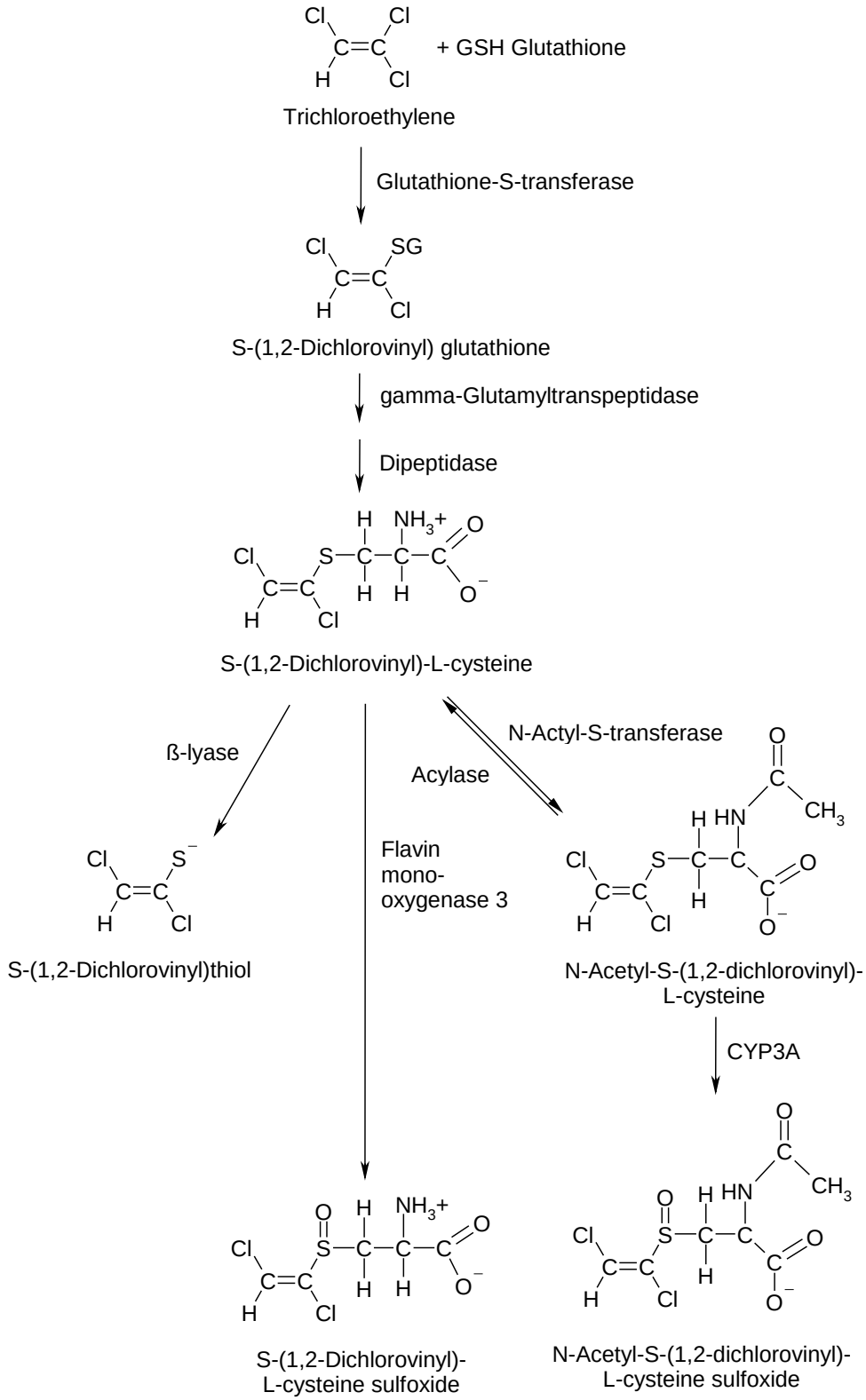
Figure 3-20. Cytochrome P450 Dependent Metabolism of Trichloroethylene



TCE-O-P450 = oxygenated trichloroethylene-P450 intermediate

Sources: EPA 2011e; Forkert et al. 2005; Lash et al. 2000a; NRC 2006; Tong et al. 1998

Figure 3-21. Glutathione Proposed Metabolism of Trichloroethylene



Sources: Bernauer et al. 1996; Chiu et al. 2006; EPA 2011e; Lash et al. 2000a, 2006; NRC 2006

trichloroethanol-glucuronide ("urochloralic acid"), and TCA (Butler 1949; Cole et al. 1975; Fisher et al. 1998; Müller et al. 1974, 1975; Nomiyama and Nomiyama 1971). Urinary trichloroethanol appears rapidly after exposure and is short lived (Skender et al. 1991; Ulander et al. 1992), whereas urinary TCA is slower to appear and is longer lived (Kostrzewski et al. 1993; Skender et al. 1991). Minor urinary metabolites in trichloroethylene-exposed humans are monochloroacetic acid (Soucek and Vlachova 1960) and N-(hydroxyacetyl)-aminoethanol (Dekant et al. 1984). Although DCA has not been reported in human urine, it has been detected in the urine of rats and in the blood of humans exposed to trichloroethylene (Fisher et al. 1998). Additional minor urinary metabolites are mercapturic acid conjugates, relatively stable metabolites resulting from the GSH-dependent metabolism of trichloroethylene (Bernauer et al. 1996; Birner et al. 1993).

The proposed cytochrome P450-dependent oxidative pathways of trichloroethylene metabolism are shown in Figure 3-20. According to the proposed metabolic scheme, trichloroethylene is oxidized by cytochrome P450 to transient intermediates: an oxygenated trichloroethylene-P450 intermediate and trichloroethylene oxide (an epoxide), which has been detected in phenobarbital-pretreated rat liver microsomes (Guengerich et al. 1991; Miller and Guengerich 1982, 1983). The oxygenated trichloroethylene-P450 intermediate results in the formation of chloral, which in the presence of water equilibrates with chloral hydrate. Chloral hydrate undergoes oxidation to TCA (Butler 1949). Alternatively, chloral hydrate can be reduced to trichloroethanol, which undergoes Phase II glucuronidation to produce trichloroethanol-glucuronide (Miller and Guengerich 1983). The oxygenated trichloroethylene-P450 intermediate also can generate trichloroethylene oxide, resulting in the formation of dichloroacetyl chloride, which rearranges to DCA (Cai and Guengerich 2000; Miller and Guengerich 1982). DCA also may be formed from the dechlorination of TCA and oxidation of trichloroethanol (Lash et al. 2000a). DCA can be further metabolized to monochloroacetic acid or glyoxylic acid, resulting in the formation of oxalic acid and CO_2 (Dekant et al. 1984; Green and Prout 1985; Lash et al. 2000a; Saghir and Schultz 2002; Tong et al. 1998).

Quantification of the amount of DCA formed is difficult because the use of strong acids in the analytical procedures can produce *ex vivo* conversion of TCA to DCA in blood, thus potentially resulting in an artifactual augmentation of DCA levels (EPA 2011e; Ketcha et al. 1996; Templin et al. 1995). The rapid metabolism of DCA at low exposure levels *in vivo* (Saghir and Schultz 2002) poses another difficulty in assessing DCA formation. Nevertheless, DCA is known to be formed from trichloroethylene oxide in aqueous systems (Cai and Guengerich 1999), and has been detected in the serum of mice orally dosed

with trichloroethylene using a method that confirmed the absence of artifactual formation of DCA from TCA during sample preparation and analysis (Kim et al. 2009a, 2009b).

Some controversy also exists regarding the role of the epoxide intermediate in trichloroethylene metabolism and toxicity. Bonse and Henschler (1976) presented theoretical considerations, based on the report of Bonse et al. (1975), suggesting that trichloroethylene is first metabolized to trichloroethylene-epoxide, which, in the presence of Lewis acids, can be rearranged to chloral *in vitro*. Since chloral is the first metabolite of trichloroethylene *in vivo*, the findings of Bonse et al. (1975) seem to support the notion that the epoxide is the intermediate between trichloroethylene and chloral. Further support for the data of Bonse et al. (1975) was provided by Uehleke et al. (1977), who showed that trichloroethylene-epoxide is formed during *in vitro* metabolism of trichloroethylene by rabbit liver microsomes and reduced nicotinamide adenine dinucleotide (NADH). However, in experiments with rat and mouse microsomes and reconstituted cytochrome P450 systems, evidence suggested the existence of a pre-epoxide transition state that involves the binding of trichloroethylene to the activated oxygen of cytochrome P450, leading to chloral formation (Miller and Guengerich 1982, 1983). The NRC (2006) and the EPA (2011e) have concluded based on this and other evidence that oxidative metabolism of trichloroethylene includes the formation of an oxygenated trichloroethylene-P450 complex as well as the epoxide as transient intermediates.

Regardless of route of exposure, and in both humans and animals, the majority of oxidative metabolism of trichloroethylene occurs in the liver (EPA 2011e; NRC 2006). The cytochrome P450-dependent metabolism of trichloroethylene was studied in hepatic microsomal fractions from 23 different humans (Lipscomb et al. 1997). As had been reported previously (Guengerich et al. 1991), CYP2E1 was the predominant form of cytochrome P450 responsible for the metabolism of trichloroethylene in human hepatic microsomes (Lipscomb et al. 1997). Incubations of trichloroethylene with the microsomal preparations resulted in hyperbolic plots consistent with Michaelis-Menten kinetics. The K_m values ranged from 12 to 55.7 μM, and were not normally distributed, and the V_{max} values range from 490 to 3,455 pmol/minute/mg protein and were normally distributed. The study authors concluded that the human variability in metabolism of trichloroethylene via cytochrome P450-dependent pathways was within a 10-fold range. CYP2E1 also is the predominant form of cytochrome P450 responsible for the metabolism of trichloroethylene in animal hepatic microsomes (Nakajima et al. 1992a). Additional cytochrome P450 isoforms identified as having a role in the oxidative metabolism of trichloroethylene are CYP1A1/2 and CYP2C11/6 (Nakajima et al. 1992a, 1993; Lipscomb et al. 1997), CYP2F and CYP2B1 (Forkert et al. 2005, 2006), and CYP3A4 (Lipscomb et al. 1997). The overall contribution of these other

cytochrome P450 isoforms is thought to be small, although CYP2F may be important in bioactivation of trichloroethylene in Clara cells in the mouse lung (Forkert et al. 2006). In addition, although trichloroethylene oxidation is decreased in CYP2E1-knockout mice exposed via inhalation, these knockout mice still had substantial capacity for trichloroethylene oxidation (Kim and Ghanayem 2006).

Experiments demonstrate that oral absorption of trichloroethylene in animals is extensive and metabolism is rapid. A study of F344 rats that were fasted for 8 hours prior to oral dosing by gavage found a rapid appearance of trichloroethylene in the blood, which peaked after 0.75 hours, while the peak concentrations of the metabolites trichloroethanol and TCA occurred at 2.5 and 12 hours, respectively (Templin et al. 1995). The same investigators also dosed beagle dogs and found that blood concentrations of trichloroethylene, trichloroethanol, and TCA peaked after 1, 2.5, and 24 hours, respectively. In both species, TCA concentration did not peak until well after the trichloroethylene concentration in blood was below detectable levels (Templin et al. 1995).

Data in animals also show that the major urinary metabolites of trichloroethylene are the relatively stable oxidative metabolites TCA, trichloroethanol, and conjugated trichloroethanol. These account for approximately 90% of the total urinary metabolites in rats (Dekant et al. 1984). Minor urinary metabolites in the rat are oxalic acid, DCA, and N-(hydroxyacetyl)-aminoethanol. Other minor urinary metabolites are mercapturic acid conjugates, relative stable metabolites resulting from the GSH-dependent metabolism of trichloroethylene (Bernauer et al. 1996; Commandeur and Vermeulen 1990; Dekant et al. 1990; Green et al. 1997). GSH conjugation, although quantitatively minor in trichloroethylene metabolism, may play an important role in the carcinogenicity/toxicity of trichloroethylene (see Section 3.5). Although specific steps involved in the formation of N-(hydroxyacetyl)-aminoethanol are unknown, one suggestion involves reaction of trichloroethylene-derived oxidative intermediates with either ethanolamine itself or with phosphatidylethanolamine (a major constituent of membranes) and subsequent metabolic breakdown of the alkylated lipids (Dekant et al. 1984); another possibility is nucleophilic attack of an endocyclic amino group of the heme moiety in cytochrome P450, resulting in inactivation of the microsomal monoxygenase system following oxidation of the trichloroethylene molecule (Dekant et al. 1984).

Phenobarbital, an inducer of some forms of cytochrome P450 (e.g., CYP2E1, CYP2B6, CYP2C9, CYP2C19), has been shown to stimulate binding and metabolism of trichloroethylene by cytochrome P450 enzymes in rat liver microsome preparations (Costa et al. 1980). Similar stimulation of cytochrome P450-mediated trichloroethylene metabolism by phenobarbital has been demonstrated *in vivo* (Carlson

1974; Moslen et al. 1977). CYP2E1 is the most prominent isozyme involved in metabolizing trichloroethylene to chloral hydrate in rat liver and human liver microsomes (Forkert et al. 2005; Guengerich and Shimada 1991; Guengerich et al. 1991; Nakajima et al. 1992a). The induction of CYP2E1 was demonstrated to be affected by the age and pregnancy status of the rat from which the microsomes were obtained (Nakajima et al. 1992b). Pregnancy decreased the metabolism of trichloroethylene, and CYP2E1 levels were lower in mature rats relative to immature rats. At puberty, the level of CYP2E1 was higher in female than in male rats. In addition, the prevalence of some isozymes was found to be greater in mice than in rats, and this difference may account for the greater capacity of mice to metabolize trichloroethylene (Nakajima et al. 1993).

Saturation of trichloroethylene metabolism in mice occurs at higher dose levels than in rats (Dallas et al. 1991; Dekant et al. 1986b; Filser and Bolt 1979; Prout et al. 1985). Male mice can metabolize inhaled trichloroethylene to a greater extent than male rats (Stott et al. 1982). In this study, virtually 100% of the net trichloroethylene uptake by mice was metabolized at both 10- and 600-ppm exposure concentrations (6-hour exposure), and there was no evidence of metabolic saturation. In rats, however, 98% of the net trichloroethylene uptake from the 10-ppm exposure was metabolized, but only 79% was metabolized at the 600-ppm exposure level. This suggested an incremental approach to the saturation of metabolism in this exposure range in the rat. Rats exposed by inhalation to trichloroethylene concentrations of 50 or 500 ppm for 2 hours showed metabolic saturation at 500 ppm (Dallas et al. 1991). This was indicated by the fact that the trichloroethylene blood levels of the 500-ppm animals progressively increased over the 2-hour period, rather than approaching equilibrium after 25 minutes, as was the case at 50 ppm.

Differential saturation of trichloroethylene metabolism by rats and mice has also been demonstrated using oral exposure regimens (Buben and O'Flaherty 1985; Prout et al. 1985). Trichloroethylene metabolism approached saturation at a dose of approximately 1,000 mg/kg for rats, whereas metabolism of trichloroethylene was still linear up to a dose of 2,000 mg/kg for mice (Prout et al. 1985). At gavage doses of trichloroethylene ≥200 mg/kg, male mice metabolized trichloroethylene at a faster rate than male rats (Larson and Bull 1992a; Prout et al. 1985); it was noted that the residence time of trichloroethylene and its metabolites was longer in rats than mice. Based on the observations of faster metabolism in mice and longer residence time in rats, the net metabolism of trichloroethylene to TCA and trichloroethanol was similar in rats and mice given single gavage doses of 1.5–23 mmol/kg (197–3,022 mg/kg) (Larson and Bull 1992a). It was also noted that the initial rates of metabolism of trichloroethylene to trichloroethanol were much higher in mice than rats, especially as the trichloroethylene dose increased, leading to greater concentrations of TCA and DCA in the blood of mice (Larson and Bull 1992a). The

greater peak blood concentrations of the metabolites TCA and DCA in mice may play an important role in the induction of hepatic tumors in mice by trichloroethylene (Larson and Bull 1992a). This has been further validated by studies in which trichloroethylene metabolites such as DCA, TCA, chloral hydrate, or 2-chloroacetaldehyde caused liver tumors in mice (Bull et al. 1993; Daniel et al. 1992; DeAngelo et al. 1991).

Although the liver is the main site of trichloroethylene metabolism in animals, there is evidence for extrahepatic trichloroethylene metabolism (Bruckner et al. 1989). After exposure to radioactive trichloroethylene vapor over an 8-hour monitoring period, Bergman (1983a) noted a continuing accumulation of trichloroethylene metabolites in the liver, kidney, and bronchi, organs in which trichloroethylene has been found to produce tumors. Further evidence for extrahepatic metabolism of trichloroethylene was presented by Hobara et al. (1986), who used a hepatic bypass procedure in dogs to demonstrate that extrahepatic metabolism of trichloroethylene accounted for 25% of the total metabolism of the chemical. Oxidation of trichloroethylene to chloral has been demonstrated in microsomal fractions from lung of rodents (Green et al. 1997; Odum et al. 1992) and from kidney of rodents and humans (Cummings et al. 2001). *In vitro* and *in vivo* data suggest that the cytochrome P450 in Type II alveolar and Clara cells of the lung is very active in metabolizing trichloroethylene, which may in turn result in pulmonary cytotoxicity and carcinogenicity (Forkert et al. 1985; Miller and Guengerich 1983; Nichols et al. 1992; Villaschi et al. 1991). As reviewed by Green (2000), the ability of the human lung to metabolize trichloroethylene is approximately 600-fold less than that of the mouse; this difference has been attributed to differences in number and morphology of Clara cells as well as species-specific differences in metabolic capacity. Clara cells have been implicated in the development of adenocarcinoma, the most frequent form of lung cancer in humans, although the role of Clara cells in lung tumorigenesis in mouse models is somewhat controversial (Reynolds and Malkinson 2010). Pulmonary cytochrome P450 isoforms important in metabolizing trichloroethylene in the Clara cells were CYP2E1 and CYP2F (Forkert et al. 2005, 2006). Results of assays using isolated rabbit pulmonary cells (Clara, Type II, and alveolar macrophages) indicate that some type of non-P450-mediated bioactivation of trichloroethylene is involved in cytotoxicity because addition of 1-aminobenzotriazole (a suicide substrate inhibitor of cytochrome P450) is not necessary to cause cytotoxicity because it failed to decrease the non-selective cytotoxicity of trichloroethylene in all three cell types (Nichols et al. 1992). Trichloroethylene metabolism also appears to be important in trichloroethylene-induced nephrotoxicity, although it appears that the principal nephrotoxic metabolites are produced via the GSH-dependent pathway, which includes the liver and kidney (Dekant et al. 1986a; Elfarra and Anders 1984).

The GSH-dependent pathway of trichloroethylene metabolism in humans and animals is outlined in Figure 3-20. Although the GSH conjugation of many compounds is associated with detoxification, trichloroethylene is bioactivated through the formation of reactive species downstream from the initial GSH conjugation; this process is thought to result in cytotoxic and carcinogenic effects, particularly in the kidney (EPA 2011e; Lash et al. 2000b; NRC 2006, 2009). The conjugation of trichloroethylene with GSH produces S-dichlorovinyl-glutathione isomers (DCVG, collectively). These isomers are S-(1,2-dichlorovinyl)glutathione (1,2-DCVG) (EPA 2011e; Lash et al. 2000a, 2000b, 2006; NRC 2006) and S-(2,2-dichlorovinyl)glutathione (2,2-DCVG) (Bernauer et al. 1996; Commandeur and Vermeulen 1990; EPA 2011e). 1,2-DCVG has been identified as a product of trichloroethylene metabolism in rat liver microsomes incubated with GSH (Dekant et al. 1990) and in isolated human and rat liver and kidney cells (Cummings and Lash 2000; Lash et al. 1995, 1999a). Following in vivo exposure to trichloroethylene, 1,2-DCVG was detected in human blood (Lash et al. 1999b) and in rat serum, blood, bile, liver, and kidney (Dekant et al. 1990; Kim et al. 2009a; Lash et al. 2006). The evidence for the 2,2-DCVG isomer is less clear and may include theoretical considerations and the identification of both 1,2- and 2,2-dichloro- downstream metabolites (Bernauer et al. 1996; Commandeur and Vermeulen 1990). Figure 3-21 shows the 1,2-dichloro- metabolites, but applies to the 2,2-dichloro- metabolites as well.

The enzymes that mediate the conjugation of trichloroethylene with GSH, glutathione S-transferases, are present in various tissues, including renal tissues, but total amounts are highest in the liver, leading to the assumption that the majority of DCVG is produced in the liver (Lash et al. 2000a, 2000b; Luo et al. 2018). Conjugation of trichloroethylene with GSH to form 1,2-DCVG was demonstrated in hepatic and renal subcellular fractions from humans, rats, and mice (Lash and Anders 1989; Lash et al. 1998, 1999a) and in isolated hepatocytes, renal cortical cells, and renal proximal tubule cells from rats (Lash and Anders 1989; Lash et al. 1998).

DCVG formed in the liver can be transported to serum and bile, taken up by the renal brush border, and metabolized to the corresponding S-dichlorovinylcysteine isomers (collectively DCVC). Metabolism of DCVG to S-(1,2-dichlorovinyl)cysteine (1,2-DCVC) or S-(2,2-dichlorovinyl)cysteine (2,2-DCVC) occurs as a two-step process by γ-glutamyl transpeptidase and dipeptidases (Elfarra and Anders 1984; Goeptar et al. 1995; Lash et al. 1988). The activities of these enzymes (measured with an alternative substrate) are much higher in the kidney than in the liver of humans, rats, and mice (EPA 2011e; Lash et al. 1998). *In vitro* rates of DCVG formation were about 8 and 13 times greater in rat and mouse liver cytosol,

respectively, than human liver cytosol (Green et al. 1997). Conversion of DCVG to DCVC also can occur in the bile or gut (EPA 2011e).

DCVC is further metabolized by N-acetyl transferases (detoxification step) to N-acetyl-S-dichlorovinyl-L-cysteine isomers (collectively NAcDCVC) in the liver or kidney (Birner et al. 1997; Duffel and Jakoby 1982). The NAcDCVC isomers, which are mercapturic acid conjugates, are N-acetyl-S-(1,2-dichloro-vinyl)-L-cysteine (NAc-1,2-DCVC) and N-acetyl-S-(2,2-dichlorovinyl)-L-cysteine (NAc-2,2-DCVC). These mercapturic acid conjugates may be released into the blood and translocated to the kidney, where they may undergo deacetylation (Wolfgang et al. 1989; Zhang and Stevens 1989) or be excreted into the urine (Bernauer et al.1996; Birner et al. 1993; Commandeur and Vermeulen 1990). Following inhalation exposure to trichloroethylene, humans excreted approximately equal concentrations of the two NAcDCVC isomers in the urine, whereas rats excreted a 3–4-fold higher concentration of NAc-2,2-DCVC than NAc-1,2-DCVC in the urine (Bernauer et al. 1996).

Alternatively, DCVC may be bioactivated by β-lyases to S-(1,2-dichlorovinyl)thiol, a transient intermediate that rearranges to reactive alkylating metabolites (Dekant et al. 1988; Goepter et al. 1995). The potential formation or fate of S-(2,2-dichlorovinyl) thiol was not mentioned in the available literature. *In vitro* studies with rat, mouse, and human kidney fractions indicated that flux through the N-acetyl transferase pathways was much higher than through β-lyase pathways; overall, the metabolic clearance through the β-lyase pathway was 11-fold greater in the rat than the human kidney (Green et al. 1997). Evidence of β-lyase activity has been reported in extrarenal tissues, such as rat and human liver and rat brain, and in intestinal microflora (EPA 2011e).

An additional bioactivating pathway involves the sulfoxidation of DCVC by flavin mono-oxygenase 3 (FMO3) and of its mercapturic acid conjugates by CYP3A. Sulfoxidation of DCVC by FMO3 was observed in microsomes from rabbit liver (Ripp et al. 1997) and human liver (Krause et al. 2003). Sulfoxidation of DCVC was not detected in microsomes from human kidney, but FMO3 expression was lower in renal than in hepatic microsomes (Krause et al. 2003). Sulfoxidation of NAc-1,2-DCVC and NAc-2,2-DCVC was catalyzed by CYP3A in microsomes from rat liver (Werner et al. 1996).

The relative flux of trichloroethylene through the cytochrome P450-dependant oxidative pathway versus the GSH-dependent conjugation pathway is uncertain, although the GSH-dependent pathway is quantitatively minor. These pathways are in competition with each other; inhibition of cytochrome P450 mediated oxidation *in vitro* with renal preparations increases the GSH conjugation of trichloroethylene

(Cummings and Lash 2000). The quantitative reliability of reported concentrations of metabolites of either pathway and of rates of GSH conjugation have been questioned because they vary greatly across studies; it has been suggested that the variance in rates of GSH conjugation may be related to different analytical methods (EPA 2011e).

There is evidence to suggest that trichloroethylene is metabolized in the male reproductive tract, primarily in the epididymal epithelium but also in testicular Leydig cells, by CYP2E1 to chloral, trichloroethanol, and TCA (Forkert et al. 2002, 2003). Furthermore, DCA protein adducts have been detected in the epididymis and efferent ducts of rats administered trichloroethylene (DuTeaux et al. 2003, 2004).

3.4.4 Elimination and Excretion

Additional information regarding metabolites excreted in the urine was summarized in Section 3.4.3 due to its relevance to metabolism.

3.4.4.1 Inhalation Exposure

Following inhalation exposure to trichloroethylene in humans, the unmetabolized parent compound is exhaled, whereas its metabolites are primarily eliminated in the urine. Excretion of trichloroethylene in the bile apparently represents a minor pathway of elimination. Balance studies in humans have shown that following single or sequential daily exposures of 50–380 ppm trichloroethylene, 11 and 2% of the dose was eliminated unchanged and as trichloroethanol, respectively, in the lungs; 58% was eliminated as urinary metabolites; and approximately 30% was unaccounted for (Monster et al. 1976, 1979). The half-lives for trichloroethylene and trichloroethanol in exhaled air were approximately 10 and 20 hours, respectively (Monster et al. 1976). Exhaled air contained notable concentrations of trichloroethylene 18 hours after exposure ended because of the relatively long half-life for elimination of trichloroethylene from the adipose tissue (i.e., 3.5–5 hours) compared to other tissues (Fernandez et al. 1977; Monster et al. 1979). Following exposure of human subjects to 1 ppm for 6 hours, terminal half-lives for trichloroethylene in alveolar air of 14–23 hours were determined (Chiu et al. 2007).

The primary urinary metabolites of trichloroethylene in humans are trichloroethanol, trichloroethanol glucuronide, and TCA (Monster et al. 1979; Nomiyama and Nomiyama 1971; Sato et al. 1977). The half-time for renal elimination of trichloroethanol and trichloroethanol glucuronide has been determined in several studies to be approximately 10 hours following trichloroethylene exposure (Monster et al. 1979; Sato et al. 1977). The renal elimination of TCA is much slower because the metabolite is very tightly and

extensively bound to plasma proteins; data from several studies indicate that the half-time for TCA is approximately 52 hours (Monster et al. 1976; Sato et al. 1977).

Sex differences in the urinary excretion of metabolites of trichloroethylene have been reported (Inoue et al. 1989; Nomiyama and Nomiyama 1971). In trichloroethylene-exposed workers, urinary levels of trichloroethanol were significantly higher in men than in women, while urinary levels of TCA did not differ between the two sexes (Inoue et al. 1989). However, it was reported that excretion of TCA in urine was greater in women than in men within 24 hours of exposure (Nomiyama and Nomiyama 1971).

The radioactivity in urine, feces, and expired breath was evaluated following exposure of mice and rats to [^{14}C]-radiolabelled trichloroethylene (Stott et al. 1982). During 50 hours of evaluation following a 6-hour exposure of mice to trichloroethylene at 10 ppm, 74% of the radioactivity was excreted in the urine, 9% was exhaled as carbon dioxide, and 4% was recovered in the feces. In similarly exposed rats, 63% was recovered in urine, 5% as exhaled carbon dioxide, and 7% in the feces. Exposure at 600 ppm resulted in similar recoveries in urine, expired air, and feces of mice, and slightly less radioactivity in the urine, expired air, and feces of rats.

3.4.4.2 Oral Exposure

A study in two Finnish villages with up to 220 ppb trichloroethylene and/or up to 180 ppb tetrachloroethylene in their drinking water found urinary TCA levels in exposed individuals to be 3–10 times higher (7.9–19 µg/day) than in unexposed controls (2–4 µg/day) (Vartiainen et al. 1993). Besides drinking the water, individuals may have been exposed to these chemicals dermally or through inhalation while bathing. TCA is a metabolite of trichloroethylene as well as tetrachloroethylene.

Seventy-two hours after a single oral dose of 2, 20, or 200 mg/kg [^{14}C]-trichloroethylene was administered to mice and rats, trichloroethylene was eliminated unchanged in exhaled air and urine, whereas the metabolites were excreted primarily in the urine (Dekant et al. 1986b). In rats, the three metabolites that accounted for approximately 90% of the total trichloroethylene urinary metabolites were TCA (15%), trichloroethanol (12%), and conjugated trichloroethanol (62%) (Dekant et al. 1984). Minor urinary metabolites in the rat (i.e., <10% of the total urinary metabolites) were oxalic acid (1.3%), DCA (2.0%), and N-(hydroxyacetyl)-aminoethanol (7.2%). In addition, 1.9% of the absorbed radiolabelled dose was found in the exhaled air as carbon dioxide in rats (Dekant et al. 1984). Male rats that consumed 0.4 mg/kg trichloroethylene from the drinking water containing 4.8 ppm of [^{14}C]-trichloroethylene

excreted 85% of the radioactivity (Koizumi et al. 1986). The percentage of radioactivity excreted in the urine was 40%, while 10.9% was in expired air as carbon dioxide, and 34.6% was in the feces, carcass, and cage wash. About 14.5% was excreted unchanged in the expired air. Four metabolites were characterized in the urine; three of these were identified as TCA, trichloroethanol, and the glucuronide conjugate of trichloroethanol and accounted for 13.1, 2.7, and 81.5% of the radioactivity excreted in the urine, respectively. An unidentified urinary metabolite accounted for 2.7% of the radioactivity (Koizumi et al. 1986).

Excretion data show that saturability of trichloroethylene metabolism occurs at lower exposure levels for rats than for mice (Dekant et al. 1986b; Prout et al. 1985). In mice receiving a single oral dose of 10, 500, 1,000, or 2,000 mg/kg trichloroethylene, urinary TCA and exhaled carbon dioxide over a 24-hour period were directly proportional to the exposure levels (Prout et al. 1985). In rats, however, the amount of TCA and carbon dioxide excreted increased linearly at ≤1,000 mg/kg trichloroethylene and then started to level off. A study of rats and mice receiving single oral doses of 2, 20, and 200 mg/kg also showed that saturation occurred in mice at higher doses than in rats, as demonstrated by the lower percentage of unchanged trichloroethylene exhaled by mice (9.5%) compared to rats (50.9%) after administration of 200 mg/kg [^{14}C]-trichloroethylene (Dekant et al. 1986b).

3.4.4.3 Dermal Exposure

Peak concentrations of trichloroethylene in expired air (approximately 7 nmol/L) occurred approximately 30 minutes following the initiation of exposure of the forearm and hand (1,000 cm^2) of volunteers to trichloroethylene vapor at 1.3 mmol/L (3.18×10^4 ppm) in a dynamic exposure cylinder for 20 minutes (Kezic et al. 2000). Trichloroethylene also was excreted in the breath of volunteers who were exposed dermally to trichloroethylene in water or soil as described in Section 3.4.1.3, generally with a slight delay (0.1–0.55 hours) thought to be due to loading of the chemical into the stratum corneum, and reaching peak levels within about 1 hour after the start of exposure (Poet et al. 2000). Elevated trichloroethylene levels in expired air were measured in subjects who immersed one hand in an unspecified concentration of trichloroethylene in water for 30 minutes (Sato and Nakajima 1978). Volunteers exposed dermally to pure trichloroethylene liquid for 1 minute expired trichloroethylene into the air; the expired air data were used to model permeation rates but were not reported (Kezic et al. 2001).

Guinea pigs, exposed to dilute concentrations of aqueous trichloroethylene (≈0.020–0.110 ppm) over a majority of their body surface area for 70 minutes, excreted 59% of the administered dose in the urine and

feces (data were reported only as combined urine and fecal excretion); 95% of the metabolized dose was excreted in 8.6 days (Bogen et al. 1992). Rats exposed dermally to trichloroethylene in water and soil as described in Section 3.4.1.3 excreted trichloroethylene in the expired air with peak concentrations occurring within 2 hours of the initiation of exposure to trichloroethylene in water and 1–2 hours of exposure to trichloroethylene in soil (Poet et al. 2000). Other excretory routes were not investigated.

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.

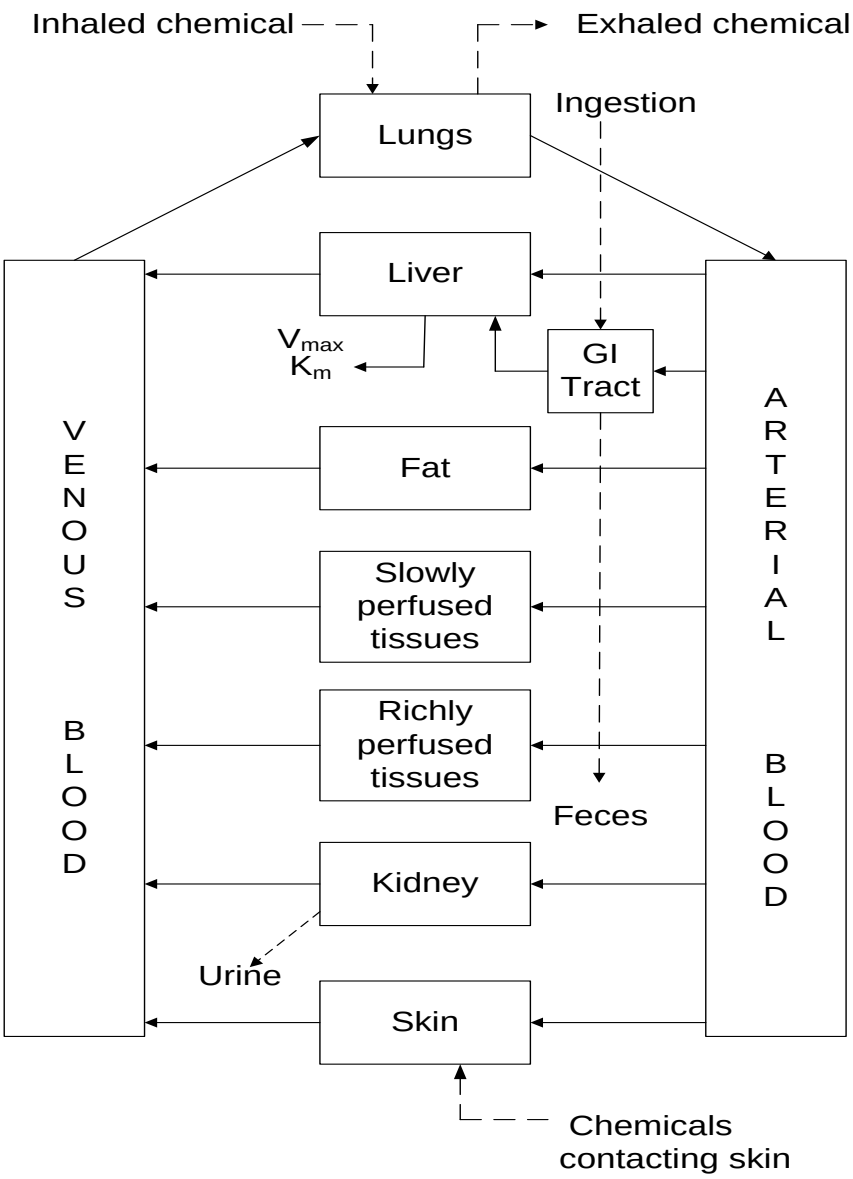
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. However, if the uptake and disposition of the chemical substance(s) are adequately described, this simplification is desirable because data are often unavailable for many 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 3-22 shows a conceptualized representation of a PBPK model.

If PBPK models for trichloroethylene 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.

Several PBPK models of trichloroethylene have been reported that have evolved in complexity to address specific problems in toxicokinetics extrapolation among rats, mice, and humans (Chiu et al. 2009; EPA 2011e; Evans et al. 2009; Fisher 2000; Hack et al. 2006; Keys et al. 2003; Poet et al. 2000; Simmons et al. 2002; Thrall and Poet 2000). The models have focused on descriptions of trichloroethylene and its major oxidative metabolites, TCA, trichloroethanol, and trichloroethanol-glucuronide conjugate. In the early models applied to dosimetry extrapolations, absorbed trichloroethylene was distributed into four flow-limited tissue compartments (liver, fat, rapidly perfused tissue, and slowly perfused tissue), and elimination was attributed to metabolism of trichloroethylene (K_m, V_{max}) in liver (Allen and Fisher 1993; Fisher and Allen 1993; Fisher et al. 1991). Metabolic production of TCA was represented as a fixed proportion of total metabolism and plasma kinetics of TCA was represented with a single-compartment, first-order model. Subsequent models extended the metabolism simulation to include more complete simulations of metabolism and of the metabolites formed (Abbas and Fisher 1997; Greenberg et al. 1999; Fisher et al. 1998). Trichloroethylene metabolism was attributed to conversion to chloral in liver (K_m,

Figure 3-22. 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: Krishnan and Andersen 1994

V_{max}), and formation of downstream metabolites (DCA, TCA, trichloroethanol, and trichloroethanol-glucuronide conjugate) were presented with first-order rate constants (k_i). These included conversion of chloral to TCA, interconversion of chloral and trichloroethanol, conjugation of trichloroethanol to trichloroethanol-glucuronide conjugate, and conversion of TCA to DCA. Kinetics of each metabolite were simulated with multi-compartment sub-models (e.g., flow-limited liver, fat, rapidly perfused and slowly perfused tissue compartments). The models also included first-order excretion of chloral, TCA, trichloroethanol, and trichloroethanol-glucuronide conjugate, and fecal excretion (i.e., biliary) of trichloroethanol-glucuronide conjugate.

An alternative to models of Fisher and colleagues was developed by Clewell et al. (2000) to specifically address dosimetry predictions of carcinogenicity in target tissues (lung, kidney, and liver). The Clewell et al. (2000) model distributes absorbed trichloroethylene into seven flow-limited tissue compartments (tracheobronchial region of the respiratory tract, gastrointestinal tract, kidney, liver, fat, and rapidly perfused and slowly perfused tissues). Metabolism is assumed to occur in the respiratory tract, kidney, and liver. Metabolism occurring in the respiratory tract includes oxidation of trichloroethylene to chloral (K_m, V_{max}) and metabolic elimination of chloral (K_m, V_{max}). The model assumes that all GSH conjugation of trichloroethylene in the liver or kidney leads to the appearance of DCVC (first order) in the kidney where DCVC is activated to a cytotoxic product (first order) or eliminated in the urine by conversion to NAcDCVC (first order). Liver metabolism is assumed to produce three metabolites (TCA, trichloroethanol-glucuronide conjugate, and DCA) which are excreted in urine (first order). These three metabolites are also assumed to be distributed in volumes of distribution (fraction of body weight), which provides for computation of their respective concentrations in blood and plasma. In the liver, trichloroethylene is converted to chloral (K_m, V_{max}), which is instantly and completely converted to TCA or trichloroethanol (proportionality constant). TCA is converted to DCA (K_m, V_{max}). Trichloroethanol undergoes three competing reactions consisting of conversion to TCA (K_m, V_{max}), trichloroethanol-glucuronide conjugate (K_m, V_{max}), or DCA (K_m, V_{max}). Trichloroethanol-glucuronide conjugate, in addition to being excreted in urine, is transferred to the gastrointestinal tract (first order), representing biliary secretion, from where it can be reabsorbed as trichloroethanol (first order), representing enterohepatic circulation. DCA, in addition to being excreted in urine, undergoes metabolic elimination (K_m, V_{max}).

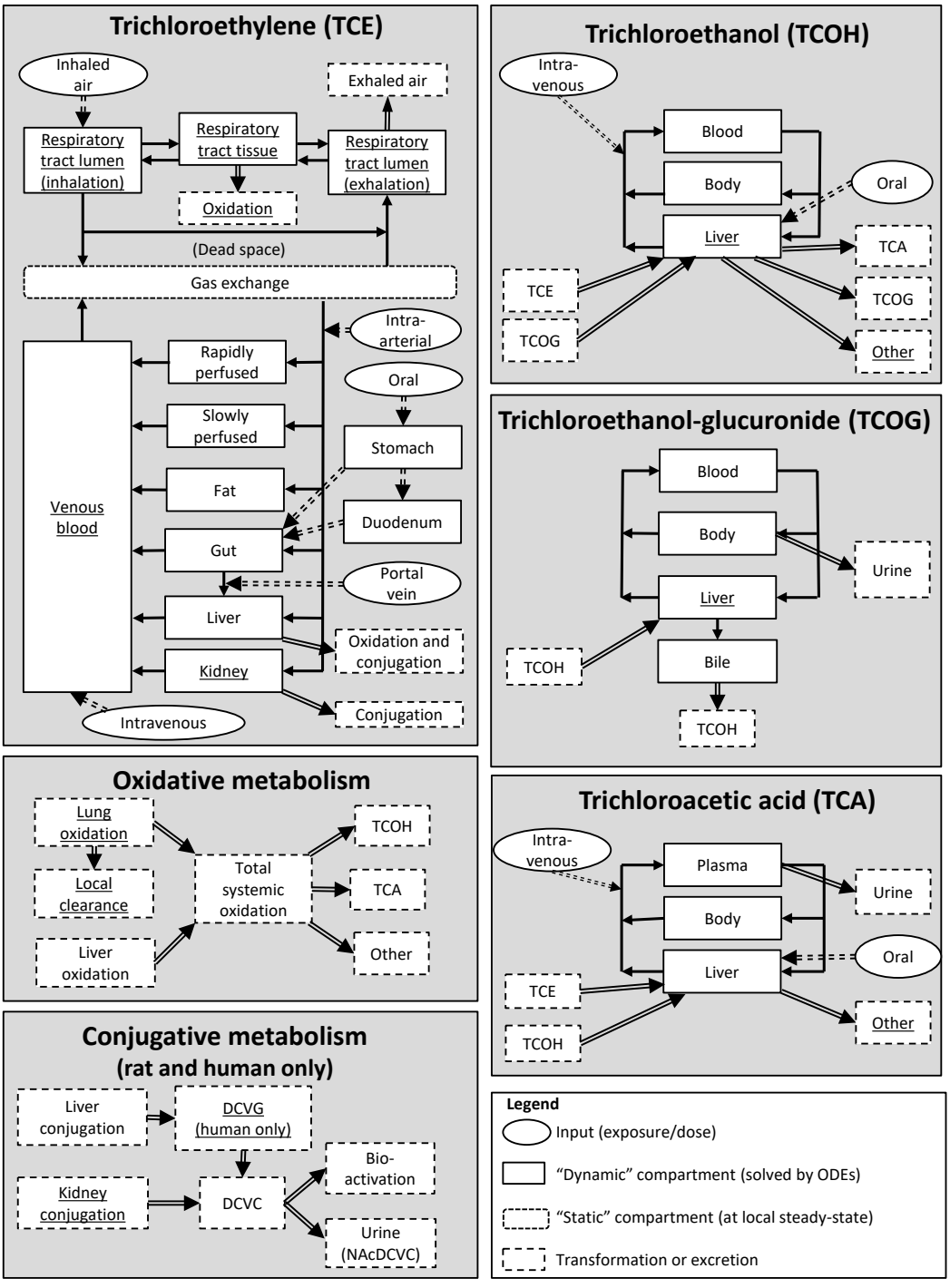
Although the Clewell et al. (2000) and Fisher (2000) models differ in many ways, the major differences are the inclusion of separate tissue compartments for metabolism in respiratory tract, kidney, and liver in the Clewell et al. (2000) model, the inclusion of GSH-dependent DCVC production, activation, and

elimination in the Clewell et al. (2000) model, and flow-limited distribution of trichloroethylene metabolites from blood to tissue compartments in the Fisher (2000) models. The two groups also used different data sets and approaches to estimating model parameters and evaluating model performance. Various statistical analyses, including Bayesian probabilistic approaches to parameter value estimation and uncertainty analyses have been performed on both models (Bois 2000a, 2000b). In 2006, the results of an EPA-U.S. Air Force (USAF) working group included a proposed structure for a harmonized model based on data included in the development of the Fisher (2000) and Clewell et al. (2000) models, along with newer data available at that time (AFRL 2004). Hack et al. (2006) also applied a Bayesian probabilistic approach to estimate parameter values for the harmonized model. The EPA reevaluated the Hack et al. (2006) model and derived a model based on newer data (Chiu et al. 2009; Evans et al. 2009). EPA re-estimated parameter values for the Chiu et al. model (Chiu et al. 2009; Evans et al. 2009) and applied the updated model to dosimetry extrapolations in support of its Toxicological Review of Trichloroethylene (EPA 2011e). The model described in EPA (2011e) is presented below in greater detail because it represents the most recent elaboration of a PBPK model for trichloroethylene for application in risk assessment. It is essentially identical to that described in Chiu et al. (2009) with small differences in the prior and posterior distributions for the central estimates (i.e., median) of parameters.

EPA Model (EPA 2011e; Chiu et al. 2009; Evans et al. 2009).

Description of the Model. The structure of the EPA (2011e) model is shown in Figure 3-23 and parameters and values for rats, mice, and humans are listed in Tables 3-7, 3-8, and 3-9. This model includes eight tissue compartments; it retains the seven-compartment structure of the Clewell et al. (2000) model (tracheobronchial region of the respiratory tract, gastrointestinal tract, kidney, liver, fat, and rapidly perfused and slowly perfused tissues) with the addition of a separate venous blood compartment. Similar to the Clewell et al. (2000) model, metabolism is assumed to occur in the respiratory tract, kidney, and liver. Metabolism occurring in the respiratory tract consists of trichloroethylene oxidation (K_m, V_{max}), with a fraction of oxidative flux undergoing instantaneous elimination within the respiratory tract or translocation to liver where further metabolism to TCA or trichloroethanol occurs. In kidney, trichloroethylene is converted to the GSH conjugate DCVG (K_m, V_{max}), which undergoes conversion to DCVC (first order), which can be activated to a cytotoxic product (first order) or eliminated by conversion to NAcDCVC and excreted in urine (first order). Inclusion of DCVG as a distinct intermediate in the production of DCVC distinguishes the kidney metabolism model in the EPA (2011e) model from other previous models and enables the use of data on DCVG kinetics in parameter estimation (Chiu et al. 2009). Unlike previous models that assume that DCVC production is limited to the kidney,

Figure 3-23. Overall Structure of PBPK Model for Trichloroethylene and Metabolites



Boxes with underlined labels are additions or modifications of the Hack et al. (2006) model.

DCVC = S-dichlorovinylcysteine; DCVG = S-dichlorovinyl-glutathione; NAcTCVC = N-acetyl trichlorovinyl cysteine; ODE = ordinary differential equation

Source: EPA 2011e

Table 3-7. Prior and Posterior Uncertainty and Variability in Mouse PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Cardiac output (L/hour)	QC	0.84 (0.59, 1.2)	1 (0.79, 1.3)	1.17 (1.1, 1.4)	1.35 (1.15, 1.54)
Alveolar ventilation (L/hour)	QP	2.1 (1.3, 3.5)	2.1 (1.5, 2.7)	1.27 (1.17, 1.54)	1.45 (1.28, 1.66)
Scaled fat blood flow	QFatC	0.07 (0.03, 0.11)	0.072 (0.044, 0.1)	1.65 (1.22, 2.03)	1.64 (1.3, 1.99)
Scaled gut blood flow	QGutC	0.14 (0.11, 0.17)	0.16 (0.14, 0.17)	1.15 (1.09, 1.19)	1.12 (1.07, 1.19)
Scaled liver blood flow	QLivC	0.02 (0.016, 0.024)	0.021 (0.017, 0.024)	1.15 (1.09, 1.19)	1.15 (1.09, 1.19)
Scaled slowly perfused blood flow	QSlwC	0.22 (0.14, 0.29)	0.21 (0.15, 0.28)	1.3 (1.15, 1.38)	1.3 (1.17, 1.39)
Scaled rapidly perfused blood flow	QRapC	0.46 (0.37, 0.56)	0.45 (0.37, 0.52)	1.15 (1.11, 1.2)	1.17 (1.12, 1.2)
Scaled kidney blood flow	QKidC	0.092 (0.054, 0.13)	0.091 (0.064, 0.12)	1.34 (1.14, 1.45)	1.34 (1.18, 1.44)
Respiratory lumen:tissue diffusive clearance rate (L/hour)	DResp	0.017 (0.000032, 15)	2.5 (1.4, 5.1)	1.37 (1.25, 1.62)	1.53 (1.37, 1.73)
Fat fractional compartment volume	VFatC	0.071 (0.032, 0.11)	0.089 (0.061, 0.11)	1.59 (1.19, 1.93)	1.4 (1.19, 1.78)
Gut fractional compartment volume	VGutC	0.049 (0.041, 0.057)	0.048 (0.042, 0.055)	1.11 (1.07, 1.14)	1.11 (1.08, 1.14)
Liver fractional compartment volume	VLivC	0.054 (0.038, 0.071)	0.047 (0.037, 0.06)	1.22 (1.12, 1.29)	1.23 (1.17, 1.3)
Rapidly perfused fractional compartment volume	VRapC	0.1 (0.087, 0.11)	0.099 (0.09, 0.11)	1.08 (1.05, 1.11)	1.09 (1.06, 1.11)
Fractional volume of respiratory lumen	VRespLumC	0.0047 (0.004, 0.0053)	0.0047 (0.0041, 0.0052)	1.09 (1.06, 1.12)	1.09 (1.07, 1.12)
Fractional volume of respiratory tissue	VRespEffC	0.0007 (0.0006, 0.00079)	0.0007 (0.00062, 0.00078)	1.09 (1.06, 1.12)	1.1 (1.07, 1.12)

Table 3-7. Prior and Posterior Uncertainty and Variability in Mouse PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Kidney fractional compartment volume	VKidC	0.017 (0.015, 0.019)	0.017 (0.015, 0.019)	1.08 (1.05, 1.11)	1.09 (1.06, 1.11)
Blood fractional compartment volume	VBldC	0.049 (0.042, 0.056)	0.048 (0.043, 0.054)	1.1 (1.06, 1.13)	1.1 (1.08, 1.13)
Slowly perfused fractional compartment volume	VSlwC	0.55 (0.5, 0.59)	0.54 (0.51, 0.57)	1.05 (1.04, 1.07)	1.05 (1.04, 1.07)
Plasma fractional compartment volume	VPlasC	0.026 (0.016, 0.036)	0.022 (0.016, 0.029)	1.24 (1.15, 1.35)	1.27 (1.19, 1.36)
TCA body fractional compartment volume (not including blood+liver)	VBodC	0.79 (0.77, 0.8)	0.79 (0.78, 0.81)	1.01 (1.01, 1.02)	1.01 (1.01, 1.02)
TCOH/G body fractional compartment volume (not including liver)	VBodTCOHC	0.84 (0.82, 0.85)	0.84 (0.83, 0.85)	1.01 (1.01, 1.02)	1.01 (1.01, 1.02)
TCE blood:air partition coefficient	PB	15 (10, 23)	14 (11, 17)	1.22 (1.12, 1.42)	1.44 (1.28, 1.53)
TCE fat:blood partition coefficient	PFat	36 (21, 62)	36 (26, 49)	1.26 (1.14, 1.52)	1.32 (1.16, 1.56)
TCE gut:blood partition coefficient	PGut	1.9 (0.89, 3.8)	1.5 (0.94, 2.6)	1.36 (1.2, 1.75)	1.36 (1.2, 1.79)
TCE liver:blood partition coefficient	PLiv	1.7 (0.89, 3.5)	2.2 (1.3, 3.3)	1.37 (1.2, 1.75)	1.39 (1.21, 1.84)
TCE rapidly perfused:blood partition coefficient	PRap	1.8 (0.98, 3.7)	1.8 (1.1, 3)	1.37 (1.2, 1.76)	1.37 (1.2, 1.77)
TCE respiratory tissue:air partition coefficient	PResp	2.7 (1.2, 5)	2.5 (1.5, 4.2)	1.36 (1.19, 1.78)	1.37 (1.19, 1.74)
TCE kidney:blood partition coefficient	PKid	2.2 (0.96, 4.6)	2.6 (1.7, 4)	1.36 (1.2, 1.77)	1.51 (1.25, 1.88)
TCE slowly perfused:blood partition coefficient	PSlw	2.4 (1.2, 4.9)	2.2 (1.4, 3.5)	1.38 (1.2, 1.78)	1.39 (1.21, 1.8)

Table 3-7. Prior and Posterior Uncertainty and Variability in Mouse PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
TCA blood:plasma concentration ratio	TCAPlas	0.76 (0.4, 16)	1.1 (0.75, 1.8)	1.21 (1.09, 1.58)	1.23 (1.1, 1.73)
Free TCA body:blood plasma partition coefficient	PBodTCA	0.77 (0.27, 17)	0.87 (0.59, 1.5)	1.41 (1.23, 1.8)	1.39 (1.24, 1.9)
Free TCA liver:blood plasma partition coefficient	PLivTCA	1.1 (0.36, 21)	1.1 (0.64, 1.9)	1.41 (1.23, 1.8)	1.4 (1.24, 1.87)
Protein:TCA dissociation constant (µmole/L)	kDissoc	100 (13, 790)	130 (24, 520)	2.44 (1.73, 5.42)	2.64 (1.75, 5.45)
Maximum binding concentration (µmole/L)	B_{MAX}	87 (9.6, 790)	140 (28, 690)	2.72 (1.92, 5.78)	2.88 (1.93, 5.89)
TCOH body:blood partition coefficient	PBodTCOH	1.1 (0.61, 2.1)	0.89 (0.65, 1.3)	1.29 (1.16, 1.66)	1.31 (1.17, 1.61)
TCOH liver:body partition coefficient	PLivTCOH	1.3 (0.73, 2.3)	1.9 (1.2, 2.6)	1.3 (1.16, 1.61)	1.35 (1.18, 1.68)
TCOG body:blood partition coefficient	PBodTCOG	0.95 (0.016, 77)	0.48 (0.18, 1.1)	1.36 (1.19, 2.05)	1.41 (1.22, 2.19)
TCOG liver:body partition coefficient	PLivTCOG	1.3 (0.019, 92)	1.3 (0.64, 2.6)	1.36 (1.18, 2.13)	1.56 (1.28, 2.52)
DCVG effective volume of distribution	VDCVG	0.033 (0.0015, 15)	0.027 (0.0016, 4.1)	1.28 (1.08, 1.97)	1.31 (1.1, 2.19)
TCE stomach absorption coefficient (/hour)	kAS	1.7 (0.0049, 450)	1.7 (0.37, 13)	4.74 (2.29, 23.4)	4.28 (2.39, 13.4)
TCE stomach-duodenum transfer coefficient (/hour)	kTSD	1.4 (0.043, 51)	4.5 (0.51, 26)	3.84 (2.09, 10.6)	4.79 (2.53, 10.9)
TCE duodenum absorption coefficient (/hour)	kAD	1.2 (0.0024, 200)	0.27 (0.067, 1.6)	4.33 (2.14, 26)	4.17 (2.34, 14.4)
TCA stomach absorption coefficient (/hour)	kASTCA	0.63 (0.0027, 240)	4 (0.2, 74)	4.26 (2.27, 23.4)	5.15 (2.56, 22)
V_{MAX} for hepatic TCE oxidation (mg/hour)	V_{MAX}	3.9 (1.4, 15)	2.5 (1.6, 4.2)	2.02 (1.56, 2.85)	1.86 (1.59, 2.47)

Table 3-7. Prior and Posterior Uncertainty and Variability in Mouse PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
K_M for hepatic TCE oxidation (mg/L)	K_M	34 (1.6, 620)	2.7 (1.4, 8)	1.25 (1.15, 1.61)	2.08 (1.48, 3.49)
Fraction of hepatic TCE oxidation not to TCA+TCOH	FracOther	0.43 (0.0018, 1)	0.023 (0.0037, 0.15)	1.23 (1, 2.13)	1.49 (1.25, 2.83)
Fraction of hepatic TCE oxidation to TCA	FracTCA	0.086 (0.00022, 0.66)	0.13 (0.084, 0.21)	1.48 (1.12, 2.56)	1.4 (1.21, 1.96)
V_{MAX} for hepatic TCE GSH conjugation (mg/hour)	V_{MAX} DCVG	3.7 (0.0071, 2,800)	0.6 (0.01, 480)	1.55 (1.33, 2.52)	1.61 (1.37, 2.91)
K_M for hepatic TCE GSH conjugation (mg/L)	K_MDCVG	250 (0.0029, 6,500,000)	2,200 (0.17, 2,300,000)	1.81 (1.47, 3.62)	1.93 (1.49, 3.68)
V_{MAX} for renal TCE GSH conjugation (mg/hour)	V_{MAX} KidDCVG	0.34 (0.00051, 180)	0.027 (0.0012, 13)	1.49 (1.26, 2.49)	1.54 (1.28, 2.72)
K_M for renal TCE GSH conjugation (mg/L)	K_MKidDCVG	150 (0.0053, 6,200,000)	160 (0.078, 280,000)	1.79 (1.43, 3.45)	1.91 (1.5, 3.91)
V_{MAX} for tracheo-bronchial TCE oxidation (mg/hour)	V_{MAX} Clara	0.24 (0.03, 3.9)	0.42 (0.1, 1.5)	2.32 (1.74, 3.66)	4.13 (2.27, 6.79)
K_M for tracheo-bronchial TCE oxidation (mg/L)	K_MClara	1.5 (0.0018, 630)	0.011 (0.0024, 0.09)	1.47 (1.25, 2.58)	1.63 (1.28, 5.02)
Fraction of respiratory metabolism to systemic circulation	FracLungSys	0.34 (0.0016, 1)	0.78 (0.18, 0.99)	1.24 (1, 2.1)	1.11 (1, 1.72)
V_{MAX} for hepatic TCOH→TCA (mg/hour)	V_{MAX} TCOH	0.064 (0.000014, 380)	0.12 (0.048, 0.28)	1.5 (1.24, 2.61)	1.6 (1.28, 2.92)
K_M for hepatic TCOH→TCA (mg/L)	K_MTCOH	1.4 (0.00018, 5,300)	0.92 (0.26, 2.7)	1.48 (1.24, 2.41)	1.49 (1.26, 2.4)

Table 3-7. Prior and Posterior Uncertainty and Variability in Mouse PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
V_{MAX} for hepatic TCOH→TCOG (mg/hour)	V_{MAX} Gluc	0.11 (0.000013, 310)	4.6 (1.9, 16)	1.48 (1.26, 2.53)	1.47 (1.26, 2.14)
K_M for hepatic TCOH→TCOG (mg/L)	K_MGluc	1.8 (0.0018, 610)	30 (5.3, 130)	1.48 (1.25, 2.48)	1.8 (1.3, 4.72)
Rate constant for hepatic TCOH→other (/hour)	kMetTCOH	0.19 (0.000039, 1,400)	8.8 (1.9, 23)	1.47 (1.25, 2.36)	1.54 (1.26, 2.92)
Rate constant for TCA plasma→urine (/hour)	kUrnTCA	32 (0.38, 1,700)	3.2 (1.2, 7.1)	1.57 (1.34, 2.61)	1.84 (1.44, 2.94)
Rate constant for hepatic TCA→other (/hour)	kMetTCA	0.12 (0.0004, 130)	1.5 (0.63, 2.9)	1.48 (1.25, 2.32)	1.51 (1.26, 2.27)
Rate constant for TCOG liver→bile (/hour)	kBile	0.3 (0.0004, 160)	2.4 (0.74, 8.4)	1.48 (1.24, 2.29)	1.51 (1.26, 2.39)
Lumped rate constant for TCOG bile→TCOH liver (/hour)	kEHR	0.21 (0.00036, 150)	0.039 (0.0026, 0.11)	1.47 (1.23, 2.29)	1.53 (1.28, 2.94)
Rate constant for TCOG→urine (/hour)	kUrnTCOG	1 (0.00015, 6200)	12 (2.6, 77)	1.71 (1.4, 3.13)	3.44 (1.89, 9.49)
Rate constant for hepatic DCVG→DCVC (/hour)	kDCVG	0.24 (0.0004, 160)	0.81 (0.0033, 46)	1.48 (1.25, 2.39)	1.52 (1.25, 2.5)
Lumped rate constant for DCVC→urinary NAcDCVC (/hour)	kNAT	0.29 (0.0004, 160)	0.37 (0.0021, 34)	1.5 (1.25, 2.49)	1.53 (1.25, 2.77)
Rate constant for DCVC bioactivation (/hour)	kKidBioact	0.18 (0.0004, 150)	0.23 (0.0024, 33)	1.48 (1.25, 2.51)	1.53 (1.25, 3.03)

Source: EPA 2011e

Table 3-8. Prior and Posterior Uncertainty and Variability in Rat PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Cardiac output (L/hour)	QC	5.3 (4.2, 6.9)	6.1 (5.2, 7.4)	1.12 (1.07, 1.28)	1.26 (1.12, 1.36)
Alveolar ventilation (L/hour)	QP	10 (5.1, 18)	7.5 (5.8, 10)	1.32 (1.18, 1.71)	1.52 (1.33, 1.84)
Scaled fat blood flow	QFatC	0.071 (0.032, 0.11)	0.081 (0.06, 0.1)	1.66 (1.21, 2.02)	1.5 (1.3, 1.86)
Scaled gut blood flow	QGutC	0.15 (0.12, 0.18)	0.17 (0.15, 0.19)	1.15 (1.09, 1.19)	1.13 (1.08, 1.18)
Scaled liver blood flow	QLivC	0.021 (0.017, 0.026)	0.022 (0.018, 0.025)	1.15 (1.09, 1.2)	1.15 (1.1, 1.19)
Scaled slowly perfused blood flow	QSlwC	0.33 (0.21, 0.46)	0.31 (0.23, 0.4)	1.31 (1.15, 1.4)	1.32 (1.22, 1.41)
Scaled rapidly perfused blood flow	QRapC	0.28 (0.15, 0.42)	0.28 (0.18, 0.36)	1.38 (0.0777, 1.72)	1.42 (0.0856, 1.75)
Scaled kidney blood flow	QKidC	0.14 (0.12, 0.16)	0.14 (0.12, 0.16)	1.11 (1.07, 1.14)	1.11 (1.08, 1.14)
Respiratory lumen:tissue diffusive clearance rate (L/hour)	DResp	9.9 (0.48, 85)	21 (9.5, 46)	1.41 (1.26, 1.77)	1.59 (1.41, 1.9)
Fat fractional compartment volume	VFatC	0.069 (0.031, 0.11)	0.069 (0.046, 0.091)	1.61 (1.2, 1.93)	1.59 (1.34, 1.88)
Gut fractional compartment volume	VGutC	0.032 (0.027, 0.037)	0.032 (0.028, 0.036)	1.11 (1.07, 1.14)	1.11 (1.08, 1.14)
Liver fractional compartment volume	VLivC	0.034 (0.026, 0.042)	0.033 (0.028, 0.039)	1.16 (1.09, 1.21)	1.17 (1.12, 1.21)
Rapidly perfused fractional compartment volume	VRapC	0.087 (0.076, 0.1)	0.088 (0.079, 0.097)	1.1 (1.06, 1.13)	1.1 (1.07, 1.13)
Fractional volume of respiratory lumen	VRespLumC	0.0046 (0.0037, 0.0057)	0.0047 (0.0039, 0.0055)	1.16 (1.1, 1.21)	1.16 (1.11, 1.21)
Fractional volume of respiratory tissue	VRespEffC	0.0005 (0.00039, 0.00061)	0.0005 (0.00041, 0.00058)	1.16 (1.09, 1.21)	1.16 (1.11, 1.2)

Table 3-8. Prior and Posterior Uncertainty and Variability in Rat PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Kidney fractional compartment volume	VKidC	0.0069 (0.0056, 0.0082)	0.007 (0.006, 0.008)	1.13 (1.08, 1.17)	1.13 (1.09, 1.17)
Blood fractional compartment volume	VBldC	0.073 (0.063, 0.085)	0.074 (0.066, 0.082)	1.1 (1.06, 1.13)	1.1 (1.07, 1.13)
Slowly perfused fractional compartment volume	VSlwC	0.6 (0.55, 0.63)	0.6 (0.57, 0.62)	1.05 (1.04, 1.06)	1.05 (1.04, 1.06)
Plasma fractional compartment volume	VPlasC	0.039 (0.025, 0.054)	0.04 (0.032, 0.049)	1.24 (1.15, 1.35)	1.22 (1.16, 1.33)
TCA body fractional compartment volume (not including blood+liver)	VBodC	0.79 (0.78, 0.81)	0.79 (0.78, 0.8)	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)
TCOH/G body fractional compartment volume (not including liver)	VBodTCOHC	0.87 (0.86, 0.87)	0.87 (0.86, 0.87)	1.01 (1, 1.01)	1.01 (1, 1.01)
TCE blood:air partition coefficient	PB	22 (14, 33)	19 (16, 24)	1.26 (1.19, 1.35)	1.3 (1.22, 1.38)
TCE fat:blood partition coefficient	PFat	27 (16, 46)	31 (24, 42)	1.32 (1.22, 1.44)	1.32 (1.23, 1.43)
TCE gut:blood partition coefficient	PGut	1.3 (0.69, 3)	1.1 (0.79, 1.7)	1.36 (1.21, 1.79)	1.36 (1.2, 1.68)
TCE liver:blood partition coefficient	PLiv	1.5 (1.2, 1.9)	1.6 (1.3, 1.8)	1.15 (1.11, 1.2)	1.15 (1.11, 1.2)
TCE rapidly perfused:blood partition coefficient	PRap	1.3 (0.66, 2.7)	1.3 (0.82, 2.1)	1.35 (1.18, 1.82)	1.37 (1.2, 1.76)
TCE respiratory tissue:air partition coefficient	PResp	0.97 (0.48, 2.1)	1 (0.62, 1.6)	1.37 (1.19, 1.77)	1.36 (1.19, 1.78)
TCE kidney:blood partition coefficient	PKid	1.3 (0.77, 2.2)	1.2 (0.9, 1.7)	1.31 (1.19, 1.5)	1.3 (1.2, 1.45)

Table 3-8. Prior and Posterior Uncertainty and Variability in Rat PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
TCE slowly perfused:blood partition coefficient	PSlw	0.57 (0.35, 0.97)	0.73 (0.54, 0.97)	1.32 (1.23, 1.43)	1.33 (1.25, 1.46)
TCA blood:plasma concentration ratio	TCAPlas	0.78 (0.6, 0.96)	0.78 (0.71, 0.86)	1.12 (1.06, 1.22)	1.11 (1.07, 1.17)
Free TCA body:blood plasma partition coefficient	PBodTCA	0.7 (0.18, 2.2)	0.76 (0.46, 1.3)	1.72 (1.39, 2.81)	1.65 (1.4, 2.19)
Free TCA liver:blood plasma partition coefficient	PLivTCA	0.84 (0.25, 3.3)	1.1 (0.61, 2.1)	1.71 (1.39, 2.78)	1.66 (1.38, 2.37)
Protein:TCA dissociation constant (µmole/L)	kDissoc	270 (95, 790)	280 (140, 530)	1.62 (1.31, 2.43)	1.6 (1.31, 2.31)
Maximum binding concentration (µmole/L)	B_{MAX}	320 (80, 1300)	320 (130, 750)	1.89 (1.5, 2.64)	1.84 (1.49, 2.57)
TCOH body:blood partition coefficient	PBodTCOH	1 (0.33, 4)	1.1 (0.51, 2.1)	1.71 (1.37, 2.69)	1.76 (1.38, 2.45)
TCOH liver:body partition coefficient	PLivTCOH	1.3 (0.39, 4.5)	1.2 (0.59, 2.8)	1.71 (1.37, 2.8)	1.78 (1.37, 2.75)
TCOG body:blood partition coefficient	PBodTCOG	0.48 (0.021, 14)	1.6 (0.091, 16)	1.39 (1.2, 1.97)	1.42 (1.21, 2.52)
TCOG liver:body partition coefficient	PLivTCOG	1.3 (0.078, 39)	10 (2.7, 41)	1.4 (1.2, 2.14)	1.42 (1.21, 2.3)
DCVG effective volume of distribution	VDCVG	0.27 (0.27, 0.27)	0.27 (0.27, 0.27)	1 (1, 1)	1 (1, 1)
TCE stomach absorption coefficient (/hour)	kAS	0.73 (0.0044, 400)	2.5 (0.32, 19)	4.16 (2.21, 20)	9.3 (4.07, 31.1)
TCE stomach-duodenum transfer coefficient (/hour)	kTSD	1.4 (0.04, 45)	3.2 (0.31, 19)	3.92 (2.13, 10.4)	5.54 (2.77, 10.7)
TCE duodenum absorption coefficient (/hour)	kAD	0.96 (0.0023, 260)	0.17 (0.038, 1)	4.17 (2.15, 20.8)	4.07 (2.51, 11.9)

Table 3-8. Prior and Posterior Uncertainty and Variability in Rat PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
TCA stomach absorption coefficient (/hour)	kASTCA	0.83 (0.0024, 240)	1.4 (0.13, 13)	4.15 (2.2, 18.7)	4.21 (2.4, 11.4)
V_{MAX} for hepatic TCE oxidation (mg/hour)	V_{MAX}	5.8 (2, 19)	5.3 (3.9, 7.7)	1.97 (1.54, 2.92)	1.69 (1.47, 2.15)
K_M for hepatic TCE oxidation (mg/L)	K_M	18 (1.9, 240)	0.74 (0.54, 1.4)	2.76 (1.89, 6.46)	1.84 (1.51, 2.7)
Fraction of hepatic TCE oxidation not to TCA+TCOH	FracOther	0.027 (0.0018, 0.59)	0.29 (0.047, 0.56)	1.42 (1.15, 2.33)	2.15 (1.32, 5.06)
Fraction of hepatic TCE oxidation to TCA	FracTCA	0.2 (0.027, 0.76)	0.046 (0.023, 0.087)	1.35 (1.11, 2.14)	1.84 (1.36, 2.8)
V_{MAX} for hepatic TCE GSH conjugation (mg/hour)	V_{MAX} DCVG	2 (0.015, 1100)	5.8 (0.16, 340)	1.52 (1.3, 2.67)	1.57 (1.32, 2.93)
K_M for hepatic TCE GSH conjugation (mg/L)	K_MDCVG	1,500 (1.2, 1,800,000)	6,300 (120, 720,000)	1.83 (1.45, 3.15)	1.88 (1.48, 3.49)
V_{MAX} for renal TCE GSH conjugation (mg/hour)	V_{MAX} KidDCVG	0.038 (0.00027, 13)	0.0024 (0.0005, 0.014)	1.52 (1.3, 2.81)	1.56 (1.29, 2.72)
K_M for renal TCE GSH conjugation (mg/L)	K_MKidDCVG	470 (0.47, 530,000)	0.25 (0.038, 2.2)	1.84 (1.47, 4.27)	1.93 (1.49, 3.57)
V_{MAX} for tracheo-bronchial TCE oxidation (mg/hour)	V_{MAX} Clara	0.2 (0.0077, 2.4)	0.17 (0.042, 0.69)	2.26 (1.71, 3.3)	4.35 (1.99, 6.7)
K_M for tracheo-bronchial TCE oxidation (mg/L)	K_MClara	0.016 (0.0014, 0.58)	0.025 (0.005, 0.15)	1.47 (1.26, 2.39)	1.65 (1.28, 10.5)
Fraction of respiratory metabolism to systemic circulation	FracLungSys	0.82 (0.027, 1)	0.73 (0.06, 0.98)	1.09 (1, 1.71)	1.13 (1.01, 1.86)

Table 3-8. Prior and Posterior Uncertainty and Variability in Rat PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
V_{MAX} for hepatic TCOH→TCA (mg/hour)	V_{MAX} TCOH	0.75 (0.037, 20)	0.71 (0.27, 2.2)	1.51 (1.25, 2.64)	1.68 (1.3, 3.23)
K_M for hepatic TCOH→TCA (mg/L)	K_MTCOH	1 (0.029, 23)	19 (3.6, 94)	1.52 (1.26, 2.7)	1.72 (1.26, 3.93)
V_{MAX} for hepatic TCOH→TCOG (mg/hour)	V_{MAX} Gluc	27 (0.83, 620)	11 (4.1, 32)	1.5 (1.25, 2.59)	2.3 (1.41, 5.19)
K_M for hepatic TCOH→TCOG (mg/L)	K_MGluc	31 (1, 570)	6.3 (1.2, 20)	1.5 (1.25, 2.74)	2.04 (1.3, 8.4)
Rate constant for hepatic TCOH→other (/hour)	kMetTCOH	4.2 (0.17, 150)	3 (0.57, 15)	1.49 (1.27, 2.67)	1.72 (1.3, 8.31)
Rate constant for TCA plasma→urine (/hour)	kUrnTCA	1.9 (0.21, 47)	0.92 (0.51, 1.7)	1.56 (1.33, 2.81)	1.58 (1.36, 2.25)
Rate constant for hepatic TCA→other (/hour)	kMetTCA	0.76 (0.037, 19)	0.47 (0.17, 1.2)	1.5 (1.26, 2.74)	1.52 (1.27, 2.45)
Rate constant for TCOG liver→bile (/hour)	kBile	1.4 (0.052, 31)	14 (2.7, 39)	1.5 (1.25, 2.8)	1.63 (1.29, 4.1)
Lumped rate constant for TCOG bile→TCOH liver (/hour)	kEHR	0.013 (0.00055, 0.64)	1.7 (0.34, 7.4)	1.5 (1.25, 2.49)	1.67 (1.26, 5.91)
Rate constant for TCOG→urine (/hour)	kUrnTCOG	11 (0.063, 1000)	12 (0.45, 370)	1.74 (1.42, 2.99)	1.86 (1.43, 3.54)
Rate constant for hepatic DCVG→DCVC (/hour)	kDCVG	30,000 (30,000, 30,000)	30,000 (30,000, 30,000)	1 (1, 1)	1 (1, 1)

Table 3-8. Prior and Posterior Uncertainty and Variability in Rat PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Lumped rate constant for DCVC→urinary NAcDCVC (/hour)	kNAT	0.15 (0.00024, 84)	0.0029 (0.00066, 0.015)	1.49 (1.24, 2.8)	1.54 (1.26, 2.45)
Rate constant for DCVC bioactivation (/hour)	kKidBioact	0.12 (0.00023, 83)	0.0092 (0.0012, 0.043)	1.48 (1.24, 2.68)	1.52 (1.25, 2.5)

Source: EPA 2011e

Table 3-9. Prior and Posterior Uncertainty and Variability in Human PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Cardiac output (L/hour)	QC	390 (280, 560)	330 (280, 390)	1.17 (1.1, 1.39)	1.39 (1.26, 1.54)
Alveolar ventilation (L/hour)	QP	380 (220, 640)	440 (360, 530)	1.27 (1.17, 1.52)	1.58 (1.44, 1.73)
Scaled fat blood flow	QFatC	0.051 (0.021, 0.078)	0.043 (0.033, 0.055)	1.64 (1.23, 2)	1.92 (1.72, 2.09)
Scaled gut blood flow	QGutC	0.19 (0.15, 0.23)	0.16 (0.14, 0.18)	1.16 (1.1, 1.21)	1.16 (1.12, 1.2)
Scaled liver blood flow	QLivC	0.063 (0.029, 0.099)	0.039 (0.026, 0.055)	1.62 (1.22, 1.92)	1.8 (1.62, 1.98)
Scaled slowly perfused blood flow	QSlwC	0.22 (0.13, 0.3)	0.17 (0.14, 0.21)	1.34 (1.18, 1.45)	1.39 (1.31, 1.46)
Scaled rapidly perfused blood flow	QRapC	0.29 (0.18, 0.4)	0.39 (0.34, 0.43)	1.31 (1.14, 1.57)	1.22 (1.16, 1.3)
Scaled kidney blood flow	QKidC	0.19 (0.16, 0.22)	0.19 (0.18, 0.21)	1.1 (1.07, 1.13)	1.1 (1.07, 1.12)
Respiratory lumen:tissue diffusive clearance rate (L/hour)	DResp	560 (44, 3300)	270 (130, 470)	1.37 (1.25, 1.61)	1.71 (1.52, 2.35)
Fat fractional compartment volume	VFatC	0.19 (0.088, 0.31)	0.16 (0.12, 0.21)	1.66 (1.23, 1.93)	1.65 (1.4, 1.9)
Gut fractional compartment volume	VGutC	0.02 (0.018, 0.022)	0.02 (0.019, 0.021)	1.07 (1.04, 1.08)	1.06 (1.05, 1.08)
Liver fractional compartment volume	VLivC	0.026 (0.018, 0.032)	0.026 (0.022, 0.03)	1.21 (1.12, 1.28)	1.2 (1.13, 1.26)
Rapidly perfused fractional compartment volume	VRapC	0.087 (0.079, 0.096)	0.088 (0.083, 0.093)	1.07 (1.05, 1.09)	1.06 (1.05, 1.08)
Fractional volume of respiratory lumen	VRespLumC	0.0024 (0.0018, 0.003)	0.0024 (0.0021, 0.0027)	1.18 (1.1, 1.23)	1.17 (1.12, 1.22)
Fractional volume of respiratory tissue	VRespEffC	0.00018 (0.00014, 0.00022)	0.00018 (0.00015, 0.00021)	1.18 (1.1, 1.24)	1.17 (1.13, 1.23)

Table 3-9. Prior and Posterior Uncertainty and Variability in Human PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Kidney fractional compartment volume	VKidC	0.0043 (0.0034, 0.0052)	0.0043 (0.0038, 0.0048)	1.15 (1.09, 1.19)	1.14 (1.1, 1.19)
Blood fractional compartment volume	VBldC	0.077 (0.066, 0.088)	0.078 (0.072, 0.084)	1.1 (1.06, 1.13)	1.1 (1.07, 1.13)
Slowly perfused fractional compartment volume	VSlwC	0.45 (0.33, 0.55)	0.48 (0.43, 0.52)	1.18 (1.1, 1.24)	1.16 (1.12, 1.22)
Plasma fractional compartment volume	VPlasC	0.044 (0.037, 0.051)	0.044 (0.04, 0.048)	1.11 (1.08, 1.14)	1.11 (1.08, 1.14)
TCA body fractional compartment volume (not including blood+liver)	VBodC	0.75 (0.74, 0.77)	0.75 (0.74, 0.76)	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)
TCOH/G body fractional compartment volume (not including liver)	VBodTCOHC	0.83 (0.82, 0.84)	0.83 (0.83, 0.83)	1.01 (1, 1.01)	1.01 (1, 1.01)
TCE blood:air partition coefficient	PB	9.6 (6.5, 13)	9.2 (8.2, 10)	1.18 (1.13, 1.26)	1.21 (1.16, 1.28)
TCE fat:blood partition coefficient	PFat	68 (46, 98)	57 (49, 66)	1.18 (1.11, 1.33)	1.18 (1.11, 1.3)
TCE gut:blood partition coefficient	PGut	2.6 (1.3, 5.3)	2.9 (1.9, 4.1)	1.37 (1.2, 1.78)	1.41 (1.21, 1.77)
TCE liver:blood partition coefficient	PLiv	4 (1.9, 8.5)	4.1 (2.7, 5.9)	1.37 (1.22, 1.81)	1.33 (1.19, 1.6)
TCE rapidly perfused:blood partition coefficient	PRap	2.6 (1.2, 5.7)	2.4 (1.8, 3.2)	1.37 (1.21, 1.78)	1.5 (1.25, 1.87)
TCE respiratory tissue:air partition coefficient	PResp	1.3 (0.65, 2.7)	1.3 (0.9, 1.9)	1.36 (1.19, 1.81)	1.32 (1.2, 1.56)
TCE kidney:blood partition coefficient	PKid	1.6 (1.1, 2.3)	1.6 (1.3, 1.9)	1.17 (1.1, 1.33)	1.15 (1.09, 1.25)

Table 3-9. Prior and Posterior Uncertainty and Variability in Human PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
TCE slowly perfused:blood partition coefficient	PSlw	2.1 (1.2, 3.5)	2.3 (1.9, 2.8)	1.28 (1.14, 1.53)	1.51 (1.36, 1.66)
TCA blood:plasma concentration ratio	TCAPlas	0.78 (0.55, 15)	0.65 (0.6, 0.77)	1.08 (1.03, 1.53)	1.52 (1.23, 2.03)
Free TCA body:blood plasma partition coefficient	PBodTCA	0.45 (0.19, 8.1)	0.44 (0.33, 0.55)	1.36 (1.19, 1.75)	1.67 (1.38, 2.2)
Free TCA liver:blood plasma partition coefficient	PLivTCA	0.59 (0.24, 10)	0.55 (0.39, 0.77)	1.36 (1.18, 1.76)	1.65 (1.37, 2.16)
Protein:TCA dissociation constant (µmole/L)	kDissoc	180 (160, 200)	180 (170, 190)	1.05 (1.03, 1.09)	1.04 (1.03, 1.07)
Maximum binding concentration (µmole/L)	B_{MAX}	830 (600, 1100)	740 (630, 880)	1.17 (1.1, 1.3)	1.16 (1.1, 1.28)
TCOH body:blood partition coefficient	PBodTCOH	0.89 (0.51, 1.7)	1.5 (1.3, 1.7)	1.29 (1.16, 1.64)	1.34 (1.25, 1.47)
TCOH liver:body partition coefficient	PLivTCOH	0.58 (0.32, 1.1)	0.63 (0.45, 0.87)	1.29 (1.16, 1.65)	1.29 (1.17, 1.5)
TCOG body:blood partition coefficient	PBodTCOG	0.67 (0.036, 16)	0.72 (0.3, 1.8)	1.38 (1.2, 2.42)	7.83 (4.86, 12.6)
TCOG liver:body partition coefficient	PLivTCOG	1.8 (0.11, 28)	3.1 (0.87, 8.1)	1.38 (1.19, 2.04)	4.94 (2.73, 8.58)
DCVG effective volume of distribution	VDCVG	73 (5.2, 36000)	6.1 (5.4, 7.3)	1.27 (1.08, 1.95)	1.1 (1.07, 1.16)
TCE stomach absorption coefficient (/hour)	kAS	1.4 (1.4, 1.4)	1.4 (1.4, 1.4)	1 (1, 1)	1 (1, 1)
TCE stomach-duodenum transfer coefficient (/hour)	kTSD	1.4 (1.4, 1.4)	1.4 (1.4, 1.4)	1 (1, 1)	1 (1, 1)
TCE duodenum absorption coefficient (/hour)	kAD	0.75 (0.75, 0.75)	0.75 (0.75, 0.75)	1 (1, 1)	1 (1, 1)

Table 3-9. Prior and Posterior Uncertainty and Variability in Human PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
TCA stomach absorption coefficient (/hour)	kASTCA	0.58 (0.0022, 210)	3 (0.061, 180)	4.26 (2.13, 17.6)	5.16 (2.57, 22.3)
TCOH stomach absorption coefficient (/hour)	kASTCOH	0.49 (0.0024, 210)	7.6 (0.11, 150)	4.19 (2.22, 21.5)	5.02 (2.44, 18.5)
V_{MAX} for hepatic TCE oxidation (mg/hour)	V_{MAX}	430 (130, 1500)	190 (130, 290)	1.98 (1.69, 2.31)	2.02 (1.77, 2.38)
K_M for hepatic TCE oxidation (mg/L)	K_M	3.7 (0.22, 63)	0.18 (0.078, 0.4)	2.74 (2.1, 5.62)	4.02 (2.9, 5.64)
Fraction of hepatic TCE oxidation not to TCA+TCOH	FracOther	0.12 (0.0066, 0.7)	0.11 (0.024, 0.23)	1.4 (1.11, 2.38)	2.71 (1.37, 5.33)
Fraction of hepatic TCE oxidation to TCA	FracTCA	0.19 (0.036, 0.56)	0.035 (0.024, 0.05)	2.55 (1.51, 3.96)	2.25 (1.89, 2.87)
V_{MAX} for hepatic TCE GSH conjugation (mg/hour)	V_{MAX} DCVG	100 (0.0057, 690,000)	340 (110, 1100)	1.91 (1.55, 3.76)	6.18 (3.35, 11.3)
K_M for hepatic TCE GSH conjugation (mg/L)	K_MDCVG	3.1 (0.21, 42)	3.6 (1.2, 11)	1.52 (1.26, 2.91)	4.2 (2.48, 8.01)
V_{MAX} for renal TCE GSH conjugation (mg/hour)	V_{MAX} KidDCVG	220 (0.028, 6,700,000)	2.1 (0.17, 9.3)	1.86 (1.51, 3.33)	4.02 (1.57, 33.9)
K_M for renal TCE GSH conjugation (mg/L)	K_MKidDCVG	2.7 (0.14, 41)	0.76 (0.29, 5.8)	1.5 (1.27, 2.56)	1.49 (1.27, 2.32)
V_{MAX} for tracheo-bronchial TCE oxidation (mg/hour)	V_{MAX} Clara	25 (1, 260)	18 (3.8, 41)	2.25 (1.85, 3.25)	2.9 (2.12, 6.49)
K_M for tracheo-bronchial TCE oxidation (mg/L)	K_MClara	0.019 (0.0017, 0.5)	0.31 (0.057, 1.4)	1.48 (1.25, 2.39)	10.8 (1.99, 37.6)

Table 3-9. Prior and Posterior Uncertainty and Variability in Human PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Fraction of respiratory metabolism to systemic circulation	FracLungSys	0.75 (0.051, 0.99)	0.96 (0.86, 0.99)	1.12 (1, 1.75)	1.02 (1, 1.1)
V_{MAX} for hepatic TCOH→TCA (mg/hour)	V_{MAX} TCOH	42 (0.77, 2200)	9.2 (5.5, 20)	1.83 (1.46, 3.43)	3.15 (2.3, 5.44)
K_M for hepatic TCOH→TCA (mg/L)	K_MTCOH	5 (0.23, 81)	2.2 (1.3, 4.5)	1.49 (1.25, 2.57)	2.58 (1.75, 4.5)
V_{MAX} for hepatic TCOH→TCOG (mg/hour)	V_{MAX} Gluc	720 (12, 50,000)	900 (340, 2,000)	1.83 (1.48, 3.5)	2.29 (1.84, 4.57)
K_M for hepatic TCOH→TCOG (mg/L)	K_MGluc	10 (0.53, 190)	130 (47, 290)	1.5 (1.25, 2.6)	1.58 (1.26, 3.69)
Rate constant for hepatic TCOH→other (/hour)	kMetTCOH	0.83 (0.035, 10)	0.25 (0.042, 0.7)	1.5 (1.26, 3)	5.13 (2.72, 16.7)
Rate constant for TCA plasma→urine (/hour)	kUrnTCA	0.26 (0.038, 4)	0.11 (0.083, 0.15)	1.48 (1.29, 2.29)	1.86 (1.58, 2.28)
Rate constant for hepatic TCA→other (/hour)	kMetTCA	0.19 (0.01, 2.6)	0.096 (0.038, 0.19)	1.48 (1.26, 2.57)	2.52 (1.79, 4.34)
Rate constant for TCOG liver→bile (/hour)	kBile	1.2 (0.059, 16)	2.5 (1.1, 6.9)	1.47 (1.25, 2.75)	1.56 (1.27, 3.21)
Lumped rate constant for TCOG bile→TCOH liver (/hour)	kEHR	0.074 (0.004, 1.4)	0.053 (0.033, 0.087)	1.52 (1.26, 2.64)	1.72 (1.35, 2.51)
Rate constant for TCOG→urine (/hour)	kUrnTCOG	2.9 (0.061, 260)	2.4 (0.83, 7)	1.75 (1.4, 3.31)	18.7 (11.6, 31.8)

Table 3-9. Prior and Posterior Uncertainty and Variability in Human PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Rate constant for hepatic DCVG→DCVC (/hour)	kDCVG	0.044 (0.000063, 22)	2.5 (1.9, 3.4)	1.48 (1.25, 2.83)	1.51 (1.3, 1.86)
Lumped rate constant for DCVC→urinary NAcDCVC (/hour)	kNAT	0.00085 (0.000055, 0.041)	0.0001 (0.000047, 0.0007)	1.51 (1.25, 2.34)	1.47 (1.24, 2.48)
Rate constant for DCVC bioactivation (/hour)	kKidBioact	0.0022 (0.000095, 0.079)	0.023 (0.0062, 0.061)	1.51 (1.25, 2.57)	1.52 (1.25, 2.69)

Source: EPA 2011e

the liver metabolism in the EPA (2011e) model includes a GSH conjugation pathway as well as oxidation pathways, which compete for trichloroethylene as a substrate. The total rate of oxidation of trichloroethylene in liver (K_m, V_{max}) is split into fractions leading to TCA and trichloroethanol or to other oxidative pathways (e.g., leading to DCA but not via trichloroethanol). TCA formed in the liver is eliminated by conversion in the liver to downstream oxidative products (first order). Trichloroethanol undergoes three competing reactions in the liver consisting of conversion to TCA (K_m, V_{max}), trichloroethanol-glucuronide conjugate (K_m, V_{max}), or elimination to other products (e.g., DCA, first order). Trichloroethanol-glucuronide conjugate in liver is transferred to the gastrointestinal tract (first order) representing biliary secretion, from where it can be reabsorbed as trichloroethanol (first order) representing enterohepatic circulation. The hepatic GSH pathway leads to formation of DCVC from DCVG in liver. Activation of DCVC is assumed to occur in kidney, but not in liver. The hepatic oxidation products, TCA, trichloroethanol, and trichloroethanol-glucuronide conjugate, enter systemic blood and undergo flow-limited distribution to liver and to a lumped tissue compartment representing tissues other than liver (body). Urinary metabolites include TCA transferred from plasma (first order), trichloroethanol-glucuronide conjugate transferred from the lumped body compartment (first order), and NAcDCVC transferred after formation in kidney (first order).

Validation of the Model. Parameter values for the EPA (2011e) model were estimated by applying a hierarchical Bayesian approach (Markov Chain Monte Carlo, MCMC). Initial (*prior*) central estimates (median) and variance (geometric standard deviation) were made for each parameter. These estimates represent initial expectations of variability in each parameter value, based on data applied to the estimate, or scientific judgment, if no data were available. Prior estimates were updated by applying MCMC using data from approximately 30 rodent studies and 8 human studies to direct the Markov chain towards convergence with observations (e.g., a distribution of parameter values that yield distributions of model predictions in agreement with observations). In MCMC, a Markov chain is produced in which each step of the chain consists of repeated (e.g., n=1,000) random draws from each parameter distribution. Each draw from all parameters yields a single set of model predictions of observations (e.g., blood TCA concentration, urinary NAcDCVC). Each step in the chain (n draws) yields a distribution for each prediction (e.g., n=1,000). The distributions of model predictions are compared to observations available for each prediction. Based on acceptance or rejection criteria (i.e., whether or not the new predictions improve agreement with observations), the randomly drawn parameter values are accepted or rejected. If accepted, they establish the prior distributions for the next step in the Markov chain. The process is repeated many times (e.g., n=100,000) until the Markov chain achieves a stable probability of predicting observations (known as *convergence*). The resulting distributions of parameter values are referred to as

posterior distributions and represent estimates of the distributions of parameter values in the population of subjects consistent with measurement error and variability within the population and other unspecified sources of error in the model. The MCMC is repeated several times to evaluate stability of the outcomes.

Some model parameters were allometrically scaled across species using standard scaling assumptions (e.g., volumes, BW^{1}, first order rates, $BW^{-0.25}$, whole body flows V_{max}, $BW^{0.75}$). However, because these standard scaling factors are only approximations and because data were available for rats, mice, and humans, the scaled parameter values were also updated in a sequential MCMC analyses to account for residual error not reduced by standard allometric scaling assumptions (EPA 2011e). The sequence began with the MCMC analysis of the mouse model. Posterior distributions of the parameters to be scaled then served, along with a "scaling" error term, as priors for the MCMC analysis of the rat model. Posterior distributions for scaled parameters for the mouse and rat were combined and, with an additional error term, used as priors for the MCMC of the human model.

EPA (2011e) utilized approximately 30 data sets from rodent studies and 8 data sets from human studies to estimate posterior distributions for parameter values. The resulting calibrated model, with parameter values assigned from the posterior distributions, was evaluated against a validation set consisting of six data sets from rodent studies and 10 human studies, not used in the calibration. A complete list of data sets used in calibration and validation analyses is provided in Tables 3-10 and 3-11. Rodent data included oral gavage, intravenous, and inhalation studies of rats (predominantly) and mice. Human studies were all inhalation exposures.

Predictions of the calibrated model were compared at two levels. The first level was a comparison of model predictions of posterior parameter distributions derived for subjects representing specific observation data sets with the observation from the same data sets (i.e., predictions based on calibration with data set *i* compared to observations in data set *i*). Since these data sets were used to establish the posterior parameter distributions, as expected, posterior parameter distributions achieved good agreement when compared to data used in the calibration (i.e., in general, residuals were <2). This comparison confirmed success of the calibration. The second level was a validation of the calibrated model in which population posterior distributions were compared to observations that were not used to inform the MCMC calibration, using the 95% CI on predictions as a metric for evaluating agreement with observation (i.e., whether or not observations fell within the 95% CI of predictions). This validation analysis was possible only for the rat and human models; all available data were needed and used in the calibration of the mouse model. In general, the rat model predicted observations not included in calibration of the rat

Table 3-10. Rodent Studies with Pharmacokinetic Data Considered for Analysis

Reference	Species (strain)	Sex	TCE exposures	Other exposures	Calibration	Validation	Not used	Comments
Mouse studies								
Abbas et al. 1996	Mouse (B6C3F1)	M	–	CH intra-venous			√	CH not in model
Abbas and Fisher 1997	Mouse (B6C3F1)	M	Oral (corn oil)	–	√[a]			
Abbas et al. 1997	Mouse (B6C3F1)	M	–	TCOH, TCA intra-venous	√			
Barton et al. 1999	Mouse (B6C3F1)	M	–	DCA intra-venous and oral (aqueous)			√	DCA not in model
Birner et al. 1993	Mouse (NMRI)	M+F	Gavage	–			√	Only urine concentrations available, not amount
Fisher and Allen 1993	Mouse (B6C3F1)	M+F	Gavage (corn oil)	–	√			
Fisher et al. 1991	Mouse (B6C3F1)	M+F	Inhalation	–	√[a]			
Green and Prout 1985	Mouse (B6C3F1)	M	Gavage (corn oil)	TCA intra-venous	√			
Greenberg et al. 1999	Mouse (B6C3F1)	M	Inhalation	–	√[a]			
Larson and Bull 1992a	Mouse (B6C3F1)	M	–	DCA, TCA oral (aqueous)	√			Only data on TCA dosing was used, since DCA is not in the model
Larson and Bull 1992b	Mouse (B6C3F1)	M	Oral (aqueous)	–	√			
Merdink et al. 1998	Mouse (B6C3F1)	M	intra-venous	CH intra-venous	√			Only data on TCE dosing was used, since CH is not in the model
Prout et al. 1985	Mouse (B6C3F1, Swiss)	M	Gavage (corn oil)	–	√[a]			
Templin et al. 1993	Mouse (B6C3F1)	M	Oral (aqueous)	TCA oral	√[a]			

Table 3-10. Rodent Studies with Pharmacokinetic Data Considered for Analysis

Reference	Species (strain)	Sex	TCE exposures	Other exposures	Calibration	Validation	Not used	Comments
Rat studies								
Andersen et al. 1980	Rat (F344)	M	Inhalation	–		√[a]		
Barton et al. 1995	Rat (Sprague-Dawley)	M	Inhalation	–			√	Initial chamber concentrations unavailable, so not used
Bernauer et al. 1996	Rat (Wistar)	M	Inhalation	–	√[a]			
Birner et al. 1993	Rat (Wistar, F344)	M+F	Gavage (ns)	–			√	Only urine concentrations available, not amount
Birner et al. 1997	Rat (Wistar)	M+F	–	DCVC intra-venous			√	Single dose, route does not recapitulate how DCVC is formed from TCE, excreted NAcDCVC ~100-fold greater than that from relevant TCE exposures (Bernauer et al. 1996)
Bruckner et al. unpublished	Rat (Sprague-Dawley)	M	Inhalation	–		√		Not published, so not used for calibration; similar to Keys et al. (2003) data.
Dallas et al. 1991	Rat (Sprague-Dawley)	M	Inhalation	–	√			
D'Souza et al. 1985	Rat (Sprague-Dawley)	M	Intra-venous, oral (aqueous)	–			√	Only TCE blood measurements, and ≥10-fold greater than other similar studies
Fisher et al. 1989	Rat (F344)	F	Inhalation	–	√			
Green and Prout 1985	Rat (Osborne-Mendel)	M	Gavage (corn oil)	TCA gavage (aqueous)	√			

Table 3-10. Rodent Studies with Pharmacokinetic Data Considered for Analysis

Reference	Species (strain)	Sex	TCE exposures	Other exposures	Calibration	Validation	Not used	Comments
Hissink et al. 2002	Rat (Wistar)	M	Gavage (corn oil), intra-venous	–	√			
Jakobson et al. 1986	Rat (Sprague-Dawley)	F	Inhalation	Various pre-treatments (oral)		√		Pretreatments not included; only blood TCE data available
Kaneko et al. 1994	Rat (Wistar)	M	Inhalation	Ethanol pre-treatment (oral)	√			Pretreatments not included
Keys et al. 2003	Rat (Sprague-Dawley)	M	Inhalation, oral (aqueous), intra-arterial	–	√			
Kimmerle and Eben 1973a	Rat (Wistar)	M	Inhalation	–	√			
Larson and Bull 1992a	Rat (F344)	M	–	DCA, TCA oral (aqueous)	√			Only TCA dosing data used, since DCA is not in the model
Larson and Bull 1992b	Rat (Sprague-Dawley)	M	Oral (aqueous)	–	√[a]			
Lash et al. 2006	Rat (F344)	M+F	Gavage (corn oil)	–			√	Highly inconsistent with other studies
Lee et al. 1996	Rat (Sprague-Dawley)	M	Arterial, venous, portal, stomach injections	–		√		Only blood TCE data available
Lee et al. 2000a; 2000b	Rat (Sprague-Dawley)	M	Stomach injection, intra-venous, intra-perivenous	p-nitro-phenol pre-treatment (intra-arterial)	√	√		Pretreatments not included; only experiments with blood and liver data used for calibration
Merdink et al. 1999	Rat (F344)	M	–	CH, TCOH intra-venous	√			TCOH dosing used; CH not in model
Poet et al. 2000	Rat (F344)	M	Dermal	–			√	Dermal exposure not in model

Table 3-10. Rodent Studies with Pharmacokinetic Data Considered for Analysis

Reference	Species (strain)	Sex	TCE exposures	Other exposures	Calibration	Validation	Not used	Comments
Prout et al. 1985	Rat (Osborne-Mendel, Wistar)	M	Gavage (corn oil)	–	√[a]			
Saghir and Schultz 2002	Rat (F344)	M	–	DCA intra-venous, oral (aqueous)			√	DCA not in model
Simmons et al. 2002	Rat (Long-Evans)	M	Inhalation	–	√			
Stenner et al. 1997	Rat (F344)	M	intra-duodenal	TCOH, TCA intra-venous	√			
Templin et al. 1995b	Rat (F344)	M	Oral (aqueous)	–	√[a]			
Thrall and Poet 2000	Rat (F344)	M	intra-venous, intra-peritoneal	with toluene			√	Only exhaled breath data available from intravenous study; intra-peritoneal dosing not in model
Yu et al. 2000	Rat (F344)	M	–	TCA intra-venous	√			

[a]Part or all of the data in the study was used for calibration in Hack et al. (2006).

CH = chloral hydrate; DCA = dichloroacetic acid; DCVC = dichlorovinyl cysteine; F = female; M = male; NAcDCVC = N-acetyl-S-(dichlorovinyl)-L-cysteine; ns = not specified; TCA = trichloroacetic acid; TCE = trichloroethylene; TCOH = trichloroethanol

Source: EPA 2011e

Table 3-11. Human Studies with Pharmacokinetic Data Considered for Analysis

Reference	Species (number of individuals)	Sex	TCE exposures	Other exposures	Calibration	Validation	Not used	Comments
Bartonicek 1962	Human (n=8)	M+F	Inhalation	–		√		Sparse data, so not included for calibration to conserve computational resources
Bernauer et al. 1996	Human	M	Inhalation	–	√[a]			Grouped data, but unique in that includes NAcDCVC urine data
Bloemen et al. 2001	Human (n=4)	M	Inhalation	–		√		Sparse data, so not included for calibration to conserve computational resources
Chiu et al. 2007	Human (n=6)	M	Inhalation	–	√			
Ertle et al. 1972	Human	M	Inhalation	CH oral			√	Very similar to Muller et al. (1975) data
Fernandez et al. 1977	Human	M	Inhalation	–		√		
Fisher et al. 1998	Human (n=17)	M+F	Inhalation	–	√[a]			
Kimmerle and Eben 1973b	Human (n=12)	M+F	Inhalation	–	√			
Lapare et al. 1995	Human (n=4)	M+F	Inhalation	–		√[b]		Complex exposure patterns, and only grouped data available for urine, so used for validation
Lash et al. 1999b	Human	M+F	Inhalation	–	√			Grouped only, but unique in that DCVG blood data available (same individuals as Fisher et al. [1998])
Monster et al. 1976	Human (n=4)	M	Inhalation	–	√[b]			Experiments with exercise not included

Table 3-11. Human Studies with Pharmacokinetic Data Considered for Analysis

Reference	Species (number of individuals)	Sex	TCE exposures	Other exposures	Calibration	Validation	Not used	Comments
Monster et al. 1979	Human	M	Inhalation	–		√[a]		Grouped data only
Muller et al. 1972	Human	NS	Inhalation	–			√	Same data also included in Muller et al. (1975)
Muller et al. 1974	Human	M	Inhalation	CH, TCA, TCOH oral	√	√[a]		TCA and TCOH dosing data used for calibration, since it is rare to have metabolite dosing data; TCE dosing data used for validation, since only grouped data available; CH not in model
Muller et al. 1975	Human	M	Inhalation	Ethanol oral		√[a]		Grouped data only
Paykoc et al. 1945	Human (n=3)	NS	--	TCA intra-venous	√			
Poet et al. 2000	Human	M+F	Dermal	–				Dermal exposure not in model
Sato et al. 1977	Human	M	Inhalation	–		√		
Stewart et al. 1970	Human	NS	Inhalation	–		√[a]		
Triebig et al. 1976	Human	NS	Inhalation	–		√[a]		
Vesterberg and Astrand 1976	Human	M	Inhalation	–			√	All experiments included exercise, so were not included

[a]Part or all of the data in the study was used for calibration in Hack et al. (2006).
[b]Grouped data from this study was used for calibration in Hack et al. (2006), but individual data were used here.

CH = chloral hydrate; DCVG = S-dichlorovinyl glutathione; F = female; M = male; NAcDCVC = N-acetyl-S-(dichlorovinyl)-L-cysteine; NS = not specified; TCA = trichloroacetic acid; TCE = trichloroethylene; TCOH = trichloroethanol

Source: EPA 2011e

model, with the observations of trichloroethylene concentrations in blood and tissues (liver, gastrointestinal tract, skeletal muscle, venous blood) within the 95% CI of predictions (U.S. EPA, 2011e). The only exception reported was an under-prediction of observed kidney levels of trichloroethylene during an inhalation exposure to 500 ppm trichloroethylene, although post-exposure levels were accurately predicted. The human model also performed well against observations not included in model calibration, although observations were limited to trichloroethylene concentrations in blood and exhaled air and TCA and trichloroethanol in blood and urine. The human model showed a tendency (not in all studies) to over-predict trichloroethylene concentrations in exhaled air.

Risk Assessment. The EPA (2011e) applied the trichloroethylene model for extrapolating external dose response relationships for cancer and noncancer end points observed in rats to humans in derivation of a chronic Reference Concentration (RfC), chronic Reference Dose (RfD), inhalation cancer unit risk, and oral cancer slope factor for trichloroethylene. Candidate inhalation exposure-response and oral dose-response relationships and corresponding BMDLs or NOAELs and LOAELs were derived from rodent bioassay data. For each candidate critical effect, internal dose metrics were selected that would be expected to relate to each response. The rodent PBPK models were used to predict internal doses that corresponded to the inhalation exposures or oral doses used in the rodent bioassay. The median of the distribution of predicted internal doses was selected to represent the typical rodent internal dose. A point of departure for internal dose (idPOD) was derived from internal dose-response analyses (e.g., BMD analysis or selection of NOAELs and/or LOAELs). The rodent idPOD was extrapolated to a human equivalent concentration (HEC, mg/m^3) for inhalation exposures or human equivalent dose (HED, mg/kg/day) for oral exposures, where the HEC and HED represent the continuous inhalation or oral exposure, respectively, corresponding to the idPOD in the human. Interspecies extrapolation was based on application of the human PBPK model, using posterior parameter distributions for humans to derive human internal dose distributions for a range of inhalation or oral exposures. The internal dose distributions at each exposure level were based on 500 random draws from the posterior parameter distributions (represented a sample of n=500) from the human population. The posterior parameter distributions in the human model represent predicted population variability in parameter values. Therefore, the model predicts distributions of internal doses corresponding to a given human exposure that reflect population variability in toxicokinetics of trichloroethylene. The median of this distribution was assumed to represent the typical internal dose corresponding to a given exposure, while the 99^{th} percentile was assumed to represent a sensitive subpopulation. Based on the predicted median and 99^{th} percentile internal doses, HECs or HEDs representing the typical internal dose and (HEC_{50}, HED_{50}) and sensitive subpopulation (HEC_{99}, HEC_{99}) were derived. The model-based derivation of the

99th percentile values was used as a rationale for eliminating the need for application of uncertainty factors to adjust the HEC_{99} or HED_{99} to account for interspecies toxicokinetics variability ($10^{0.5}$) and for human variability in toxicokinetics ($10^{0.5}$). Uncertainty factors applied to the HEC_{99} or HED_{99} were $10^{0.5}$ to account for possible interspecies variability in toxicodynamics, and $10^{0.5}$ to account for possible human population variability in toxicodynamics.

Several internal dose metrics were considered in analyses supporting the derivation of the RfC, RfD, inhalation cancer unit risk, and oral cancer slope factor (EPA 2011e). These included the AUC for trichloroethylene, TCA, or trichloroethanol concentrations in blood, amounts of trichloroethylene metabolized (to GSH conjugates, oxidized) per unit body weight of metabolizing tissue weight (liver or kidney), and amount of DCVC activated per unit of body weight or kidney weight. The RfC was ultimately based on production of developmental heart defects and immunological effects as critical effects, supported by dose-response relationships for nephropathy. The internal dose metric selected to represent the developmental heart effects was the total amount of trichloroethylene metabolized through oxidative pathways in all metabolizing tissues per unit of body weight. This internal dose metric is considered appropriate because results of several studies demonstrate that selected oxidative trichloroethylene (TCA or DCA) induce cardiac malformations. The internal dose metric selected to represent the immunological effects was the total amount of trichloroethylene metabolized through all pathways in all metabolizing tissues per unit of body weight due to a lack of information on the role of metabolites or mode of action for trichloroethylene-induced immunological effects. Internal dose metrics used to represent kidney effects were the amount of DCVC activated per unit of body weight or the amount of trichloroethylene conjugated with GSH per unit of body weight, based on the conclusion that trichloroethylene-induced kidney toxicity is caused primarily by GSH conjugation metabolites (particularly DCVC). The RfD was also based on developmental heart defects and immunological effects as critical effects, supported by nephropathy. Internal dose metrics selected to represent these effects were the same as those used in the derivation of the RfC. A variety of internal dose metrics were evaluated in support for the derivation of the inhalation cancer unit risk and oral cancer slope factor, which depended on the tissue location of the cancers observed (e.g., lung, liver, kidney, or other tissues).

Target Tissues. The trichloroethylene model (EPA 2011e) was calibrated to predict blood trichloroethylene, TCA, and trichloroethanol kinetics; rates of metabolism of trichloroethylene in lung, liver, and kidney; and excretion of trichloroethylene metabolites following inhalation or oral exposures to trichloroethylene. As noted above, the model has been used to predict various internal dose metrics of trichloroethylene exposure in rats and humans (EPA 2011e). These include the AUC for

trichloroethylene, TCA, or trichloroethanol concentrations in blood; amounts of trichloroethylene metabolized (to GSH conjugates, oxidized) formed per unit body weight or metabolizing tissue weight (liver or kidney); and amount of DCVC activated per unit of body weight or kidney weight.

Interspecies Extrapolation. As described above, models simulating toxicokinetics in mice, rats, and humans have been used in interspecies extrapolation of external-internal dose response relationships (EPA 2011e). Models for the above species were developed by a combination of allometric scaling across species and optimization of scaled model parameters (metabolism V_{max} and rate constants) using hierarchical Bayesian analyses. The scaled rat and human models have been evaluated against independent observations not used to estimate model parameter values (EPA 2011e).

Interroute Extrapolation. The trichloroethylene model (EPA 2011e) as it is currently configured simulates trichloroethylene kinetics associated with inhalation, oral, and intravenous dosing. Simulation of other potential routes of exposure (e.g., dermal) would require development of models for the absorption of trichloroethylene deposited on the skin. EPA (2011e) used the PBPK model to perform oral-to-inhalation extrapolation in deriving a chronic RfC for trichloroethylene based on internal dose. EPA (2011e) used the human model to extrapolate from an inhalation cancer unit risk to an oral cancer slope factor. The basis of the inhalation cancer unit risk was epidemiological evidence of cancers in humans exposed to trichloroethylene along with supporting evidence from rodent bioassays. The interroute extrapolation was based on the internal dose metrics considered to be related to cancer, the amount of DCVC activated in kidney per unit of body weight, or the total amount of trichloroethylene metabolized per unit of body weight.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Trichloroethylene, like other volatile hydrocarbons, disrupts the cellular phospholipid membrane, thereby allowing for easy absorption. Trichloroethylene-induced changes in fatty acid composition in rat brain and liver may influence its ability to cross affected membranes (Okamoto and Shiwaku 1994). However, at concentrations found in most occupational and environmental settings, diffusion is the mechanism whereby small uncharged lipophilic molecules such as trichloroethylene are absorbed through the skin.

Distribution. Once inside the body, trichloroethylene is readily absorbed into and distributed throughout the body via the circulatory system. The amount that is not absorbed initially on inhalation is expired unchanged (see Section 3.3.1.1). Absorption from the gastrointestinal tract often leads to a first pass through the liver, where toxic and nontoxic metabolites can form (see Section 3.4.3). Trichloroethylene's metabolites may bind to, or form adducts with, blood proteins; the metabolite glyoxylate becomes incorporated into amino acids (Stevens et al. 1992).

Storage. The primary storage area for trichloroethylene in the body is the adipose tissue, as would be expected based on the lipophilicity of the compound (Fernandez et al. 1977; Monster et al. 1979).

Excretion. Much of the initially inhaled trichloroethylene is expired unchanged. Trichloroethylene has been detected in the breath of people exposed orally and dermally as well. Once absorbed, trichloroethylene is rapidly metabolized by well-characterized pathways of xenobiotic metabolism, such as the cytochrome P450 oxidation and GSH conjugation pathways, and many metabolic products are then excreted, mainly in the urine. No evidence exists for reabsorption from the kidney, although a decreased rate of excretion may be observed in persons with extra fat tissue because of trichloroethylene's tendency as a lipophilic compound to sequester in fat. The urinary excretion of TCA is slower than that of other trichloroethylene metabolites because TCA is very tightly and extensively bound to plasma proteins (Monster et al. 1976; Sato et al. 1977).

Route Dependent Toxicity. The toxicity of trichloroethylene does not seem to be heavily dependent upon its route of entry. Inhalation and ingestion are the primary exposure routes. As discussed in the *Health Effects by Route of Exposure* sections of this profile, health effects are similar across these routes. Toxic effects from dermal exposure are generally confined to the skin, although broad systemic effects can be induced under conditions of high exposure (Bauer and Rabens 1974). Attributing such effects solely to dermal exposure, however, is difficult because inhalation exposure is often a factor in these cases as well.

3.5.2 Mechanisms of Toxicity

Effects of Metabolism on Toxicity. For trichloroethylene, the mechanisms of target organ toxicity are closely related to its metabolism. Therefore, some of the information regarding the relationship between metabolism and toxicity is presented in the following section on Target Organ Toxicity.

An example is the rate by which the oxidative metabolism of trichloroethylene produces carcinogenic byproducts such as TCA. B6C3F1 mice, which are far more prone to trichloroethylene-induced liver cancer, exhibit rapid metabolism of inhaled trichloroethylene, while F344 rats and humans, which are less prone to such cancer, exhibit limited rates of metabolism (Abelson 1993; Stott et al. 1982). Larson and Bull (1992b) found that peak blood concentrations of TCA and trichloroethanol following a single oral dose of trichloroethylene (197–3,022 mg/kg) were much greater in mice than in rats, whereas the residence time of trichloroethylene (and therefore TCA and trichloroethanol) was greater in rats (a consequence of the slower rate of trichloroethylene metabolism in rats relative to mice). The net metabolism of trichloroethylene to TCA and trichloroethanol is similar in rats and mice. However, the initial rate of metabolism is higher in mice, especially as the trichloroethylene dose is increased; thus, the blood concentration of TCA is higher in mice. Since the target organs of mice are exposed to higher concentrations of potentially mutagenic/carcinogenic compounds, they are more susceptible to hepatotoxicity and hepatocarcinogenicity (Stott et al. 1982; Templin et al. 1993).

Isomers of DCVC, a product of trichloroethylene conjugation with GSH, are mutagenic in the *in vitro* Ames assay (Commandeur et al. 1991; Dekant et al. 1986c; Irving and Elfarra 2013). Additional information is provided in the Target Organ Toxicity section, under Renal Effects.

Metabolic differences between humans and other animals may account for some of the interspecies differences in specific organ toxicity of trichloroethylene (see below). Among humans, gender differences due mainly to the effects of body fat content (generally higher in women) on trichloroethylene absorption are expected based on PBPK modeling (see Section 3.4.5).

Target Organ Toxicity. Based on effects reported in humans and/or animals, the primary targets for trichloroethylene toxicity appear to be the nervous system, liver, kidney, immune system, male reproductive system, and developing fetus.

Neurological Effects. Although mechanistic studies of trichloroethylene neurotoxicity have been performed, the mechanisms for this toxicity are not well established (EPA 2011e; NRC 2006). Trichloroethylene and some of its metabolites such as chloral hydrate are central nervous system depressants and this property, mediated through effects on inhibitory neuronal receptors, may account for some of the behavioral changes associated with trichloroethylene exposure (EPA 2011e). Oxidative stress may also contribute to trichloroethylene-induced abnormal motor abnormalities. In mice deficient in superoxide dismutase, motor activity was significantly depressed compared to mice with superoxide

dismutase (Otsuki et al. 2016). Although it has been suggested that changes in trigeminal nerve function may be due to dichloroacetylene, which is produced under non-biological conditions (high alkalinity or temperature) during volatilization of trichloroethylene, exposure to this chemical has not been identified or measured in epidemiologic studies. In addition, changes in trigeminal nerve function also have been reported in humans exposed orally (EPA 2011e), and changes in trigeminal nerve morphology have been reported in rats exposed orally (Barret et al. 1991, 1992). Oral exposures are not expected to involve exposure to dichloroacetylene. Dopamine neuron disruption, including degeneration of dopamine neurons in the substantia nigra, has been reported in animal studies (Gash et al. 2008; Guehl et al. 1999) and has been suggested as a potential mechanism for clinical psychomotor effects from trichloroethylene exposure (EPA 2011e). A possible mechanism of hearing impairment was hypothesized, by analogy to aromatic hydrocarbons such as toluene, to involve toxicity to supporting cells in the cochlea, which then alters structural elements, ultimately resulting in hair cell displacement and death (EPA 2011e). Another potential mechanism is blockade of neuronal nicotinic receptors on the auditory cells and changes in calcium transmission seen with toluene and speculated to be relevant to trichloroethylene (EPA 2011e). Pre- and postnatal exposure of male MRL+/+ mice to trichloroethylene resulted in altered glutathione redox homeostasis (indicating a more oxidized state) and dose-related increased levels of glutathione precursors within the hippocampus, alterations in plasma metabolites involved in transsulfuration and transmethylation pathways (indicating redox imbalance and altered methylation capacity), significantly increased levels of 3-nitrotyrosine (a biomarker of protein oxidative stress) in plasma and hippocampus, and significantly decreased expression of key neurotrophic factors (brain-derived neurotrophic factor, nerve growth factor, neurotropin-3) compared to controls (Blossom et al. 2012). These results indicate that trichloroethylene-mediated neurotoxicity following repeated exposure might include modulation of neurotropin gene expression in the hippocampus. Blossom et al. (2013) demonstrated that postnatal oral exposure of male MRL+/+ mice to trichloroethylene resulted in effects within the cerebellum that included altered homeostasis, increased cysteinylglycine, increased 3-nitrotyrosine (a marker of oxidative protein damage), decreased methionine, and decreased global DNA methylation; the trichloroethylene-treated mice exhibited increased locomotor and exploratory activity. The study authors postulated that postnatal exposure to trichloroethylene resulted in key metabolic changes in the cerebellum that may contribute to global DNA methylation deficits and altered behavior.

Hepatic Effects. The oxidative metabolites of trichloroethylene, particularly chloral hydrate, TCA, and DCA, are thought to contribute to liver toxicity in humans and animals and to liver cancer in mice (EPA 2011e; NRC 2006). This conclusion is based on the studies in animals showing the potentiation of liver effects by pretreatment with cytochrome P450 inducers and the similarity of effects, such as increased

liver weight, peroxisome proliferation, and liver cancer, produced by trichloroethylene and these metabolites. *In vitro* exposure of human hepatic L-02 cells to trichloroethylene was performed to provide insight into possible mechanisms of trichloroethylene hepatotoxicity. Yang et al. (2012) reported decreased cell viability, increased apoptosis and elevated inhibitor 2 of protein phosphatase 2A (I2PP2A) mRNA and protein levels, and reduced PP2A activity; lentivirus-mediated I2PP2A knockdown partially reversed the effect on cell viability, apoptosis, and PP2A activity, and prevented caspase-3-mediated activation. The results indicated that I2PP2A may play a crucial role in mediating trichloroethylene hepatotoxicity. Hong et al. (2012) performed a proteomic analysis to identify the proteins that interact with I2PP2A (also known as SET/TAF-1α) and found that trichloroethylene significantly upregulated two SET/TAF-1α-binding proteins (elongation factors eEF1A1 and eEF1A2) and two isoforms of SET, as well as induced a redistribution of SET from nucleus to cytoplasm and eEF1A1 from cytoplasm to nucleus. Xu et al. (2012) observed significantly increased transcript levels of hepatic metabolic enzyme genes (CYP1A2, CYP3A4, CYP2E1) and apoptosis genes (BAD, BAX), suggesting that trichloroethylene-induced alteration of mRNA expression of hepatic metabolic enzyme genes and apoptosis genes may be involved in trichloroethylene hepatotoxicity.

Several potential modes of action for trichloroethylene-induced liver tumors in animals have been proposed. One hypothesis is a mutagenic mode of action in which key events include the oxidative metabolism of trichloroethylene in the liver to chloral hydrate or some other oxidative metabolite, resulting in mutations, DNA damage, and/or micronuclei induction (EPA 2011e). Another proposed mode of action suggests that trichloroethylene's metabolite TCA activates the peroxisome proliferator activated receptor alpha (PPARα) in the liver, which causes alterations in cell proliferation and apoptosis, and clonal expansion of initiated cells (EPA 2011e). Additional proposed hypotheses for modes of action for liver cancer include:

- Polyploidization: Trichloroethylene and other substances that contribute to liver tumor induction also cause polyploidy in hepatocytes.

- Changes in glycogen storage: The trichloroethylene metabolite, DCA, has been demonstrated to cause accumulation of glycogen in hepatocytes of mice (Kato-Weinstein et al. 1998). In humans, glycogenesis due to glycogen storage disease or poorly controlled diabetes has been associated with increased risk of liver cancer (Adami et al. 1996; La Vecchia et al. 1994; Rake et al. 2002; Wideroff et al. 1997).

- Inhibition of glutathione-S-transferase zeta (GSTz): Studies in rodents have demonstrated that the trichloroethylene metabolite, DCA (a proximate hepatotoxicant), inhibits GSTz1-1 (an enzyme that catalyzes the glutathione-dependent conversion of DCA itself to glyoxylate), thus resulting in a longer biological half-life for DCA (Guo et al. 2006; Schultz et al. 2002).

- Oxidative stress and resultant DNA damage.

- Changes in gene expression, particularly DNA methylation induced by reactive metabolites of trichloroethylene. For example, altered expression of cell cycle regulating genes (p53, p21, bax and bcl-2) was observed in workers exposed to trichloroethylene (Varshney et al. 2015).

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

- Cytotoxicity and subsequent induction of reparative hyperplasia.

EPA (2011e), however, concluded that the data are inadequate to support the conclusion that any of these hypotheses are operant, and that therefore, the mode of action for trichloroethylene induction of liver tumors is unknown. The human relevance of trichloroethylene-induced hepatocarcinogenicity in mice is questionable based on the following observations. Relatively high trichloroethylene exposure levels were required to induce hepatocarcinogenicity in mice and trichloroethylene did not induce liver tumors in rats. Mice metabolize trichloroethylene more rapidly than rats, and metabolism of trichloroethylene in humans is thought to be more comparable to that of rats than mice. A major trichloroethylene metabolite, trichloroacetate, induces liver tumors in mice via a PPARα mode of action as demonstrated by the lack of trichloroethylene-induced liver tumors in PPARα-null mice, a mode of action that is of questionable relevance to humans (for more in-depth mode of action discussions regarding trichloroethylene and liver cancer, see Corton 2008; EPA 2011e, Klaunig et al. 2003; NRC 2009).

Renal Effects. The GSH-dependent metabolites of trichloroethylene, DCVC, and related GSH conjugation metabolites, are considered to be the active agents of trichloroethylene renal toxicity and carcinogenicity (EPA 2011e). *In vivo* and *in vitro* studies show that 1,2-DCVC causes renal effects that are similar to those of trichloroethylene, and that it is formed in sufficient amounts after trichloroethylene exposure to account for these effects. EPA (2011e) concluded that renal carcinogenicity occurs through a mutagenic mode of action mediated by the GSH-conjugation metabolites of trichloroethylene, predominantly DCVC. This conclusion is based on evidence that these metabolites are genotoxic, including *in vivo* evidence of renal-specific genotoxicity from exposure to trichloroethylene or 1,2-DCVC. The mode of action includes cytotoxicity resulting in compensatory cellular proliferation, also due to DCVC. Again, the evidence was primarily from studies with 1,2-DCVC. The combination of these mechanisms, with increased rates of mutation and regenerative proliferation enhancing cell survival or clonal expansion is considered biologically plausible, but without experimental support.

The plasma kallikrein-kinin system may also have a role in trichloroethylene-induced renal effects. In mice sensitized with trichloroethylene, inflammatory cell infiltration was observed. In addition, immunochemistry evaluation of the proximal tubule showed increase expression of bradykinin and plasma kallikrein (Wang et al. 2016). Cytokine deposition was observed in the proximal tubule of trichloroethylene-sensitized guinea pigs, suggesting that immune dysfunction may be involved in the development of renal damage (Yu et al. 2017). Oxidative stress may be important in trichloroethylene-induced renal damage and altered renal function. In rats administered intraperitoneal injections of trichloroethylene (200–2,000 mg/kg/day) for 7 days, vitamin E, an antioxidant, significantly reduced toxicity (Heydari et al. 2017).

Immunological Effects. The mechanism of action for immunological effects, including autoimmune disease and lymphoma, is not known (EPA 2011e). Some mechanistic studies have focused on oxidative stress as a potential mechanism for induction of immune effects (Khan et al. 2001; Wang et al. 2008, 2007b). Studies in mice susceptible to autoimmune disease indicate that trichloroethylene oxidative metabolites such as chloral (also known as trichloroacetaldehyde) or dichloroacetyl chloride may be responsible, at least in part, for activating T-cells or altering T-cell regulation and survival associated with polyclonal disease (Blossom and Gilbert 2006; Blossom et al. 2007; Cai et al. 2006; Gilbert et al. 2004). Results of a local lymph node assay in mice suggest that transforming growth factor-β activated kinase-1 may be involved in trichloroethylene-induced contact hypersensitivity (Yao et al. 2016).

Seo et al. (2012) reported trichloroethylene-induced enhancement of histamine release from antigen-stimulated mouse bone marrow-derived mast cells and noted that this effect was not produced by major trichloroethylene metabolites, TCA or chloral. Blossom et al. (2010) found that the trichloroethylene metabolite, trichloroacetaldehyde hydrate, promoted increased reactive oxygen species associated with alterations in the expression of genes involved in differentiation of thymocytes from autoimmune-prone MRL+/+ and non-autoimmune-prone mice.

A group of 28 trichloroethylene-induced hypersensitivity dermatitis patients exhibited significantly higher levels of serum interleukins (IL-1β, IL-6, IL-8) and tumor necrosis factor-α than trichloroethylene-exposed workers without hypersensitivity dermatitis (n=22) or non-exposed controls (n=22) (Jia et al. 2012). *In vitro* assessment of cytokine expression in the keratinocyte cell line (HaCaT) exposed to trichloroethanol or TCA (metabolites of trichloroethylene) revealed that trichloroethanol (but not trichloroacetate) increased levels of IL-1α and IL-6 in a dose-dependent manner and activated the nuclear factor kappa B pathway. Bay 11-7082 (a nuclear factor kappa B inhibitor) significantly attenuated the

trichloroethanol-induced production of IL-6, but not IL-1α (Jia et al. 2012). These results suggest that trichloroethanol-induced IL-6 expression via activation of the nuclear factor kappa B pathway in HaCaT cells may be involved in trichloroethylene-induced skin hypersensitivity.

Male Reproductive Effects. The evidence suggests that trichloroethylene is metabolized in the male reproductive tract, primarily in the epididymal epithelium, but also in testicular Leydig cells, by CYP2E1 to chloral, trichloroethanol, and TCA (Forkert et al. 2002, 2003). The finding of dichloroacetyl protein adducts in the epididymis and efferent ducts of rats administered trichloroethylene and of oxidized proteins on the surface of their spermatozoa suggested that male reproductive toxicity was initiated by metabolic activation of trichloroethylene to reactive metabolites (DuTeaux et al. 2003, 2004). The mechanism of male reproductive toxicity, however, is not clearly established.

Developmental Effects. A number of studies of the potential mechanisms for trichloroethylene-induced fetal cardiac defects have focused on disruptions in cardiac valve formation using chickens as a model. The use of an avian model is supported by the substantial concordance in the stages and events of cardiac valve formation between mammals and birds (NRC 2006). These studies demonstrated alterations in endothelial cushion development, which could be associated with defects in septal and valvular morphogenesis (e.g., Boyer et al. 2000; Mishima et al. 2006). The proposed mechanism is inhibition of endothelial separation and formation of mesenchymal cells (from which the septum and valves are formed). An additional study in bovine coronary endothelial cells (Ou et al. 2003) supported a mechanism of interference with the role of endothelial nitric oxide synthase in endothelial cell proliferation.

3.5.3 Animal-to-Human Extrapolations

PBPK models for trichloroethylene have evolved in complexity to address specific problems in toxicokinetics extrapolation (Chiu et al. 2009; EPA 2011e; Evans et al. 2009; Fisher 2000; Hack et al. 2006; Keys et al. 2003; Poet et al. 2000; Simmons et al. 2002; Thrall and Poet 2000). The most recent model (Chiu et al. 2009; Evans et al. 2009) was utilized by EPA (2011e) to derive chronic RfD and RfC values for trichloroethylene using animal-to-human and route-to-route (oral-to-inhalation) extrapolation. This model serves as basis for derivation of the intermediate- and chronic-duration oral and inhalation MRLs as well (see Section 2.3).

In the mouse, rat, and human, metabolism of trichloroethylene occurs via two major capacity-limited pathways: oxidation by CYP2E1 and conjugation with GSH. The GSH conjugation pathway results in production of reactive intermediates that are thought to contribute to trichloroethylene toxicity (see Section 3.5.2). Based on comparisons of predictions from the mouse, rat, and human PBPK models, humans are predicted to have a lower capacity to oxidize trichloroethylene via the CYP2E1 pathway and a higher capacity to conjugate trichloroethylene with GSH. As a result, a larger fraction of an absorbed dose of trichloroethylene is expected to be metabolized through the GSH conjugation pathway in humans compared to rodents (Chiu et al. 2009). This is predicted to result in a higher toxic potency of trichloroethylene in humans, based on external dose (or exposure). The PBPK models provide a basis for accounting for these differences in metabolism and generation of toxic reactive species by allowing the dose-response relationships to be derived based on internal dose metrics such as amount of metabolite(s) at any given external dose (EPA 2011e).

Species differences in elimination kinetics may also result in species differences in temporal profiles of trichloroethylene or its metabolites during repeated dosing. Rodents are predicted to have higher rates of elimination than humans based on allometric assumptions of scaling of metabolism to body size (Chiu et al. 2009). PBPK models provide a means for accounting for these differences.

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).

Limited information is available regarding the potential for trichloroethylene to affect endocrine function. It is not likely that trichloroethylene would act as a hormonal agonist or antagonist because its chemical structure does not resemble endogenous hormones.

In occupational studies of men who used trichloroethylene to degrease electronic equipment, increasing years of exposure to trichloroethylene was associated with increased serum dehydroepiandrosterone sulphate and decreases in serum levels of testosterone, follicle-stimulating hormone, and sex-hormone binding globulin (Chia et al. 1997; Goh et al. 1998). Serum androstenedione, cortisol, and aldosterone levels were in normal ranges.

Significantly decreased serum testosterone (31–48% less than that of controls) and decreased testicular 17β-hydroxy steroid dehydrogenase were noted in rats exposed to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 12 or 24 weeks (Kumar et al. 2000a). No histopathological changes in the pituitary gland, adrenal glands, or pancreas were observed in rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988).

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 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).

Intake from trichloroethylene-contaminated drinking 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. Fan (1988) estimated that average doses to a 10-kg infant, a 22-kg child, and a 70-kg adult would be 0.3, 0.204, and 0.086 mg trichloroethylene/kg/day, respectively, from consumption of drinking water containing 3 ppm of trichloroethylene, and that trichloroethylene doses via dermal and inhalation routes from bathing or

showering in water containing 3 ppm of trichloroethylene would be greater in children than adults. Household dust and dirt are potential sources of greater potential dermal contact and ingestion exposure in small children. Trichloroethylene intake from the ambient air is expected to be greater in infants and children than adults because infants and children have increased ventilation rates per kg body weight and increased cardiac output per kg body weight (EPA 2008; NRC 2009; Snodgrass 1992). Following inhalation exposure, peak concentrations of trichloroethylene in the blood of lactating rat pups were higher than those in similarly-exposed adult rats (Rodriguez et al. 2007). Levels of enzymes that metabolize xenobiotics are lower in neonates than adults, an indication that neonates may exhibit a lesser degree of susceptibility to the adverse effects of reactive trichloroethylene metabolites. In apparent contrast, the observation that half-lives of chloral hydrate (a reactive metabolite of trichloroethylene) are 3–4 times longer in premature and full-term newborns than in young children (Reimche et al. 1989) suggests that infants may be more susceptible than older children and adults to the toxic effects of reactive trichloroethylene metabolites. Greater metabolic clearance of trichloroethylene and many other drugs in children 1–6 years old than in adults is apparently due to children's larger liver volume and higher blood flow rate (Murray et al. 1995), rather than higher CYP2E1 activity (Blanco et al. 2000).

Trichloroethylene is lipophilic and distributes to all body tissues (see Section 3.4.2). At comparable absorption levels, such lipophilic substances may become more concentrated in the fat of infants and small children due to their lower amounts of fat per kilogram body weight compared to adolescents and adults (NRC 1993). Nursing infants can be exposed to trichloroethylene via the breast milk; Fisher et al. (1990) modeled distribution of trichloroethylene and TCA in the nursing mother rat and pup. In the past, when trichloroethylene was administered to some pregnant mothers during childbirth, ratios of trichloroethylene in fetal:maternal blood ranged from 0.5 to 2 (Laham 1970), indicating that trichloroethylene could accumulate in the fetus. Trichloroethylene crosses the blood-brain barrier, and the extent of transfer could possibly be greater in young children, although trichloroethylene is expected to readily cross the blood-brain barrier in all age groups. Age-related differences in trichloroethylene metabolism could result in differences in susceptibility to trichloroethylene toxicity. One study in rats reported increased trichloroethylene metabolism in 3-week-old rat weanlings compared to 18-week-old adult rats (Nakajima et al. 1992b). However, age-related differences in trichloroethylene metabolism have not been demonstrated in humans.

As discussed in detail in Section 3.2, results of some epidemiological studies indicate that trichloroethylene in the drinking water, ambient air, or workplace environments may be associated with developmental effects such as increased rates of spontaneous abortion (Windham et al. 1991), congenital

heart defects (ATSDR 2006, 2008; Goldberg et al. 1990; Yauck et al. 2004), ocular and auditory defects and other central nervous system abnormalities (ATSDR 1999; Bove et al. 1995; Lagakos et al. 1986a; MDPH 1996; Narotsky et al. 1995; White et al. 1997), oral cleft (Bove et al. 1995; Lagakos et al. 1986a), neural tube defects (Bove et al. 1995), and choanal atresia (a rare respiratory disorder) and hypospadias/congenital chordee (MDPH 1996). Results of some animal studies indicate that trichloroethylene can cause cardiac malformations (Dawson et al. 1993; Johnson et al. 1998, 2003), decreases in litter size and perinatal survival (Manson et al. 1984; Narotsky and Kavlock 1995; Narotsky et al. 1995; NTP 1986), compromised postnatal immune function (Blossom and Doss 2007; Blossom et al. 2008; Peden-Adams et al. 2006), altered behavior (Fredriksson et al. 1993; NTP 1986; Taylor et al. 1985), and alterations in brain morphology and physiology (Isaacson and Taylor 1989; Noland-Gerbec et al. 1986). It should be noted that human and animal data do not suggest that trichloroethylene is teratogenic.

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).

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 trichloroethylene 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 trichloroethylene 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 Trichloroethylene

Biological monitoring for exposure to trichloroethylene is possible by measuring levels of the parent compound or the metabolites in exhaled air, blood, or urine. However, it should be noted that metabolites of trichloroethylene may also come from other sources; they are not specific to trichloroethylene exposure alone. Biological monitoring for trichloroethylene exposure has been performed for occupational exposures as well as for the general population. Following inhalation exposure in humans, most (approximately 58%) of the retained dose of trichloroethylene is metabolized and excreted as metabolites in the urine (Monster et al. 1976). Only a small amount (10–11%) of the absorbed dose is exhaled as unchanged trichloroethylene through the lungs, and 2% of the dose is eliminated by the lungs as trichloroethanol. Correlations were found between levels of trichloroethylene in ambient air and levels of trichloroethylene in human breath (Kimmerle and Eben 1973b; Monster et al. 1979; Stewart et al. 1970, 1974b; Wallace 1986; Wallace et al. 1985). Thus, this exposure-excretion relationship supports the use of breath levels for the prediction of exposure levels.

Monitoring for exposure to trichloroethylene has been performed by measuring trichloroethylene and its principal metabolites (TCA, trichloroethanol, trichloroethanol glucuronide) in blood and urine (Csanády et al. 2010; Ertle et al. 1972; Ikeda et al. 1972; Imamura and Ikeda 1973; Imbriani et al. 2001; Kimmerle and Eben 1973b; Monster et al. 1979; Müller et al. 1972, 1974, 1975; Nomiyama 1971; Nomiyama and

Nomiyama 1977; Ogata et al. 1971; Skender et al. 1993; Stewart et al. 1970; Vartiainen et al. 1993). A linear correlation was reported between the concentration of trichloroethylene in breathing zone air and the resulting urinary levels of trichloroethanol and TCA recorded within the day (Inoue et al. 1989). However, because urinary TCA has a longer half-life than trichloroethanol, it better reflects long-term exposure, whereas urinary trichloroethanol has been recommended as an indicator of recent exposure (Ulander et al. 1992). Lash et al. (1999a) detected the GSH-derived conjugate of trichloroethylene (DCVG) in the blood of all male and female subjects from 30 minutes after the start of a 4-hour exposure to trichloroethylene vapors at 50 or 100 ppm to up to 8 hours after the end of the exposure period. DCVG levels were approximate 3.5-fold higher in males than females.

There are two biological exposure indices (BEIs) for exposure to trichloroethylene at the ACGIH threshold limit value (TLV-TWA) of 10 ppm (ACGIH 2012). When measured at the end of an 8-hour shift at the end of a 40-hour workweek, the BEI for TCA in urine is 15 mg/g creatinine and the BEI for trichloroethanol in the blood is 0.5 mg/L.

The use of the methods for monitoring metabolites of trichloroethylene in blood and urine is rather limited since the levels of TCA in urine have been found to vary widely, even among individuals with equal exposure (Vesterberg and Astrand 1976). Moreover, exposure to other chlorinated hydrocarbons such as tetrachloroethane, tetrachloroethylene, and 1,1,1-trichloroethane would also be reflected in an increase in urinary excretion of TCA. In addition, there may be sex differences regarding the excretion of trichloroethylene metabolites in urine since one experiment shows that trichloroethylene-exposed men excreted more trichloroethanol than similarly-exposed women (Inoue et al. 1989).

Differences in relevant physiological parameters among individuals can partially explain the differences in the before-workshift and end-of-workshift levels of trichloroethylene and its metabolites. Increased respiration rate during a workday, induced by physical workload, has been shown to affect levels of unchanged trichloroethylene more than its metabolites, while the amount of body fat influences the levels of the solvent and its metabolites in breath, blood, and urine samples before workshift exposure (Sato 1993). Additionally, liver function affects measurements of exhaled solvent at the end of workshift; increased metabolism of trichloroethylene will tend to decrease the amount exhaled after a workshift. Differences in renal output would affect levels of TCA and trichloroethanol in blood before a workshift in the same way, but it probably would not affect urine values between the beginning and the end of the workshift because of the slow excretion rate of TCA.

Results of Brogren et al. (1986) indicate that urinary concentration of the renal tubular enzyme, NAG, may be used as an indicator of renal damage resulting from exposure to chlorinated organic solvents such as trichloroethylene. Other studies specifically examining the influence of factors such as age or alcohol consumption on associations between trichloroethylene exposure and NAG levels have found a weak, nonsignificant correlation (Rasmussen et al. 1993b; Selden et al. 1993).

Serum bile acid levels, which are indicative of liver function, have been shown to increase in a dose-dependent manner in rats exposed via inhalation to trichloroethylene (Wang and Stacey 1990), as well as in occupationally exposed humans (Driscoll et al. 1992). Subsequent investigations revealed that these increases in rats occurred at exposure concentrations that produced no evidence of liver cell damage, thus suggesting that this assay is a sensitive indicator of low-level exposure (Bai and Stacey 1993; Hamdan and Stacey 1993). In contrast, a study of metal degreasers found that the association between the level of γ-glutamyltransferase enzyme (another indicator of liver function) and trichloroethylene exposure became nonsignificant after controlling for the effects of age and alcohol consumption (Rasmussen et al. 1993b).

3.8.2 Biomarkers Used to Characterize Effects Caused by Trichloroethylene

The nervous system is a target of toxicity from acute inhalation exposure to trichloroethylene. However, effects such as dizziness and drowsiness can occur for many reasons and cannot be used as biomarkers for exposure to trichloroethylene. Cranial nerves V and VII are specific targets of trichloroethylene and/or its metabolites, but conclusive studies distinguishing the toxicity of trichloroethylene, its metabolites, and combinations thereof have not been found. A sensitive test, blink reflex latency, can determine damage to the nerves, and it has been used to show prolonged effects from exposure to trichloroethylene in the drinking water at concentrations as high as 200–400 ppb (Feldman et al. 1988). Other neurological functional tests from well-documented neurobehavioral test batteries (e.g., WHO Neurobehavioral Core Test Battery, Neurobehavioral Evaluation System; ATSDR Adult Environmental Neurobehavioral Test Battery) or measurement of sensory-evoked potentials could be useful for screening individuals in the context of documented trichloroethylene exposure (ATSDR 1995; Arezzo et al. 1985; Baker et al. 1985).

The chlorinated hydrocarbons as a class are known to affect the liver and kidney. To determine the potential for human kidney damage resulting from workplace air exposure to trichloroethylene, urinary total protein and β2-microglobulin were tested. These were measured in the urine of workers who had a history of exposure to approximately 15 ppm trichloroethylene (duration of exposure and age were 8.4±7.9 and 36.6±13.6 years, respectively) (Nagaya et al. 1989b). Slight increases in urinary total protein

and β2-microglobulin were noted in the exposed population when compared to controls, except for a significant change in the 35–44-year-old workers. The authors of this study concluded that the adverse effect on the kidney was mild and glomerular rather than tubular. In contrast, Brogren et al. (1986) found increased urinary excretion of N-acetyl-β-D-glucosaminidase, which is released upon necrosis of renal tubular cells in workers exposed to trichloroethylene, trichloroethane, and freon. Both of these markers (β2-microglobulin and N-acetyl-β-D-glucosaminidase) are indicators of kidney damage, but neither marker is specific to trichloroethylene-induced damage; a number of short-chain halogenated hydrocarbons can produce similar effects. Similarly, changes in serum levels of total protein have been used to assess exposure to trichloroethylene, but are not specific to trichloroethylene (Konietzko and Reill 1980; Rasmussen et al. 1993b).

Bolt et al. (2004) reported increased urinary α_1-microglobulin in trichloroethylene-exposed renal cancer patients compared to renal cancer patients and healthy controls without trichloroethylene exposure. Although increased urinary α_1-microglobulin may serve as an indicator of renal toxicity, it is not unique to trichloroethylene exposure.

Brüning et al. (1999) reported increased glutathione-S-transferase alpha (a marker of distal renal tubular damage) in the urine of 39 workers exposed to high levels of trichloroethylene for up to 19 years compared to a group of 46 male office and administrative workers without known exposure to trichloroethylene. However, glutathione-S-transferase levels do not represent a biomarker of effects unique to trichloroethylene, because levels of this enzyme are affected by numerous other xenobiotics. Tabrez and Ahmad (2009) observed increased glutathione-*S*-transferase activity in the liver and kidneys (50 and 218% greater than that of controls) of rats administered trichloroethylene by gavage at 1,000 mg/kg/day for 15 days.

Increased urinary kidney injury molecule-1 levels were reported among trichloroethylene-exposed workers in China (Vermeulen et al. 2012). Kidney injury molecule-1 is a transmembrane protein expressed in dedifferentiated proximal tubular epithelial cells within damaged regions (Huo et al. 2010) and has been shown to outperform traditional biomarkers of renal injury (serum creatinine and BUN) in rat studies (Vaidya et al. 2010). However, as is the case for other potential biomarkers discussed above, increased kidney injury molecule-1 is not specific to trichloroethylene exposure.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Alcohol can affect the metabolism of trichloroethylene. This is noted in both toxicity and pharmacokinetic studies. In a controlled study of male volunteers, consumption of alcohol following 3- or 7.5-hour exposures to trichloroethylene vapors at 200 ppm resulted in approximately 2-fold higher mean trichloroethylene levels in expired air than levels measured without consumption of alcohol (Stewart et al. 1974c). These subjects also showed “degreaser's flush”, a transient vasodilation of superficial skin vessels. In rats, trichloroethylene-induced depressant effects in the central nervous system were exacerbated by oral administration of ethanol (Utesch et al. 1981).

Ethanol administration can potentially increase or decrease trichloroethylene metabolism, depending on two factors: the time interval between ethanol and trichloroethylene administration, and the doses administered. With a short time interval, ethanol and trichloroethylene compete for enzymatic sites, decreasing trichloroethylene metabolism. For example, increased blood levels of trichloroethylene and decreased blood levels of trichloroethanol and TCA were observed in rabbits given ethanol 30 minutes prior to trichloroethylene (White and Carlson 1981). Alternatively, with an extended time interval (e.g., 24–36 hours) after ethanol administration, necessary to enzyme induction, trichloroethylene metabolic rates would be expected to increase. This may explain the decreased blood levels of trichloroethylene that were measured with increased urinary excretion of total trichlorocompounds (trichloroethanol and TCA) when ethanol was given to rats 18 hours prior to inhalation exposure to 500 ppm trichloroethylene (Sato et al. 1981). In a similar study, rats were pre-exposed to a 3-week ethanol, low-carbohydrate, high-fat diet (to induce cytochrome P-450) prior to trichloroethylene inhalation. When compared with rats fed control diets, the pre-exposed rats had significant increases in urinary metabolites at high trichloroethylene concentrations (>500 ppm) (Kaneko et al. 1994).

When trichloroethylene is metabolized to chloral hydrate by the cytochrome P-450 system, the chloral hydrate is either oxidized by chloral hydrate dehydrogenase to TCA or reduced by alcohol dehydrogenase to trichloroethanol (Sato et al. 1981). The oxidation steps require the oxidized form of nicotinamide adenine dinucleotide (NAD^+), while the reduction steps require the reduced form NADH. Ethanol is known to alter the ratio of NAD^+/NADH in hepatocytes and to produce a subsequent shift toward reduction to trichloroethanol. Support for this was found in studies with rats that were exposed to trichloroethylene with and without ethanol. Ethanol coadministration resulted in an increased urinary trichloroethanol/TCA ratio at all dose levels, consistent with the hypothesis of a more reduced state in the hepatocyte caused by generation of excessive reducing agents by ethanol metabolism (Larson and Bull

1989). It should be noted that the lowest doses employed in this study were 200 mg/kg trichloroethylene and 70 mg/kg ethanol.

Other low molecular weight alcohols (e.g., isopropanol), as well as other compounds that inhibit alcohol metabolizing enzymes (e.g., alcohol dehydrogenase) and the hepatic drug metabolizing system, have been shown to alter steady-state blood levels of trichloroethylene. When administered orally to female rats in conjunction with trichloroethylene inhalation exposures, disulfiram, isopropanol, pyrazole, and tetrachloroethylene each increased the steady-state concentration of trichloroethylene in the venous blood (Jakobson et al. 1986). Treatment with disulfiram (an inhibitor of alcohol dehydrogenase) resulted in a significant increase in the amount of trichloroethylene exhaled by women exposed to 186 ppm for 5 hours (Bartonicek and Teisinger 1962). Excretion of trichloroethanol and TCA in the urine decreased by 40–64 and 72–87%, respectively. By enhancing the metabolism of trichloroethylene to its cytotoxic metabolites, compounds that induce the hepatic monoxygenase system can potentiate the hepatotoxicity of trichloroethylene. Pretreatment with phenobarbital and 3-methylcholanthrene, which like ethanol, are inducers of the liver monoxygenase system, increased the extent of liver injury following exposure to trichloroethylene (Carlson 1974). Similar results were found with other inducers of the hepatic monoxygenase system (Allemand et al. 1978; Moslen et al. 1977; Nakajima et al. 1990b). Cheikh Rouhou et al. (2013) assessed the effects of selected pharmaceuticals on the rate of trichloroethylene metabolism in rat hepatocytes *in vitro*. TCA and trichloroethanol levels were increased by naproxen and salicylic acid and decreased by acetaminophen, cimetidine, diclofenac, gliclazide, and valproic acid. Erythromycin and sulphasalazine decreased TCA, (but not trichloroethanol) levels.

Animal studies indicate that high concentrations of trichloroethylene can sensitize the heart to epinephrine-induced arrhythmias, albeit at relatively high trichloroethylene doses. Other chemicals can affect these epinephrine-induced cardiac arrhythmias in animals exposed to trichloroethylene. Phenobarbital treatment, which increases the metabolism of trichloroethylene, has been shown to reduce the trichloroethylene-epinephrine-induced arrhythmias in rabbits (White and Carlson 1979), whereas high concentrations of ethanol, which inhibits trichloroethylene metabolism, have been found to potentiate trichloroethylene-epinephrine-induced arrhythmias in rabbits (White and Carlson 1981). These results indicate that trichloroethylene itself (and not a metabolite) is responsible for the epinephrine-induced arrhythmias. In addition, caffeine has been found to increase the incidence of epinephrine-induced arrhythmias in rabbits exposed to trichloroethylene; the caffeine treatment had no effect on trichloroethylene blood concentration, but caused a reduction in blood trichloroethanol and TCA levels (White and Carlson 1982). The investigators speculated that caffeine may have caused this effect by

stimulating the release of catecholamines from the adrenal medulla and thus elevating circulating levels of epinephrine or by stimulating the release of norepinephrine from adrenergic nerve endings.

Trichloroethylene may occur in drinking water along with other chlorinated hydrocarbons, so effects of these chemicals in combination are of interest to public health. Hepatotoxicity, as measured by plasma enzyme activity, was increased synergistically in rats by oral administration of carbon tetrachloride combined with trichloroethylene (Borzelleca et al. 1990). In addition, synergistic effects were implicated in a 3-day study in which rats were pretreated with trichloroethylene, and then subsequently challenged with carbon tetrachloride, both administered intraperitoneally by gavage or in drinking water (Steup et al. 1991). Trichloroethylene exposure enhanced the subsequent carbon tetrachloride challenge, as measured by increased liver necrosis and plasma ALT levels, although the study authors noted that the exposure levels were far above those normally encountered by humans in their drinking water. In a follow-up study, a single gavage dose of trichloroethylene (0.5 mL/kg) had no toxic effects, but when it was coadministered with carbon tetrachloride, the time-course for synergistic action (measured by a decline of serum ALT and SDH levels and an increase in hepatocyte damage) followed the decline of the GSH level (Steup et al. 1993). This finding may either implicate GSH in the trichloroethylene potentiation of carbon tetrachloride toxicity or simply be a result of general hepatic injury. Concurrent administration of trichloroethylene and tetrachloroethylene 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). In a PBPK modeling exercise designed to analyze data describing the metabolism of vinyl chloride and trichloroethylene mixtures in rats, a single saturable pathway representing CYP2E1 was modeled; results from the modeling exercise and *in vitro* assays indicated that competitive inhibition of cytochrome P-450 metabolism was elicited by mixtures of vinyl chloride and trichloroethylene (Barton et al. 1995).

A study examining the effects of trichloroethylene and styrene inhalation on the rat auditory system found that the combined effect of these compounds was additive, suggesting that their mechanisms of action are similar (Rebert et al. 1993). A 5-day exposure to 1,500 ppm trichloroethylene had no effect on brainstem auditory-evoked response unless combined with a simultaneous exposure to 500 ppm styrene, in which case substantial hearing loss was noted. Co-exposure to trichloroethylene and other chemicals that are metabolized by common cytochrome P450 isozymes to reactive metabolites would be expected to result in decreased trichloroethylene toxicity due to competitive metabolic inhibition and resulting decreased metabolic activation.

Coexposure to mercury was reported to increase trichloroethylene-induced autoimmune hepatitis in autoimmune-prone MRL+/+ mice (Gilbert et al. 2011). Co-exposure to trichloroethylene and mercury also generated a liver-specific antibody response in the mice that was not observed in mice exposed to mercury or trichloroethylene alone.

Muijser et al. (2000) reported that mice exposed to trichloroethylene vapors (3,000 ppm) and noise (95 dB) experienced significantly greater hearing loss at the 4 kHz frequency than mice exposed to either trichloroethylene or noise alone; the results were considered indicative of an interaction between exposures to trichloroethylene and noise in combination.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to trichloroethylene than will most persons exposed to the same level of trichloroethylene in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of trichloroethylene, or compromised function of organs affected by trichloroethylene. Populations who are at greater risk due to their unusually high exposure to trichloroethylene 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), infants and young children may be more susceptible than adults to trichloroethylene toxicity based on age-related differences in the pharmacokinetics of trichloroethylene. For example, trichloroethylene may be absorbed in greater concentrations in children exposed by inhalation due to increased ventilation rates (e.g., inspired volume per minute per kg body weight per unit alveolar surface area) and increased cardiac output per kg body weight compared to adults (EPA 2008; NRC 2009; Snodgrass 1992). Intake from trichloroethylene-contaminated drinking 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. Nursing infants can be exposed to trichloroethylene via the breast milk (Pellizzari et al. 1982). Household dust and dirt are potential sources of greater potential dermal contact and ingestion exposure in small children, although no information was located regarding trichloroethylene levels in household dust or dirt. At comparable absorption levels, lipophilic substances such as trichloroethylene may become more concentrated in the

fat of infants and small children due to their lower amounts of fat per kilogram body weight compared to adolescents and adults (NRC 1993). In cases where metabolic products are more toxic than the parent compound, an individual with higher metabolic rates (as may occur in some children and adolescents) would be expected to have greater toxicity; conversely, lower metabolic rates would be expected to result in a lesser degree of toxicity.

Some people who have worked with trichloroethylene for long periods of time may develop an allergy to it or become particularly sensitive to its effects on the skin (e.g., Bauer and Rabens 1974; Chittasobhaktra et al. 1997; Czirjak et al. 1993; El Ghawabi et al. 1973; Goh and Ng 1988; Hayashi et al. 2000; Huang et al. 2006; Kamijima et al. 2007; Pantucharoensri et al. 2004; Xu et al. 2009). People who consume alcohol or who are treated with disulfiram may be at greater risk of trichloroethylene poisoning because ethanol and disulfiram can both inhibit the metabolism of trichloroethylene and can cause it to accumulate in the bloodstream, potentiating its effects on the nervous system. Compromised hepatic and renal function may place one at higher risk upon exposure to trichloroethylene or its metabolites since the liver serves as the primary site of trichloroethylene metabolism and the kidney serves as the major excretory organ for trichloroethylene metabolites. When trichloroethylene was used as an anesthetic or inhaled in high concentrations intentionally or occupationally, it caused cardiac arrhythmias in some people. Thus, some individuals with a history of cardiac rhythm disturbances may be more susceptible to high-level trichloroethylene exposure. Results of a study in which trichloroethylene-exposed workers with generalized skin disorders accompanied by hepatic dysfunction and healthy trichloroethylene-exposed workers were assessed for possible risk factors for rash and hepatitis indicated that those with human herpesvirus 6 were more likely to suffer trichloroethylene-induced skin disorders and hepatic dysfunction (Huang et al. 2006). Giovanetti et al. (1998) found increased numbers of vacuolated Clara cells in the lungs of mice administered a copper-deficient diet and exposed to trichloroethylene vapors.

The metabolism of trichloroethylene, as measured by the levels of excreted urinary metabolites, may differ between men and women (Inoue et al. 1989; Kimmerle and Eben 1973b; Nomiyama and Nomiyama 1971). For example, it has been reported that women excrete more urinary TCA (a metabolite of trichloroethylene and other chlorinated substances such as tetrachloroethylene) than do men (Kimmerle and Eben 1973b; Nomiyama and Nomiyama 1971). Lash et al. (1999a) reported that trichloroethylene-exposed male subjects produced approximately 3.5-fold higher levels of DCVG in the blood than similarly-exposed female subjects, indicating that males may be more susceptible to trichloroethylene-induced renal toxicity. Testosterone has been implicated as a factor in the lower dermal absorption of trichloroethylene in male rats compared with females (McCormick and Abdel-Rahman 1991).

There is some indication of gene-related susceptibility to trichloroethylene toxicity. Selected genotypes/phenotypes may be more sensitive to trichloroethylene based on differences in metabolic rates (Brüning and Bolt 2000; Dai et al. 2009; Moore et al. 2010; NRC 2009). Li et al. (2007) reported an association between the presence of a particular allele for human leucocyte antigen (HLA-B*1301) and hypersensitivity dermatitis among trichloroethylene-exposed workers.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to trichloroethylene. 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 trichloroethylene. 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 trichloroethylene can be consulted for medical advice. The following texts provide specific information about treatment following exposures to trichloroethylene:

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

Shusterman D. 2018. Trichloroethane, trichloroethylene and tetrachloroethylene. In: Olson R, Olson IB, Anderson NL, et al., eds. Poisoning and drug overdose: Section II: Specific poisons and drugs: Diagnosis and treatment. Seventh ed. New York, NY: McGraw-Hill.

Palmer RB, Phillips SD. 2007. Chlorinated hydrocarbons. In: Shannon MW, Borron SW, Burns MJ. Haddad and Winchester's clinical management of poisoning and drug overdose. 4th ed. Philadelphia, PA: Saunders Elsevier, 1347-1361.

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

Human exposure to trichloroethylene may occur by inhalation, ingestion, or dermal contact. Mitigation methods for reducing exposure to trichloroethylene have included the general recommendations of separating contaminated food, water, air, and clothing from the exposed individual (HSDB 2013).

The following recommendations for treating trichloroethylene poisoning are taken from Grummin (2014) and Shusterman et al. (2018). There is no specific antidote. Following suspected overexposure to trichloroethylene, 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. Anesthetic overexposure may require respiratory assistance and the treatment of cardiac arrhythmias. Do not induce emesis or administer activated charcoal. In the case of eye exposure, irrigation with copious amounts of water or saline has been recommended. For dermal exposure, the removal of contaminated clothing and a thorough washing of any exposed areas with mild soap and water have been recommended.

3.11.2 Reducing Body Burden

No methods to reduce body burden of trichloroethylene have been identified (Shusterman et al. (2018). Trichloroethylene is exhaled following inhalation and oral exposures, whereas metabolites are mainly excreted in the urine. See Sections 3.4.3 (Toxicokinetics, Metabolism) and 3.4.3 (Toxicokinetics, Elimination and Excretion) for a more detailed discussion of metabolism and excretion of trichloroethylene and metabolites.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action of trichloroethylene in the body is not well understood, and there are no proven methods of interfering with the mechanism of action for toxic effects. Based on the limited understanding of the mechanisms of action, methods of interference can be suggested. These methods require additional research before they can be put into use.

Reports of cardiac arrhythmias following exposure to trichloroethylene are not uncommon (Bell 1951; Kleinfeld and Tabershaw 1954; Morreale 1976; Smith 1966). Anti-adrenergic agents, such as propranolol and esmolol, block β-adrenergic receptors, thus preventing catecholamines such as epinephrine from binding; these agents may be useful in preventing cardiac arrhythmias that can occur with exposure to trichloroethylene. The consequences of using a β-adrenergic blocker for treatment of high exposure to trichloroethylene must be taken into consideration. Catecholamines (especially beta agonists) act in concert with trichloroethylene, increasing the risk of cardiac arrhythmias. Hence, catecholamines should be avoided if possible. Ethanol should also be avoided because concurrent exposure to trichloroethylene and ethanol can cause vasodilation and malaise and may potentiate central nervous system depression at high dosage levels of either compound. Because physical activity appears to increase the chance of

cardiac effects, reducing physical exertion after exposure to trichloroethylene may be useful. Reduction of stress may be helpful by reducing catecholamine release. Oxygen therapy might be useful, as hypoxia potentiates trichloroethylene-induced arrhythmias.

Administration of antioxidants such as curcumin diminished trichloroethylene-induced oxidative stress in mouse liver cells (Watanabe and Fukui 2000); however, this response was only demonstrated *in vitro*. Trichloroethylene has been shown to decrease methylation of the *c-jun* and *c-myc* protooncogenes and increase levels of their messenger ribonucleic acid (mRNA) in the livers of mice (Tao et al. 2000). Co-treatment with methionine prevented both decreased methylation and increased levels of the mRNA and proteins of the *c-jun* and *c-myc* protooncogenes. The study authors hypothesized that trichloroethylene may act as a carcinogen by depleting the availability of S-adenosylmethionine and that methionine could prevent DNA hypomethylation by maintaining sufficient S-adenosylmethionine. However, methionine treatment has not been suggested as a method for protecting against trichloroethylene carcinogenicity.

3.12 ADEQUACY OF THE DATABASE

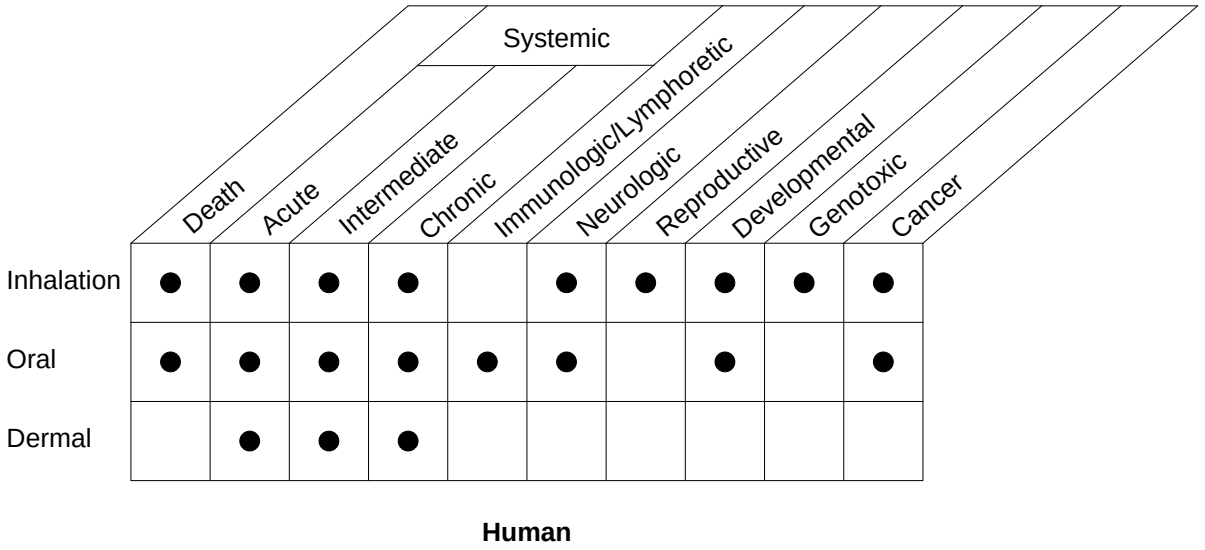
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of trichloroethylene is available. Where adequate information 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 trichloroethylene.

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.

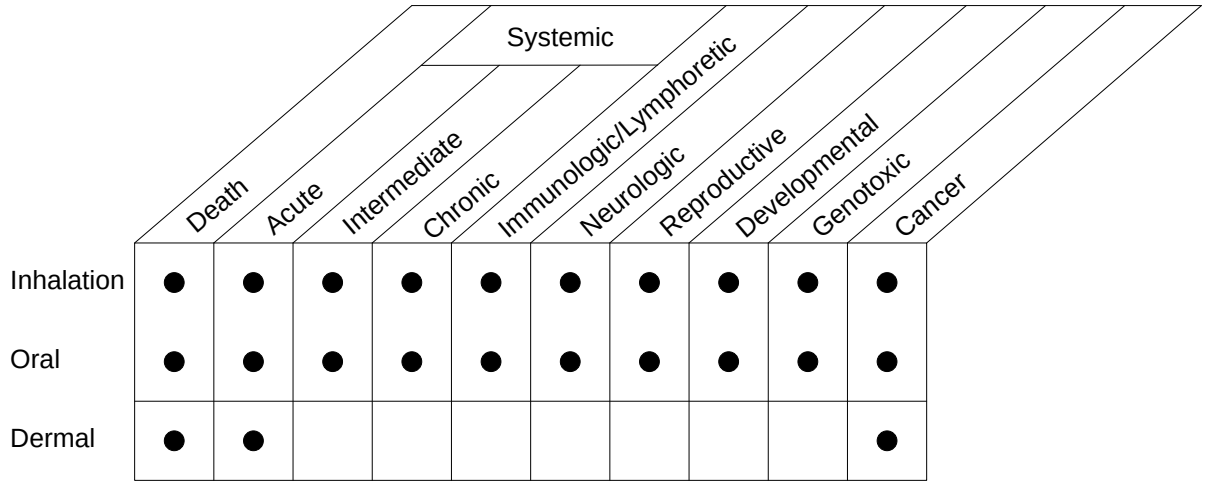
3.12.1 Existing Information on Health Effects of Trichloroethylene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to trichloroethylene are summarized in Figure 3-24. The purpose of this figure is to illustrate the existing information concerning the health effects of trichloroethylene. Each dot in the figure indicates that one or

Figure 3-24. Existing Information on Health Effects of Trichloroethylene



Human



Animal

● Existing Studies

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.

Studies of workers and volunteers have provided most of the data on health effects of inhaled trichloroethylene in humans. Most of the information on reported effects in humans following oral exposure is from data of questionable validity on populations exposed to well water contaminated with trichloroethylene and other compounds. Information regarding lethality in humans resulting from inhalation or oral exposure is limited to case reports of acute exposures that are poorly quantified at best.

Data are available for central nervous system effects in humans resulting from acute and chronic inhalation exposure. A few reports of acute oral and inhalation exposures have indicated that adverse hepatic and renal effects occur in humans. As discussed in detail in Sections 3.2.1.7 and 3.2.2.7, numerous reports are available regarding possible associations between exposure to trichloroethylene and risk for cancer. EPA (2011e) developed quantitative estimates of cancer risk based on results of a case-control study that reported a statistically significant association between self-reported occupational exposure to trichloroethylene and occurrence of renal cancer (Charbotel et al. 2006) and adjusted for potential risk for non-Hodgkin's lymphoma and liver cancer. Quantitative estimates included an inhalation unit risk if 0.02 per ppm and an oral slope factor of 0.05 per mg/kg/day that was derived using PBPK model-based route-to-route extrapolation of the inhalation unit risk.

Studies have been performed in animals that cover all of the health effects areas listed in Figure 3-24 for inhalation and oral exposure. Few dermal data exist, other than case reports of effects in humans following acute exposures, animal lethality data, and one animal carcinogenicity study. Studies with animals identify the general range of lethality and principal toxic effects of inhalation and oral exposure to trichloroethylene. Although trichloroethylene toxicity has been extensively studied, quantitative dose-response data are insufficient to fully characterize effects for some of the critical targets. One of the limitations to interpreting results from some of the oral studies is that they employ bolus or gavage administration of trichloroethylene in oil (often corn oil), which do not adequately represent kinetics relevant to an exposure to trichloroethylene in drinking water.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Deaths have resulted from the early use of trichloroethylene as an anesthetic (DeFalque 1961), from accidental exposure to unusually high levels in workplace environments (Bell 1951; Coopman et al. 2003; Ford et al. 1995; James 1963; Kleinfeld and Tabershaw 1954; McCarthy and Jones 1983; Pantucharoensri et al. 2004; Smith 1966; Thorburn et al. 2004), and from the presumed intentional inhalation of concentrated fumes from trichloroethylene-containing substances (Clearfield 1970; Jones and Singer 2008; Takaki et al. 2008; Troutman 1988). Two acute lethality studies are available for animals (Kylin et al. 1962; Siegel et al. 1971). Cardiac effects including tachycardia, ECG abnormalities, and arrhythmias have been reported in humans following acute inhalation exposure (Clearfield 1970; DeFalque 1961; Dhuner et al. 1957; Gutch et al. 1965; Hewer 1943; Pembleton 1974). A number of human deaths following acute inhalation exposure to trichloroethylene exposure have been attributed to cardiac effects (Bell 1951; Ford et al. 1995; Kleinfeld and Tabershaw 1954; Troutman 1988). Deaths of humans often occurred following physical exertion. Acute inhalation studies in animals reveal that trichloroethylene sensitizes the heart to catecholamines (Reinhardt et al. 1973; White and Carlson 1979, 1981, 1982). In cases of acute accidental or intentional overexposure to trichloroethylene, neurological effects include euphoria, giddiness, lethargy, confusion, dizziness, headache, nausea, difficulty swallowing, facial effects that indicate possible trigeminal nerve damage (including sensation deficits, jaw weakness, increased blink reflex latency), which may be irreversible, memory deficits, and unconsciousness (Adamek and Krupiński 2007; Buxton and Hayward 1967; Carrieri et al. 2007; Clearfield 1970; Feldman 1970; Feldman et al. 1985; James 1963; Lawrence and Partyka 1981; Lachnit and Pietschmann 1960; Leandri et al. 1995; Longley and Jones 1963; Milby 1968; Miller et al. 2002; Pembleton 1974; Thierstein et al. 1960; Troutman 1988).

Sufficient human and animal information is available to identify the nervous system as a sensitive target for the acute effects of trichloroethylene encountered via the inhalation route. The chemical was once used as a surgical anesthetic, so its central nervous system depressant effects in humans are well known. Experimental exposures have revealed decrements in complex reaction time, immediate memory, and perception in humans inhaling 110 ppm for 8 hours (Salvini et al. 1971). However, other human studies have shown that the effect threshold may be somewhat higher (Ettema et al. 1975; Stewart et al. 1970; Vernon and Ferguson 1969) or lower (Nomiyama and Nomiyama 1977). The Nomiyama and Nomiyama (1977) study is limited by the use of only three test subjects for each exposure concentration, lack of statistical analysis, sporadic occurrence of the effects, and a lack of a clear dose-response relationship. The cranial nerves (V and VII) may be especially sensitive to trichloroethylene effects. However, it is not

clear if this neuropathy results from trichloroethylene exposure directly because there is evidence that damage to these nerves may result from exposure to the trichloroethylene decomposition product dichloroacetylene.

Additional adverse effects noted in humans following acute inhalation exposure to trichloroethylene include nausea and vomiting (Clearfield 1970; David et al. 1989; DeFalque 1961; Gutch et al. 1965; Lachnit and Pietschmann 1960), mild evidence of liver damage (Clearfield 1970), renal failure (David et al. 1989; Gutch et al. 1965), and muscle necrosis (Thorburn et al. 2004); the single case of muscle necrosis included a dermal exposure component. Additional adverse effects noted in animals following acute inhalation exposure to trichloroethylene include liver damage (Carlson 1974; Fujita et al. 1984; Okino et al. 1991), kidney damage (Chakrabarti and Tuchweber 1988; Crofton and Zhao 1993), and respiratory effects (Odum et al. 1992; Villaschi et al. 1991).

Acute oral LD_{50} values are available from animal studies (Smyth et al. 1969; Tucker et al. 1982). Following acute oral exposure to trichloroethylene, effects noted in humans include neurological effects (Dhuner et al. 1957; Morreale 1976; Perbellini et al. 1991; Stephens 1945; Todd 1954), gastrointestinal effects (De Baere et al. 1997; Liotier et al. 2008; Moritz et al. 2000; Vattemi et al. 2005), cardiac effects (Brüning et al. 1998; Dhuner et al. 1957; Moritz et al. 2000; Morreale 1976; Perbellini et al. 1991; Vattemi et al. 2005), hepatic effects (Kleinfeld and Tabershaw 1954), pulmonary effects (De Baere et al. 1997), and musculoskeletal effects (Vattemi et al. 2005). Effects noted in animals following acute oral exposure to trichloroethylene include hepatic effects (Atkinson et al. 1993; Berman et al. 1995; Dees and Travis 1993; Elcombe 1985; Elcombe et al. 1985; Goldsworthy and Popp 1987; Stott et al. 1982), renal effects (Berman et al. 1995), neurological effects (Moser et al. 1995; Narotsky and Kavlock 1995; Narotsky et al. 1995; Nunes et al. 2001), and immunological effects (Sanders et al. 1982).

Further studies on the developmental neurological effects of trichloroethylene in both animals and humans could contribute to more fully characterizing these effects.

Pain and erythema have been reported by study subjects who placed their hands (Sato and Nakajima 1978) or thumbs in trichloroethylene (Stewart and Dodd 1964). Application of trichloroethylene to the skin of guinea pigs resulted in erythema and edema.

Additional information regarding doses/concentrations that result in cardiac effects and conditions that may make persons more sensitive to these effects would be beneficial, although such information is not likely due to present-day occupational exposure limits.

When accidental human exposures occur, investigations to determine trichloroethylene exposure levels might add valuable information regarding exposure-response relationships. Similarly, studies on the acute effects of dermal exposure to trichloroethylene in animals may be useful in determining the risk for these exposures in humans at hazardous waste sites. However, there appear to be sufficient data regarding neurological effects after acute inhalation exposure.

Intermediate-Duration Exposure. Neurological effects are the most consistent effects reported in humans exposed to trichloroethylene for intermediate exposure durations (Mitchell and Parsons-Smith 1969; Steinberg 1981). Caprioli et al. (2001) reported loss of strength and polyneuropathy in a woman who had been exposed to trichloroethylene during a 3-month period of degreasing and antiquing processes (7–8 hours/day) in a poorly-ventilated garage. In a group of patients diagnosed with hypersensitivity dermatitis where the average trichloroethylene exposure time was 38.2 days (range 5–90 days), estimated trichloroethylene air concentrations were in the range of 18–683 mg/m^3 (3.24–122.9 ppm) (Xu et al. 2009). Stevens-Johnson syndrome, a severe dermatologic reaction, was seen in five people occupationally exposed to trichloroethylene for 2–5 weeks at levels ranging from 19 to 164 ppm (Phoon et al. 1984). Body weight loss has been reported in humans occupationally exposed to trichloroethylene for intermediate or chronic durations at concentrations resulting in neurological effects (Mitchell and Parsons-Smith 1969; Schattner and Malnick 1990).

Effects of trichloroethylene exposure in animals following intermediate-duration inhalation exposures include neurological effects (Adams et al. 1951; Albee et al. 1993, 2006; Arito et al. 1994a; Baker 1958; Battig and Grandjean 1963; Blain et al. 1992; Boyes et al. 2000, 2003, 2005; Crofton and Zhao 1997; Fechter et al. 1998; Goldberg et al. 1964a; Haglid et al. 1981; Jaspers et al. 1993; Kulig 1987; Muijser et al. 2000; Rebert et al. 1991; Silverman and Williams 1975; Waseem et al. 2001), respiratory effects (Kumar et al. 2002b), hepatic effects (Adams et al. 1951; Kjellstrand et al. 1983a; Kumar et al. 2001a), kidney effects (Mensing et al. 2002), endocrine effects (Kumar et al. 2000a), developmental effects (Blossom et al. 2008; Dawson et al. 1993; Dorfmueller et al. 1979; Johnson et al. 1998, 2003; Peden-Adams et al. 2006), and body weight effects (Adams et al. 1951; Kjellstrand et al. 1983a; Kumar et al. 2001b).

Available information regarding health effects in humans following intermediate-duration oral exposure to trichloroethylene is limited to studies examining reproductive outcome in people exposed to trichloroethylene in drinking water (ATSDR 1997; MDPH 1996). Effects in animals following intermediate-duration oral exposure include neurological effects (Barret et al. 1991, 1992; Gash et al. 2008; Isaacson et al. 1990), liver effects (Buben and O'Flaherty 1985; Merrick et al. 1989; NTP 1985, 1986; Stott et al. 1982), respiratory effects (NTP 1990), kidney effects (NTP 1985, 1990; Tucker et al. 1982), gastrointestinal effects (Tucker et al. 1982), hematological effects (Tucker et al. 1982), body weight effects (Blossom and Doss 2007; Cai et al. 2008; NTP 1986, 1990; Zenick et al. 1984), and immunological effects (Blossom and Doss 2007; Blossom et al. 2008; Cai et al. 2008; Gilbert et al. 1999; Griffin et al. 2000a, 2000b; Keil et al. 2009; Kobayashi et al. 2010, 2012; Peden-Adams et al. 2006; Sanders et al. 1982; Seo et al. 2008b, 2012; Wang et al. 2007a, 2007b). Intermediate-duration dermal studies of trichloroethylene in humans or animals were not available.

Additional animal studies of trichloroethylene following intermediate-duration oral exposure could further define dose-response relationships. Animal studies of intermediate-duration dermal exposure might be useful in determining whether targets following dermal exposure differ from those identified in inhalation and oral studies.

Chronic-Duration Exposure and Cancer. Studies of humans exposed to trichloroethylene in the air for chronic periods in the workplace provide evidence of trichloroethylene-induced neurological effects (Bardodej and Vyskocil 1956; Barret et al. 1987; Bauer and Rabens 1974; El Ghawabi et al. 1973; Kohlmuller and Kochen 1994; Rasmussen et al. 1993c; Ruijten et al. 1991), liver effects (Bauer and Rabens 1974; Schuttmann 1970), and kidney effects (Brogren et al. 1986). Chronic-duration studies of animals exposed to trichloroethylene via the inhalation route were not located.

Information on chronic human exposure to trichloroethylene via oral and/or dermal routes derives largely from studies of people who consumed trichloroethylene and other solvents from their drinking water for several years and experienced dermal exposure when washing with the contaminated water (ATSDR 1999; Bove et al. 1995; Burg and Gist 1999; Burg et al. 1995; Byers et al. 1988; Cohn et al. 1994; Davis et al. 2005; Fagliano et al. 1990; Feldman et al. 1988; Freni and Bloomer 1988; Goldberg et al. 1990; Kilburn and Warshaw 1992; Lagakos et al. 1986a; Vartiainen et al. 1993; Waller et al. 1994). The effects associated with trichloroethylene in these studies included cardiovascular effects (Byers et al. 1988), dermal effects (Byers et al. 1988; Waller et al. 1994), immunological effects (Byers et al. 1988; Kilburn and Warshaw 1992; Waller et al. 1994), neurological effects (Feldman et al. 1988), increased incidences

of birth defects (Bove et al. 1995; Goldberg et al. 1990; Lagakos et al. 1986a), and cancer (Cohn et al. 1994; Fagliano et al. 1990; Lagakos et al. 1986a). An exposure subregistry was established by ATSDR to monitor people living in areas where they were exposed to trichloroethylene from domestic water sources (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). Data in the Trichloroethylene Subregistry indicate excess prevalence of stroke, anemia (and other blood disorders), liver disease, and skin disorders. There was some evidence of increased prevalence of kidney disease and diabetes as well. The greatest limitations to these studies are the difficulty in estimating dose, and exposure to multiple chemicals.

Chronic oral exposure studies in animals have mainly focused on carcinogenicity and relatively insensitive noncancer end points and are not helpful in defining relatively sensitive noncancer end points in humans following long-term exposure. In one recent study in which mice were exposed to trichloroethylene via their mothers during gestation and lactation and via the drinking water for up to 12 months thereafter, depressed mean terminal body weight was noted at an estimated trichloroethylene oral dose level of 3.3 mg/kg/day and decreased thymic cellularity was noted at estimated doses ≥0.33 mg/kg/day (Peden-Adams et al. 2008). Additional chronic-duration oral studies of trichloroethylene in animals could serve to further define studies that provide information on sensitive end points of trichloroethylene toxicity.

Some workers who have had dermal contact with trichloroethylene have had adverse responses, but potential effects of low levels of trichloroethylene exposure on the skin at hazardous waste sites are not known. Chronic-duration dermal studies in animals were not identified. A chronic-duration dermal study in animals may also be useful to identify critical targets of trichloroethylene toxicity.

The most convincing evidence for an association between exposure to trichloroethylene and cancer in humans is for kidney cancer. Upon critical review of the available epidemiological data regarding the possible carcinogenicity of trichloroethylene, the NRC (2006) and the EPA (2011e) determined that there is convincing evidence for a causal association between trichloroethylene exposure and kidney cancer. The EPA (2011e) performed a meta-analysis using up to 15 cohort and case-control studies considered to be of adequate quality and with a high probability for trichloroethylene exposure to individual subjects and reported a significant association between overall trichloroethylene exposure and increased risk for kidney cancer. EPA (2011e) performed a meta-analysis using up to 16 cohort and case-control studies considered to be of adequate quality and with a high probability for trichloroethylene exposure to individual subjects and reported a slight, but significant, association between overall trichloroethylene

exposure and increased risk for non-Hodgkin's lymphoma. EPA (2011e) performed a meta-analysis using up to nine cohort studies considered to be of adequate quality and with a high probability for trichloroethylene exposure to individual subjects and reported a slight, but significant, association between overall trichloroethylene exposure and increased risk for liver and biliary tract cancer. Some epidemiological studies provide suggestive evidence for an association between trichloroethylene in the drinking water and the occurrence of certain cancers (Byers et al. 1988; Cohn et al. 1994; Fagliano et al. 1990; Kotelchuck and Parker 1979; Lagakos et al. 1986a; MDPH 1997; Parker and Rosen 1981). However, these studies are limited by lack of information regarding individual intake of trichloroethylene and the presence of other drinking water contaminants.

Animal studies have shown chronic-duration inhalation exposure (Fukuda et al. 1983; Henschler et al. 1980; Maltoni et al. 1986) and oral exposure (Anna et al. 1994; Henschler et al. 1984; NCI 1976; NTP 1990) to trichloroethylene can result in tumors. Some of these studies (NCI 1976) are limited in that they use carcinogenic epoxide stabilizers with the trichloroethylene, which may contribute to the carcinogenicity. The studies also show different responses depending on the sex, species, and strains of animals used. Other studies are flawed because of excess mortality. The studies to date indicate that trichloroethylene is carcinogenic in mice, based on the findings of liver cancer in some studies (Fukuda et al. 1983; Henschler et al. 1980; Maltoni et al. 1986; NTP 1990); the evidence for the carcinogenicity of trichloroethylene in rats is equivocal (Maltoni et al. 1986; NTP 1988, 1990), with kidney tumors developing in male rats, but not female rats.

The nephrocarcinogenicity of trichloroethylene has been adequately assessed. Additional human and animal studies should focus on the carcinogenicity of trichloroethylene at other organ and tissue sites. Additional epidemiological studies would be of benefit in assessing health risks for people living near hazardous waste sites. Additional chronic-duration inhalation studies of trichloroethylene in animals could help to define the thresholds of toxicity following chronic inhalation exposure.

Genotoxicity. The genotoxicity studies of trichloroethylene have produced mixed results. Some *in vivo* human and animal data suggest that trichloroethylene may cause genotoxic effects such as gene mutation (Bronzetti et al. 1978; Fahrig 1977), sister chromatid exchange (Gu et al. 1981b; Kligerman et al. 1994), chromosomal aberrations (Rasmussen et al. 1988), single-strand breaks (Nelson and Bull 1988; McLaren et al. 1994; Robbiano et al. 2004; Toraason et al. 1999; Walles 1986), micronuclei (Robbiano et al. 1998, 2004; Sujatha and Hegde 1998), C-mitotic changes (Sujatha and Hegde 1998), DNA damage (Toraason et al. 1999), and DNA and protein adduct formation (Halmes et al. 1997; Kautiainen et al.

1997; Mazzullo et al. 1992). Other *in vivo* studies reported negative results for gene mutations (Rossi et al. 1983), chromosomal aberrations (Beliles et al. 1980; Kligerman et al. 1994; Sujatha and Hegde 1998), micronuclei (Allen et al. 1994; Kligerman et al. 1994), sister chromatid exchange (Nagaya et al. 1989a), single-strand breaks (Parchman and Magee 1982), and DNA damage (Clay 2008; Mirsalis et al. 1989).

Some *in vitro* studies show positive results for such effects as gene mutations, recombination, mitotic aneuploidy, single-strand breaks, micronuclei, DNA damage, cell transformation, and protein adduct formation (Baden et al. 1979; Bartsch et al. 1979; Beliles et al. 1980; Bronzetti et al. 1978; Callen et al. 1980; Crebelli et al. 1985; Griffin et al. 1998; Koch et al. 1988; McGregor et al. 1989; Price et al. 1978; Robbiano et al. 2004; Simmon et al. 1977; Tu et al. 1985). However, many additional studies testing these or other genotoxic effects have been negative (Amacher and Zelljadt 1983; Beliles et al. 1980; Callen et al. 1980; Emmert et al. 2006; Greim et al. 1975; Henschler et al. 1977; Koch et al. 1988; McGregor et al. 1989; Mortelmans et al. 1986; Nagaya et al. 1989a; Rossi et al. 1983; Shimada et al. 1985; Slacik-Erben et al. 1980; Waskell 1978). Currently, the sister chromatid exchange data on the effects of trichloroethylene in humans are confounded by the effects of smoking. More information is needed regarding the effects of trichloroethylene on frequency of sister chromatid exchange in humans who do not smoke. Further investigation is needed regarding chromosomal aberrations and sister chromatid exchange following *in vivo* trichloroethylene exposure in both humans and animals following inhalation (in the workplace) and oral (through contaminated drinking water) routes of exposure.

Reproductive Toxicity. Possible associations between exposure to organic solvents (including trichloroethylene) and measures of fertility and fecundity have been assessed to some extent in occupationally-exposed men and women. Increased miscarriages were reported in one study of nurse-anesthetists exposed to trichloroethylene and other solvents (Corbett et al. 1974). A retrospective case-control study reported an approximate 3-fold increase in spontaneous abortion in women exposed to trichloroethylene and other solvents (Windham et al. 1991). Other epidemiologic studies have evaluated possible associations between occupational exposure of women to organic solvents (including trichloroethylene) and measures of fertility including time-to-pregnancy, spontaneous abortion, and menstrual cycle disturbance (Bardodej and Vyskocil 1956; Corbett et al. 1974; Lindbohm et al. 1990; Sallmén et al. 1995; Taskinen et al. 1994; Windham et al. 1991; Zielinski 1973); none of these studies provided convincing evidence of significant associations between exposure to trichloroethylene and impaired fertility or menstrual cycle disturbance. Some studies have reported reproductive effects in men occupationally exposed to trichloroethylene such as decreased potency or unspecified sexual disturbances (Bardodej and Vyskocil 1956; El Ghawabi et al. 1973) and changes in sperm morphology (Chia et al.

1996, 1997; Goh et al. 1998). Significant effects on sperm parameters were not observed in another study of men occupationally exposed to trichloroethylene (Rasmussen et al. 1988). Sallmén et al. (1998) found no effect on male fertility in a study that examined paternal occupational exposure to trichloroethylene and time-to-pregnancy among their wives. Adverse reproductive effects were not noted in humans who ingested water contaminated with trichloroethylene and other solvents (Byers et al. 1988; Freni and Bloomer 1988; Lagakos et al. 1986a). The human studies are typically limited due to concomitant exposure to other potential reproductive toxicants and lack of quantitative exposure-response data.

Studies in animals demonstrate the toxicity of trichloroethylene to the male reproductive system. Repeated inhalation exposures of male rats or mice to trichloroethylene vapors resulted in effects such as Testicular atrophy, degeneration of epididymal epithelium, changes in sperm morphology, decreases in sperm count and motility, and decreased numbers of sperm capable of attaching to eggs (Beliles et al. 1980; Forkert et al. 2002; Kan et al. 2007; Kumar et al. 2000a, 2000b, 2001b; Land et al. 1981; Xu et al. 2004), Beliles et al. 1980). In a continuous breeding protocol, NTP (1985) reported a 45% decrease in sperm motility in male F0 and F1 mice receiving trichloroethylene from drinking water for up to 18 weeks at a concentration resulting in an estimated dose of 737 mg/kg/day. Reproductive performance was not tested in most of the animal studies. However, Zenick et al. (1984) reported impairment in copulatory behavior, mount/ejaculation latency, and intromissions in male rats administered trichloroethylene by gavage at 1,000 mg/kg/day, 5 days/week for 6 weeks.

There is a need to further assess relationships between exposure to trichloroethylene and reproductive outcomes among humans exposed to trichloroethylene in the workplace and from contaminated drinking water. Additional animal studies should be designed to assess reproductive performance.

Developmental Toxicity. Epidemiological data are typically limited by concomitant exposure to other potentially hazardous substances, and case-control studies are limited by small numbers of cases. Thus, definitive positive associations between exposure to trichloroethylene and the occurrence of developmental effects are not possible from the available data.

There is some evidence of trichloroethylene-related increased rates of birth defects among nurse-anesthetists who were exposed to trichloroethylene and other anesthetic gases during pregnancy (Corbett et al. 1974) and increased risk of spontaneous abortion among women occupationally or nonoccupationally exposed to trichloroethylene and other solvents (Windham et al. 1991). Increased risk of congenital heart defects was reported among offspring of mothers living in the vicinity of

trichloroethylene-emitting sites (ATSDR 2006, 2008; Bove et al. 1995; Forand et al. 2012; Yauck et al. 2004). Increased risk of other birth defects or low birth weight have been reported among populations living in areas with trichloroethylene-contaminated drinking water (ATSDR 1997, 1998; Bove et al. 1995; Goldberg et al. 1990; Lagakos et al. 1986a; MDPH 1996) or where elevated airborne levels of trichloroethylene have been measured (Forand et al. 2012). White et al. (1997) provided evidence of cognitive impairment in children living in areas with reported high levels of trichloroethylene in the drinking water. Oral studies have suggested that exposure to trichloroethylene, along with other volatile hydrocarbons, may increase the risk of childhood leukemia (Lagakos et al. 1986b). An increase in hearing impairment in children ≤9 years old was reported among participants in the ATSDR exposure subregistry for trichloroethylene at baseline assessment, but not at several follow-up timepoints (ATSDR 1994, 1999, 2002; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). Firm conclusions on the levels of trichloroethylene that might be associated with adverse birth outcomes or developmental effects in growing children are not possible from the existing database. There are no known studies in humans of developmental effects from dermal exposure to trichloroethylene.

Limited information is available regarding the developmental toxicity of trichloroethylene in animals exposed by the inhalation route. Decreased fetal weight and incomplete ossification were reported in fetuses of rats exposed to trichloroethylene vapors during gestation at exposure levels that were not overtly toxic to the dams (Dorfmueller et al. 1979). There were no indications of trichloroethylene-induced developmental effects in other rat or mouse studies that employed the inhalation exposure route (Beliles et al. 1980; Carney et al. 2006; Hardin et al. 1981; Healy et al. 1982; Schwetz et al. 1975).

Oral studies in animals exposed during gestation only or gestation and postnatal development include reports of trichloroethylene-induced decreased litter size and micro- or anophthalmia (Narotsky and Kavlock 1995; Narotsky et al. 1995), increased perinatal mortality (Manson et al. 1984; NTP 1985), increased incidences of fetal heart abnormalities (Dawson et al. 1993; Johnson et al. 1998, 2003), decreased numbers of myelinated fibers and other changes in the hippocampus (Blossom et al. 2012; Isaacson and Taylor 1989), decreased uptake of glucose by the brain (Noland-Gerbec et al. 1986), and behavioral changes (NTP 1986; Taylor et al. 1985). One study reported behavioral changes in mice exposed orally during postnatal days 10–16 only (Fredriksson et al. 1993). Recent studies assessed effects of trichloroethylene on the immune system of developing animals. Exposure of MRL+/+ mouse dams to trichloroethylene in the drinking water during gestation and lactation and continued exposure of the pups via the drinking water for an additional 4 weeks resulted in effects that included increased IFN-γ production by splenic CD4+ cells; decreased splenic CD+4, CD8+, and B220+ lymphocytes; increased

splenic CD4+ T-cell production of cytokines IFN-γ and IL-2 in females and TNF-α in males; and altered thymocyte profiles (Blossom and Doss 2007; Blossom et al. 2008). Another study noted a significantly decreased PFC response in male and female mouse pups and increased hypersensitivity response in male mouse pups exposed to trichloroethylene via their mothers during gestation and lactation and via their drinking water until they reached up to 8 weeks of age (Peden-Adams et al. 2006).

Further monitoring for birth defects in humans exposed to trichloroethylene are needed, especially in populations in which exposure concentrations could be determined.

Immunotoxicity. Immunological abnormalities (altered ratios of T-lymphocyte subpopulations, increased incidence of auto-antibodies, and increased infections) were noted in adults from 28 families exposed to trichloroethylene-contaminated well water. These families also had children with leukemia who had been exposed to trichloroethylene *in utero* (Byers et al. 1988). Isolated cases of dermal sensitivity and allergic responses in humans have been reported (Bauer and Rabens 1974; Conde-Salazar et al. 1983; Czirjak et al. 1993; Goh and Ng 1988; Nakayama et al. 1988; Phoon et al. 1984; Schattner and Malnick 1990; Waller et al. 1994). An increase in the symptoms of systemic lupus erythematosus has been reported in persons exposed to trichloroethylene in their drinking water (Kilburn and Warshaw 1992). Significantly lower total numbers of lymphocytes, T cells, CD4+ T cells, CD8+ T cells, B cells and NK cells were reported in trichloroethylene-exposed workers at factories in China that used trichloroethylene for cleaning a variety of materials and products (Lan et al. 2010). There is some evidence for an association between occupational exposure to trichloroethylene and the occurrence of scleroderma (Diot et al. 2002; EPA 2011e; Garabrant et al. 2003; Nietert et al. 1998).

Immunological end points have been studied to some extent in animals exposed to trichloroethylene; some assessments of the potential for trichloroethylene to accelerate autoimmune diseases employed strain of mice that spontaneously develop conditions resembling the human disease, systemic lupus erythematosus (SLE). A limited study in animals presents evidence for increased susceptibility to *S. zooepidomicus* (Aranyi et al. 1986). Immune system effects observed in mice exposed orally to trichloroethylene include inhibition of cell-mediated immunity, delayed type hypersensitivity, and inhibition of antibody-mediated immunity (Sanders et al. 1982). Female mice appeared to be more sensitive than male mice. Some studies of autoimmune-prone mice indicate that trichloroethylene can accelerate autoimmune responses (Cai et al. 2008; Gilbert et al. 1999; Griffin et al. 2000a, 2000b; Khan et al. 1995). Keil et al. (2009) reported decreased thymus weight and increased serum levels of IgG and selected autoantibodies in female MRL+/+ mice administered trichloroethylene in the drinking water for

up to 30 weeks, but there was no evidence that trichloroethylene accelerated the onset of autoimmune disease. Seo and coworkers (Kobayashi et al. 2010, 2012; Seo et al. 2008b, 2012) presented evidence of trichloroethylene-induced enhancement of allergic or hypersensitivity reactions in animals exposed by the oral route.

Additional human and animal studies are needed to better characterize the immunological effects of trichloroethylene and determine the potential for immunological effects among people exposed to trichloroethylene in the vicinity of hazardous waste sites.

Refer to Developmental Toxicity (above) for a summary of developmental immunotoxicity.

Neurotoxicity. Sufficient human information exists to identify the nervous system as a primary target for acute toxicity. In cases of acute accidental or intentional overexposure to trichloroethylene, neurological effects include euphoria, giddiness, lethargy, confusion, dizziness, headache, nausea, difficulty swallowing, facial effects that indicate possible trigeminal nerve damage (including sensation deficits, jaw weakness, increased blink reflex latency), which may be irreversible, memory deficits, and unconsciousness (Adamek and Krupiński 2007; Buxton and Hayward 1967; Carrieri et al. 2007; Clearfield 1970; Feldman 1970; Feldman et al. 1985; James 1963; Lawrence and Partyka 1981; Lachnit and Pietschmann 1960; Leandri et al. 1995; Longley and Jones 1963; Milby 1968; Miller et al. 2002; Pembleton 1974; Thierstein et al. 1960; Troutman 1988). At one time, trichloroethylene was used as a surgical anesthetic in humans (Brittain 1948). Occupational studies show that workers also had neurological complaints such as dizziness and headaches (Bardodej and Vyskocil 1956; Barret et al. 1987; Buxton and Hayward 1967; Cavanagh and Buxton 1989; El Ghawabi et al. 1973; Grandjean et al. 1955; Lawrence and Partyka 1981; McCunney 1988; Nomiyama and Nomiyama 1977) as well as residual cranial nerve damage in some cases for which the exposure concentration or duration was generally greater (Barret et al. 1987; Buxton and Hayward 1967; Cavanagh and Buxton 1989; Feldman 1970; McCunney 1988; Ruijten et al. 1991).

Among persons known to have ingested large amounts of trichloroethylene, observed symptoms included muscle weakness, general motor restlessness, tremor, delirium, and coma (Liotier et al. 2008; Moritz et al. 2000; Morreale 1976; Perbellini et al. 1991; Stephens 1945; Todd 1954). Several studies of the population in Woburn, Massachusetts, exposed to trichloroethylene (along with other contaminants) in the drinking water did not reveal increases in neurological complaints (Byers et al. 1988; Lagakos et al. 1986b), but one study found possible residual cranial nerve damage when comparing the exposed and

nonexposed population cohorts (Feldman et al. 1988). Among persons in the ATSDR exposure subregistry, a statistically significant increase in impairment of hearing was reported in children <10 years of age at baseline assessment, but not at several follow-up timepoints (ATSDR 1994, 1999, 2002; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005).

In a study that assessed possible associations between exposure to solvents and risk of Parkinson's disease, ever exposure to trichloroethylene was associated with a significantly increased risk (Goldman et al. 2012).

Acute exposure via the inhalation route results in adverse central nervous system effects in animals, as indicated by quicker fatigue when rats were placed in a tank of water with weights loaded to their tails (Grandjean 1963). The shuttle box or maze performances of these rats were not affected by the exposure. Other inhalation studies in animals include reported behavioral changes (Albee et al. 1993; Arito et al. 1994a; Battig and Grandjean 1963; Bushnell 1997; Bushnell and Oshiro 2000; Goldberg et al. 1964a; Kulig 1987; Silverman and Williams 1975; Waseem et al. 2001), biochemical and histopathological alterations (Haglid et al. 1981; Savolainen et al. 1977), and impaired hearing and vision (Albee et al. 1993, 2006; Blain et al. 1992, 1994; Boyes et al. 2000, 2003, 2005; Crofton and Zhao 1993, 1997; Crofton et al. 1994; Fechter et al. 1998; Jaspers et al. 1993; Kulig 1987; Muijser et al. 2000; Rebert et al. 1991).

Oral studies in animals include reports of trichloroethylene-induced neurological effects that include altered behavior (Moser et al. 1995; Narotsky et al. 1995; NTP 1988), increased foot splay (Nunes et al. 2001), and histopathological changes in the central nervous system (Barret et al. 1992; Gash et al. 2008; Henschler et al. 1984; Isaacson et al. 1990).

Application of a complete battery of neurological tests in animals exposed to trichloroethylene via the oral pathway is needed, although available data indicate that large oral doses are required to elicit neurological effects in animals. Neurological testing of humans with documented oral exposure to trichloroethylene could provide valuable insight as well.

Epidemiological and Human Dosimetry Studies. The epidemiological data for inhalation exposure to trichloroethylene derives from exposure in the workplace or intentional overexposure by inhalation. Many of the studies do not include adequate characterization of exposure levels and associated health effects. Epidemiological data for oral exposure to trichloroethylene are predominantly

available from studies of trichloroethylene in the drinking water where trichloroethylene has been associated with cardiovascular effects, dermal effects, immunological effects, neurological effects, increased incidences of selected birth defects, and cancer. The greatest limitations of most epidemiological studies are the difficulty in estimating dose and exposure to multiple chemicals. Additional epidemiological studies are needed that focus on the effects of low levels of trichloroethylene 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.

Biomarkers of Exposure and Effect

Exposure. There is a large body of literature concerning the measurement of trichloroethylene in the breath and its principal metabolites (TCA, trichloroethanol, and trichloroethanol glucuronide) in the urine and blood (Csanády et al. 2010; Ertle et al. 1972; Ikeda et al. 1972; Imamura and Ikeda 1973; Imbriani et al. 2001; Kimmerle and Eben 1973b; Monster et al. 1979; Müller et al. 1972, 1974, 1975; Nomiyama 1971; Nomiyama and Nomiyama 1977; Ogata et al. 1971; Skender et al. 1993; Stewart et al. 1970; Vartiainen et al. 1993). However, there is a high degree of variation among individuals, so these methods should be used with caution for determining exposure levels. ACGIH has developed BEIs for trichloroethylene metabolites in urine (TCA, trichloroethanol) and blood (trichloroethanol) (ACGIH 2012).

Effect. Reliable biomarkers of effects are not available for trichloroethylene. There is no clinical disease state that is unique to trichloroethylene exposure. Interpretation of the behavioral observations in humans is complicated by many factors, such as possible irritant effects of the odor and nonspecific effects on the nervous system (e.g., fatigue). Further studies in this area would be useful in determining the exposure levels that may be associated with adverse effects in exposed populations. There is also a need to further explore the use of blink reflex latency as a marker for possible cranial nerve damage. This method has proven useful in detecting differences between exposed and nonexposed groups of people, but further refinement of the method is needed for its use in individual assessment. A limited number of studies of workers occupationally exposed to trichloroethylene for chronic periods have reported increases in serum levels of liver enzymes (Bauer and Rabens 1974; Schuttmann 1970), liver enlargement (Schuttmann 1970), and increased urinary NAG activity (Brogren et al. 1986). Although these effects are not specific

for trichloroethylene exposure, additional research further defining dose-response relationships for these effects would be useful.

Absorption, Distribution, Metabolism, and Excretion. There are some gaps in the current literature concerning information on the pharmacokinetics of trichloroethylene in humans and animals. Inhalation and oral absorption data for trichloroethylene in humans are based largely on poisoning cases, and no actual rates of absorption are available (Astrand and Ovrum 1976; Fernandez et al. 1977; Kleinfeld and Tabershaw 1954; Sato and Nakajima 1978). Dermal absorption studies of trichloroethylene dissolved in water (as a vehicle) are lacking, and studies using pure liquid trichloroethylene to measure dermal absorption are complicated by the fact that trichloroethylene defats the skin and enhances its own absorption. Data on the distribution of trichloroethylene in humans and animals are very limited, although the systemic distribution of trichloroethylene has been extensively studied in animals. Several investigators are working on PBPK models of trichloroethylene distribution in animals, and studies are underway to compare the differences in distribution of trichloroethylene following oral and inhalation exposure in rats. Some new metabolites of trichloroethylene in humans and animals have been reported in the recent literature, but these reports are still awaiting confirmation. Saturation of metabolism has been postulated to occur in humans, but few experimental data are available (Feingold and Holaday 1977). In animals, there are species differences in concentrations at which trichloroethylene metabolism becomes saturated, with mice reaching saturation at higher concentrations than rats (Dallas et al. 1991; Dekant et al. 1986b; Filser and Bolt 1979; Prout et al. 1985). Thus, the blood of mice can be found to contain greater concentrations of toxic metabolites, which are hypothesized to lead to induction of hepatocellular carcinoma in mice exposed to trichloroethylene (Fisher et al. 1991; Larson and Bull 1992b). Additional data clarifying the rate of absorption, the distribution, and the metabolism of trichloroethylene in humans would be useful.

Comparative Toxicokinetics. In humans, the targets for trichloroethylene toxicity are the liver, kidney, cardiovascular system, and nervous system. Experimental animal studies support this conclusion, although the susceptibilities of some targets, such as the liver, appear to differ between rats and mice. The fact that these two species could exhibit such different effects allows us to question which species is an appropriate model for humans. A similar situation occurred in the cancer studies, where results in rats and mice had different outcomes. The critical issue appears to be differences in metabolism of trichloroethylene across species (Andersen et al. 1980; Buben and O'Flaherty 1985; Filser and Bolt 1979; Prout et al. 1985; Stott et al. 1982). Further studies relating the metabolism of humans to those of rats and mice are needed to confirm the basis for differences in species and sex susceptibility to trichloroethylene's

toxic effects and in estimating human health effects from animal data. PBPK models have been developed to estimate human health effects from animal data and to estimate effects across exposure routes (see Section 3.4.5 for descriptions of PBPK models for trichloroethylene).

Methods for Reducing Toxic Effects. The general recommendations for reducing the absorption of trichloroethylene following acute inhalation, oral, dermal, or ocular exposure are well established and have a proven efficacy (D'Souza et al. 1985; HSDB 2013; Withey et al. 1983). No additional investigations are considered necessary at this time.

No clinical treatments other than supportive measures are currently available to enhance elimination of trichloroethylene following exposure. Studies designed to assess the potential risks or benefits of increasing ventilation to enhance pulmonary elimination or of stimulating excretion of trichloroethylene and its decomposition products are needed.

The mechanism of action for liver toxicity and carcinogenicity may involve the formation of reactive products (Bonse and Henschler 1976; Bonse et al. 1975; Fisher et al. 1991; Larson and Bull 1992b). Methods for reducing the destructive damage caused by these intermediates, or for blocking their formation through inhibition of metabolic pathways, may prove effective in reducing hepatic toxicity, but are not currently available for clinical use.

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.

Intake from trichloroethylene-contaminated drinking water is expected to be greater in children than adults because children tend to drink more water on a per kg bodyweight basis than adults. Nursing infants can be exposed to trichloroethylene via the breast milk (Pellizzari et al. 1982). Household dust and dirt are potential sources of greater potential dermal contact and ingestion exposure in small children, although no information was located regarding trichloroethylene levels in household dust or dirt. Trichloroethylene intake from the ambient air is expected to be greater in infants and children than adults because infants and children have increased ventilation rates per kilogram body weight and alveolar surface area is 2-fold higher in infants compared to adults (EPA 2008). Trichloroethylene is lipophilic and distributes to all body tissues (see Section 3.4.2). At comparable absorption levels, such lipophilic substances may become more concentrated in the fat of infants and small children due to their lower amounts of fat per kilogram

body weight compared to adolescents and adults (NRC 1993). Trichloroethylene crosses the blood-brain barrier, and the extent of transfer could possibly be greater in young children, although trichloroethylene is expected to readily cross the blood-brain barrier in all age groups. Age-related differences in trichloroethylene metabolism could result in differences in susceptibility to trichloroethylene toxicity.

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

Under the auspices of ATSDR's Voluntary Research Program (VPR), the Halogenated Solvents Industry Alliance (HSIA) has planned to study PBPK dose route conversion for immunological effects described in a rat inhalation study (Boverhof et al. 2013). The HSIA has also planned an oral developmental neurotoxicity study in rats. These studies are designed to address priority data needs identified by ATSDR (2011a) and as cited in the Federal Register (FR Doc. 05-23361; FR Doc. 96-7852).

Other ongoing studies pertaining to trichloroethylene have been identified and are shown in Table 3-12.

Table 3-12. Ongoing Studies on Trichloroethylene

Principal investigator	Study topic	Institution	Sponsor
Blossom, SJ	CD4+ T cell-mediated neurotoxicity with continuous trichloroethylene exposure	Arkansas Children's Hospital Research Institute, Little Rock, Arkansas	National Institute of Environmental Health Sciences
Khan, MF	Trichloroethylene exposure and autoimmune hepatitis	University of Texas, Galveston, Texas	National Institute of Environmental Health Sciences
Loch-Caruso, RK	Mechanisms of action related to risk of preterm birth and other adverse birth outcomes associated with environmental contaminants	Northeastern University, Boston, Massachusetts	National Institute of Environmental Health Sciences

PBPK = physiologically-based pharmacokinetic

Source: RePORTER 2018