2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 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.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals or exposure levels below which no adverse effects have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or h4RLs) 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 2-l and 2-2 and Figures 2-1 and 2-2.

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

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

repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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

2.2.1 Inhalation Exposure

2.2.1.1 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, often during its use in degreasing operations (Ford et al. 1995; James 1963; Kleinfeld and Tabershaw 1954; McCarthy and Jones 1983; Smith 1966) or dry-cleaning operations (Bell 1951). These studies usually attributed death to ventricular fibrillation or central nervous system depression, since gross post-mortem abnormalities were not apparent. 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 intentional inhalation of concentrated fumes from trichloroethylene-containing typewriter correction fluid (Troutman 1988) and cleaning fluids (Clear-field 1970). 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.

Animal experimentation has revealed inhaled concentrations that result in death following acute, intermediate, and chronic exposure. An LC_{50} value for acute exposure in rats was reported as 12,500 ppm for a 4-hour exposure (Siegel et al. 197i). 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 2-l and plotted in Figure 2- 1.

2.2.1.2 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 2- 1 and plotted in Figure 2- 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.

Morphology of lung cells and P-450 activity in the lungs has been studied in rats and mice exposed to trichloroethylene. A 30minute inhalation exposure to 500 ppm resulted in vacuole formation and endoplasmic reticulum dilation specifically in the nonciliated epithelial cells (Clara cells) of the bronchial tree (Villas&i 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 P-450 enzyme 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).

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)		Reference
	ACUTE EXPOSURE									
	Death									
1	Rat (Sprague-Dawley)	4 hr						12500 M	(LC_{50})	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

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)	Reference
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
7	Rat (Alpk: APfSD)	6 hr	Resp		500 F	(reduction of aldrin epoxidase and cytochrome C reductase activity)		Odum et al. 1992
8	Mouse (CD-1)	6 hr	Resp	20 F	100 F	(vacuolization of Clara cells, reduction of P-450 activity)		Odum et al. 1992
9	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
10	Mouse (B6C3F1)	30 min	Resp		500 M	(vacuolization and dilation of endoplasmic reticulum in Clara cells)		Villaschi et al. 1991

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		Serious (ppm)		Reference
11	Dog (Beagle)	10 min	Cardio	5000 M			10000 M	(7/12 ventricular fibrillation after epinephrine challenge, 1/12 cardiac arrest)	Reinhardt et al. 1973
	Immunological/Lymphoreticular								
12	Mouse (CD-1)	3 hr		5 F	10 F	(increased susceptibility to *Streptococcus zooepidemicus*)			Aranyi et al. 1986
	Neurological								
13	Human	2.5 hr		300 M					Ettema et al. 1975
14	Human	~1 hr					3000 M	(unconsciousness)	Longley and Jones 1963
15	Human	5 d 7 hr/d			200[b]	(headache, fatigue, drowsiness)			Stewart et al. 1970
16	Human	2 hr		300 M			1000 M	(decreased depth perception and motor skills)	Vernon and Ferguson 1969
17	Human	2.5 hr		200 M					Windemuller and Ettema 1978

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)		Reference
18	Rat (Wistar)	8 hr			3000	(lethargy)	4800	(anesthesia)	Adams et al. 1951
19	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
20	Rat (Long-Evans)	5 d 6 hr/d		2000 M			4000 M	(postexposure mid-frequency hearing loss, sedation)	Crofton and Zhao 1993
21	Rat (CFE)	10 d 5 d/wk 4 hr/d		1568 F			4380 F	(ataxia)	Goldberg et al. 1964b
22	Rat (NS)	6 hr		400 M	800 M	(impaired swimming performance both with and without a load)			Grandjean 1963
23	Rat (Wistar)	4 hr			250 M	(decreased shock avoidance and Skinner box lever press)			Kishi et al. 1993
24	Rat (pigmented	1 hr			2754	(impaired oculomotor control)			Niklasson et al. 1993

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
25	Rat (Sprague-Dawley)	4 d 6 hr/d			200 M (decreased brain RNA, hyperactivity)		Savolainen et al. 1977
	Reproductive						
26	Mouse (C57Bl/ 6J)	5 d 6 hr/d		500 M			Allen et al. 1994
27	Mouse (CD-1)	5 d 7 hr/d			100 M (6% increase in abnormal sperm morphology)		Beliles et al. 1980
28	Mouse (C57BL/ 6N)	5 d 4 hr/d		200 M	2000 M (1% increase in abnormal sperm morphology)		Land et al. 1981
	Developmental						
29	Rat (Sprague-Dawley)	Gd 0-18 5 d/wk 7 hr/d		500			Beliles et al. 1980; Hardin et al. 1981
30	Rat (Long-Evans)	Gd 0-20 7 d/wk 6 hr/d			1800 (decreased fetal weight, incomplete skeletal ossification)		Dorfmueller et al. 1979
31	Rat (Sprague-Dawley)	Gd 6-15 7 hr/d		300			Schwetz et al. 1975

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
32	Mouse (Swiss-Webster)	Gd 6-15 7 hr/d		300				Schwetz et al. 1975
	INTERMEDIATE EXPOSURE							
	Systemic							
33	Monkey (Rhesus)	6 mo 5 d/wk 7 hr/d	Hepatic	400	M			Adams et al. 1951
			Renal	400	M			
			Bd Wt	400	M			
34	Rat (Wistar)	6 mo 5 d/wk 7 hr/d	Hemato	400				Adams et al. 1951
			Hepatic	400				
			Renal	400				
			Bd Wt	400				
35	Rat (Wistar)	10 wk 5 d/wk 8 hr/d	Hepatic	2000				Laib et al. 1979

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
36	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			
37	Rat (Sprague-Dawley)	90 d 24 hr/d	Resp	35			Prendergast et al. 1967
			Cardio	35			
			Hemato	35			
			Hepatic	35			
			Renal	35			
38	Mouse (NMRI)	30 d 24 hr/d	Hepatic	37 M	75 M	(increased BuChE activity, liver weight)	Kjellstrand et al. 1983a
				150 F	300 F	(increased BuChE activity, liver weight)	
			Bd Wt	75 M	150 M	(body weights 10% lower than controls)	
				150 F	300 F	(body weights 16% lower than controls)	

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)		Reference
39	Rabbit (NS)	6 mo 5 d/wk 7 hr/d	Hepatic	400					Adams et al. 1951
			Renal	400					
			Bd Wt	400					
40	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)			
	Neurological								
41	Rat (Fischer-344)	13 wk 5 d/wk 6 h/d		250	800	(altered amplitude of flash-evoked potentials)			Albee et al. 1993
42	Rat (JCL-Wistar)	6 wk 5 d/wk 8 hr/d			50 cM	(decreased wakefulness during exposure, decreased postexposure sleeping heart rate)	100 M	(decreased postexposure wakefulness, decreased time-averaged postexposure heart rate)	Arito et al. 1994a
43	Rat (NS)	44 wk 5 d/wk 8 hr/d			400 M	(decreased swimming speed)			Battig and Grandjean 1963

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
44	Rat (CFE)	30 d 5 d/wk 4 hr/d			125 M (decreased shock avoidance)		Goldberg et al. 1964a
45	Rat (Wistar)	3 wk 5 d/wk 18 hr/d			1500 (reduced acoustic startle response)		Jaspers et al. 1993
46	Rat (Wistar)	18 wk 5 d/wk 16 hr/d		500 M	1000 M (increased latency in visual discrimination task)		Kulig 1987
47	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
48	Rat (Fischer-344)	3 wk 6 d/wk 12 hr/d			2000 M (depressed amplitude of auditory-evoked potentials)		Rebert et al. 1991
49	Rat (Wistar)	5 wk 5 d/wk 6 hr/d			100 M (reduced social behavior: exploration, escape, submission)		Silverman and Williams 1975
50	Rabbit (New Zealand)	12 wk 4 d/wk 4 hr/d			350 (altered amplitude of visual-evoked potentials)		Blain et al. 1992

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
51	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
52	Gerbil (Mongolian)	3 mo 24 hr/d			60 (astroglial hypertrophy)		Haglid et al. 1981
	CHRONIC EXPOSURE						
	Systemic						
53	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			
			Derm	600			
			Ocular	600			
			Bd Wt	600			
	Cancer						
54	Rat (Sprague-Dawley)	104 wk 5 d/wk 7 hr/d				100 M (CEL: Leydig cell tumors)	Maltoni et al. 1986

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)		Reference
55	Mouse (ICR)	104 wk 5 d/wk 7 hr/d				150 F	(CEL: lung adenomas and adenocarcinomas)	Fukuda et al. 1983
56	Mouse (NMRI)	18 mo 5 d/wk 6 hr/d				100 F	(CEL: increased lymphomas)	Henschler et al. 1980
57	Mouse (B6C3F1)	78 wk 5 d/wk 7 hr/d				600 F	(CEL: pulmonary tumors)	Maltoni et al. 1986
58	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 2-1. Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 2-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

[b]Used to derive an acute-duration inhalation Minimal Risk Level (MRL) of 2 ppm for trichloroethylene; 200 ppm duration-adjusted (7/24 hr) to 58.3 ppm, divided by an uncertainty factor of 30 (3 for use of a minimal LOAEL, 10 for human variability) = 1.9 ppm, rounded to 2 ppm.

[c]Used to derived an intermediate-duration inhalation Minimal Risk Level (MRL) of 0.1 ppm for trichloroethylene; 50 ppm adjusted for duration (5/7 days x 8 hr/d) and species-specific ratio of daily inhalation volume (m^3/day)/body weight(kg) ratio for rat (0.23/2.17) to human (20/70) to 44.2 ppm, divided by an uncertainty factor of 300 (10 for using a LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability) = 0.147 ppm, rounded to 0.1 ppm.

Bd Wt = body weight; BuChE = butyrylcholinesterase; Cardio = cardiovascular; CEL = cancer effect level; contin = continuous; d = day(s); Derm = dermal; Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day(s); Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s)

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

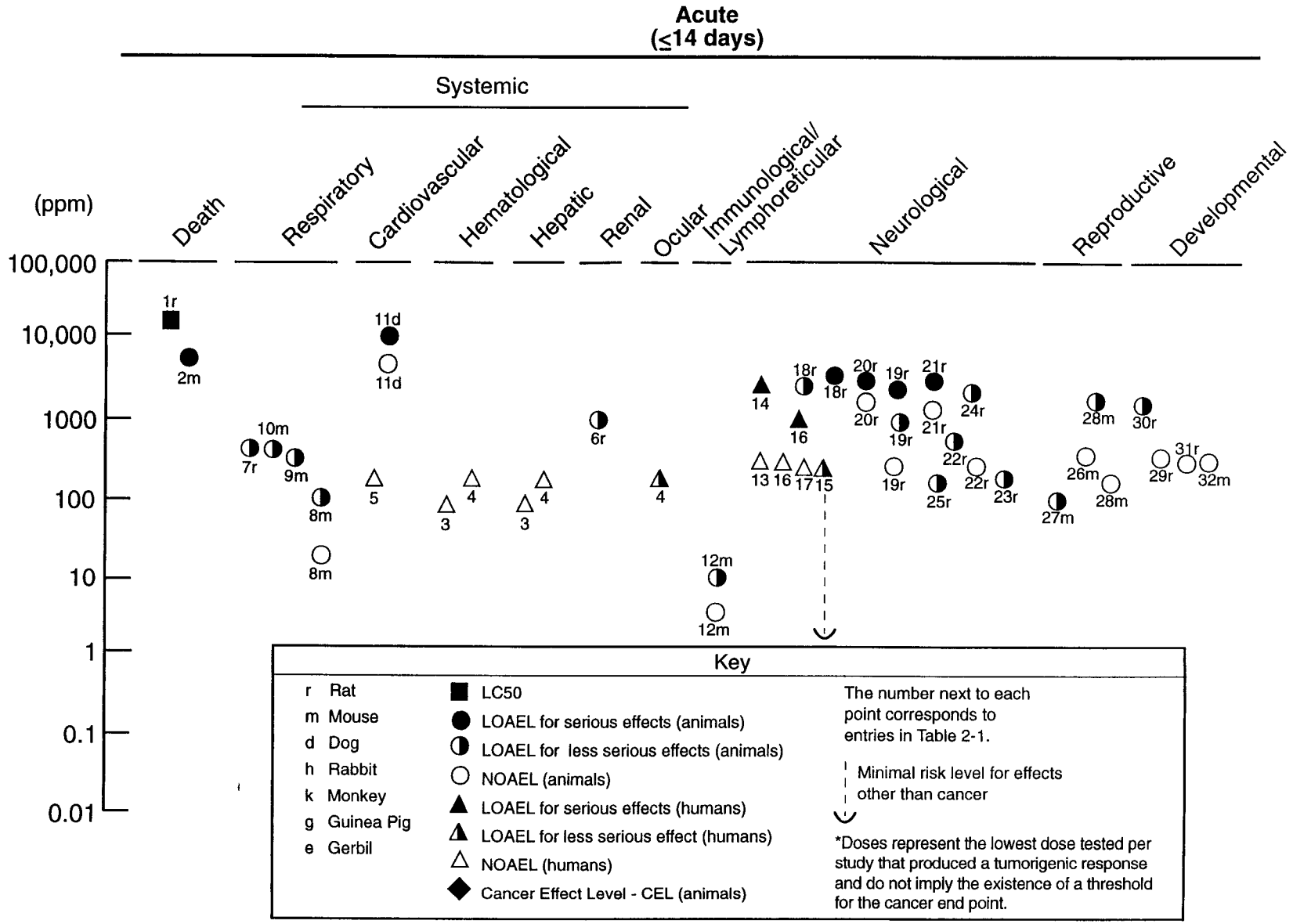


Figure 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)

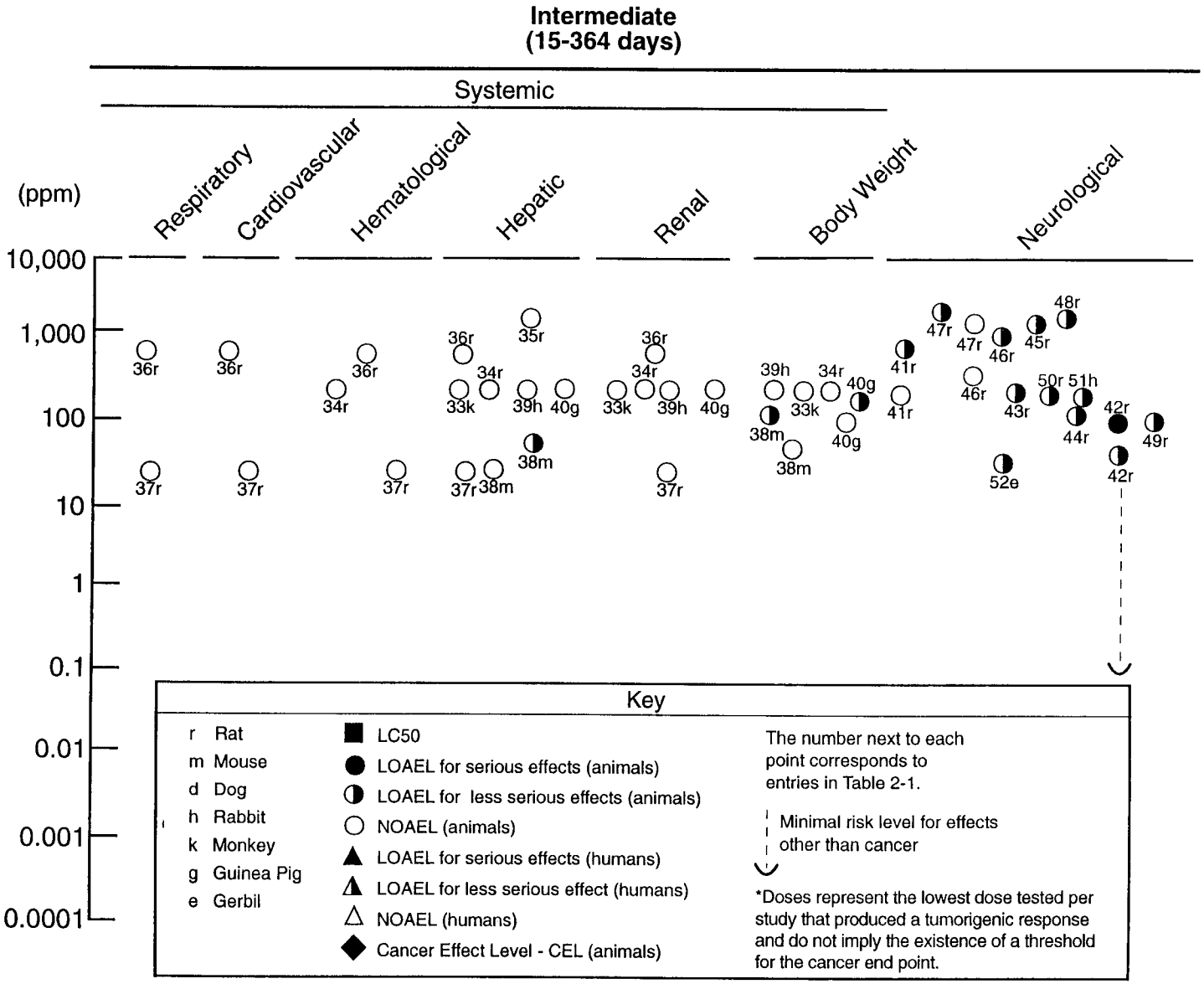
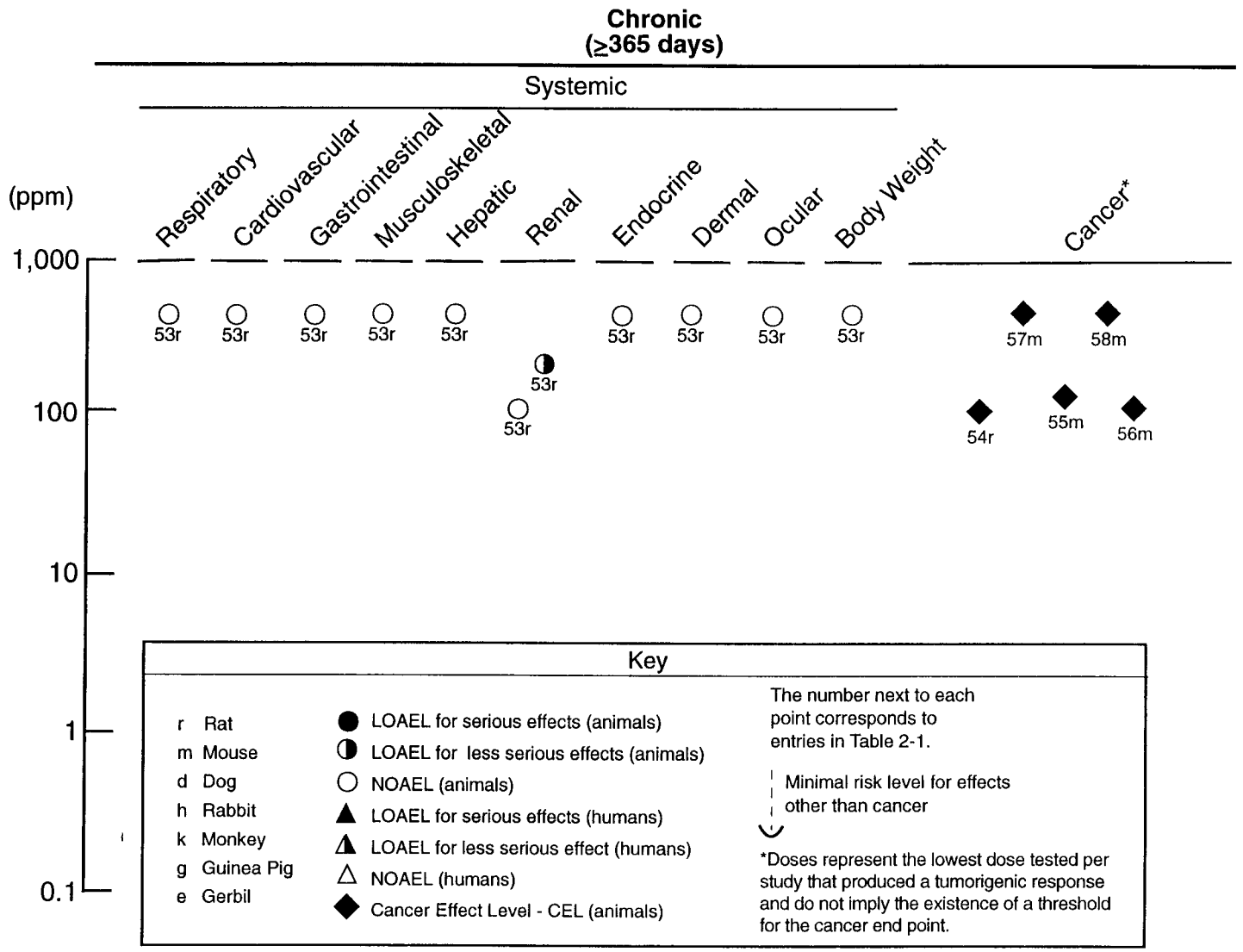


Figure 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)



Cardiovascular Effects. Exposure of 15 male volunteers to 200 ppm trichloroethylene for 2.5 hours had no effect on heart rate or sinus arrhythmia (Windemuller and Ettema 1978). Electrocardiograms of workers exposed to trichloroethylene in the range of 38-172 ppm for periods ranging from less than 1 year to more than 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). Hypertension, enlarged heart, and arrhythmia were seen in some workers (number, sex, and exposure period unspecified) accidentally exposed to trichloroethylene at a level that was unspecified but at least 15 ppm (Sidorin et al. 1992). Previous chronic exposure to trichloroethylene from using shoemaker's glue in an unventilated shop was implicated in a case of cardiac arrest and subsequent arrhythmia (Wemisch et al. 1991). 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 Mahrick 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 an acute 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 95 ppm trichloroethylene 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 less than 1 year to more than 5 years (El Ghawabi et al. 1973).

Various minor hematological effects have been noted in animals. Rats exposed to 50-800 ppm of trichloro-ethylene 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 400 ppm (Adams et al. 1951) or 55 ppm (Kimmerle and Eben 1973a).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to trichloroethylene. Trichloroethylene exposure can result in nervous system effects that result in secondary effects on muscle strength, especially in the face (Leandri et al. 1995). See Section 2.2.1.4 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 of trichloroethylene exposure that support the liver as an end point of trichloroethylene toxicity are described below. There is one report that occupational exposure to high concentrations of trichloroethylene resulted in death, with acute massive liver necrosis 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 succumbed to trichloroethylene exposure following 10 years of intentional overexposure.

A review of older case studies includes some 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). A more recent report (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 (SGOT) which returned to normal within 2 or 3 days. One patient had a doubling of the SGOT 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 data available 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 (Capellini and Grisler 1958; 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). Case studies 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). Case studies of 289 British workers, who had neurological effects from trichloroethylene, revealed no cases with a clear diagnosis of hepatotoxicity (McCarthy and Jones 1983). 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 (Schuttmann 1970). Liver function tests were normal in human 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). The available evidence suggests that hepatic damage may occur in some people following chronic exposure to relatively high levels in the workplace, but the available reports are conflicting.

Inhalation of trichloroethylene for acute or intermediate periods can cause liver enlargement in laboratory animals. Usually this effect is 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 enlarged and vacuolated hepatocytes. Liver weight, liver histology, and serum BuChE activity returned to normal 4 months later, indicating reversibility of the hepatic effects. Male mice were more sensitive to this effect 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), 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). Relative liver weight was increased 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. Pathological examinations were not conducted in this study.

Other investigators either found no microscopic lesions in the liver of animals exposed to trichloroethylene or did not perform histopathology. 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 noted (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 a day, 5 days per week for 10 weeks (Laib et al. 1979). Histopathological changes were also not observed in the livers of rats exposed to 300 ppm trichloroethylene 7 hours per day, 5 days per week for 104 weeks (Maltoni et al. 1988).

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 exposed 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 (Cleat-field 1970). Slight renal effects indicated by changes in urinary proteins (Brogren et al. 1986) and N-acetyl-P-D-glucosaminidase (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 the tubules.

Exposure of rats to extremely high levels (1,000 ppm or higher) for periods of less than 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). Increased kidney weight has been found in rats, mice, and gerbils exposed for intermediate periods (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. Other investigators also found increases in kidney weight following intermediate-duration exposure but no histopathological changes in squirrel monkeys or dogs (Prendergast et al. 1967); in rhesus monkeys (Adams et al. 1951); or in rats, guinea pigs, or rabbits

(Adams et al. 1951; Prendergast et al. 1967). Since the histological observations were unremarkable, and other functional tests were not performed, the levels at which only kidney weight was altered were considered to be NOAELs. Male rats, but not females, that were exposed to 300 ppm trichloroethylene in a chronic study showed renal tubular meganucleocytosis (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 2.2.1.8.

Endocrine Effects. No studies were located regarding endocrine effects in humans after inhalation exposure to trichloroethylene.

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).

Dermal Effects. Humans that 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. Skin irritation and rashes have resulted from occupational exposure to trichloroethylene (Bauer and Rabens 1974; El Ghawabi et al. 1973). The dermal effects 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.

Stevens-Johnson syndrome, a severe erythema, 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). The study authors suggested that the erythema was caused by a hypersensitivity reaction to trichloroethylene. An exfoliative dermatitis (Goh and Ng 1988) and scleroderma (Czirjak et al. 1993), also thought to have an immune component, have been reported in persons occupationally exposed to trichloroethylene.

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 that 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.

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).

Body weights were lower than controls (18% males, 16% females) in mice exposed continuously to 300 ppm trichloroethylene for 30 days (Kjellstrand et al. 1983a). At 150 ppm, body weights of male mice were 10% lower than controls, while no effects on body weight were observed in female mice. Male guinea pigs also appear to be more sensitive to effects on body weight compared to females. Body weights were 18% lower than controls in male guinea pigs exposed to 200 ppm trichloroethylene 7 hours per day, 5 days per week for 6 months (Adams et al. 1951). No effects on body weight were noted in female guinea pigs exposed to 400 ppm. Body weight was not affected in rhesus monkeys, rats, or rabbits exposed to 400 ppm 7 hours per day, 5 days per week for 6 months (Adams et al. 1951); in rats exposed to 700 ppm 8 hours per day, 5 days per week for 6 weeks, or to 35 ppm continuously for 90 days (Prendergast et al. 1967); or in rats exposed to 600 ppm 7 hours/day, 5 days per week for 104 weeks (Maltoni et al. 1988).

2.2.1.3 Immunological and Lymphoreticular Effects

It has been suggested that in some cases dermal effects in persons occupationally exposed to trichloroethylene may be a sensitivity reaction (Czirjak et al. 1993; Goh and Ng 1988; Phoon et al. 1984).

Only one study of immunological function in animals after inhalation exposure to trichloroethylene was located. 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. The specific mechanism of the increased susceptibility is unknown. The NOAEL and LOAEL identified in this study are recorded in Table 2- 1 and plotted in Figure 2-l. 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).

2.2.1.4 Neurological 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 2-l. 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 exposures of 2-2.5 hours at 1,000 ppm include impaired visual-motor coordination (measured by groove-type hand steadiness, depth perception, and pegboard tests) (Vernon and Ferguson 1969) and, at 200 ppm, an increase in heart and breathing rates when trichloroethylene was inhaled simultaneously with ethanol ingestion (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 less than 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 each 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 from five to six volunteers exposed to 200 ppm for 5 days, 7 hours/day, although they did complain of fatigue, 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. Based on the LOAEL of 200 ppm observed in humans in the Stewart et al. (1970) study, an acute-duration inhalation MBL of 2 ppm was calculated as described in the footnote in Table 2-l.

In cases of acute occupational exposure, the circumstances are usually accidental and the actual exposure level is unquantified. One such instance resulted in dizziness, loss of facial sensation, and difficulty swallowing (Lawrence and Partyka 1981), while more severe cases of nausea and unconsciousness have also been reported (Lachnit and Pietschmann 1960; Sidorin et al. 1992). Two men collapsed while working for about an hour in a closed room contaminated with trichloroethylene from spilled paint (Longley and Jones 1963). The exposure concentration was estimated to be about 3,000 ppm. A 24-year-old man who breathed air contaminated with an unspecified concentration of trichloroethylene for 15 minutes exhibited trigeminal nerve damage when tested up to 4 months later, as demonstrated by loss of facial sensation. This was manifested by increased thermal and tactile thresholds, altered trigeminal evoked potentials, and increased latency of blink reflex (Leandri et al. 1995). Workers exposed to high levels of trichloroethylene have also noted a feeling of euphoria or giddiness (Feldman 1970; Milby 1968). This is often accompanied by feelings of sleepiness and confusion. Follow-up of an acute exposure case indicated permanent nerve damage

resulting from exposure to an unknown level of trichloroethylene, with residual deficits in neurological functions noted 12-18 years after the exposure (Feldman et al. 1985). These deficits entailed neuro-ophthalmological impairments such as asymmetric pupillary responses and also neuropsychological impairments such as memory deficits. Similar symptoms have been seen in people who have intentionally inhaled high concentrations of trichloroethylene for its intoxicating effects (Clear-field 1970; James 1963; Pembleton 1974; Thierstein et al. 1960; Troutman 1988). This use has led to adverse systemic effects and death, as described elsewhere in this profile. 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.

Trichloroethylene has been 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 has also been used, with variable success, in the treatment of painful symptoms of trigeminal neuralgia (Glaser 1931).

Acute exposure to trichloroethylene and its decomposition products (e.g., dichloroacetylene) has also led to residual neuropathy, characterized by nerve damage. This neuropathy is characterized by facial numbness, jaw weakness, and facial discomfort (indicating damage to cranial nerves V and VII) which can persist for several months (Buxton and Hayward 1967; Feldman 1970). Chronic exposure in the workplace has also been associated with damage to the cranial nerves in several cases (Bardodej and Vyskocil 1956; Barret et al. 1987; Cavanagh and Buxton 1989). Persons who have died from overexposure have shown degeneration of cranial nuclei in the brain stem (Buxton and Hayward 1967). Some of these effects may be attributed to

dichloroacetylene, a decomposition product of trichloroethylene, which may form under nonbiological conditions of heat or alkalinity (Humphrey and McClelland 1944; Saunders 1967). However, it is not yet clear from other reports of cranial nerve damage whether the causal agent was trichloroethylene alone (Buxton and Hayward 1967; Feldman et al. 1985; Leandri et al. 1995; Saunders 1967). Thus, the evidence for associating cranial nerve damage with exposure to trichloroethylene itself remains equivocal.

Intermediate and chronic exposures of workers 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 trigeminal nerve impairment as measured by blink reflex, but did observe a significant association between years of exposure and masseter reflex, which is another measure of trigeminal nerve function (Ruitjen 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 l-2 hours per 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.

Other reported neurological effects of chronic occupational exposure to unquantified trichloroethylene levels include memory loss (Grandjean et al. 1955; Smith 1966), mood swings (Barr-et et al. 1987; Milby 1968; Rasmussen et al. 1993d), trigeminal neuropathy (Bar-ret et al. 1987; Feldman et al. 1992; Mitchell and Parsons-Smith 1969; Smith 1966), cranial nerve VII 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 a significant effect, including the facial (Feldman et al. 1985), olfactory (Rasmussen et al. 1993a), and acoustic nerves. Interestingly, the study by Rasmussen et al. (1993a) found no significant association between length of exposure and trigeminal nerve effect, although a nonsignificant trend was seen, indicating that the sample size may have simply been too small.

Studies on the neurological effects of acute trichloroethylene inhalation in animals have produced results similar to human studies. In rats, exposures of 8 hours or less 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 per day, 5 days per week for 10 days (Goldberg et al. 1964b). No neurological effects were observed at 1,568 ppm. 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 l l-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).

A study that examined the interaction between exposure concentration and time of exposure on nervous system function found that concentration, rather than time of exposure, was more important in determining effects (Bushnell 1997). Rats were trained to press two levers for food reward; one lever when a light flashed, the second lever produced food when there was no signal. 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.

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). 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 per day 5 days per 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 Fischer-344 rats exposed for 3 weeks to 2,000 ppm and to 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. Fischer-344 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 (Albee et al. 1993). Altered flash evoked potentials were not observed in rats exposed to 250 ppm.

After 10 days of exposure, reduced social behavior and reduced exploratory behavior were observed in rats exposed to 100 ppm trichloroethylene 6 hours per day 5 days per week for a total of 5 weeks (Silverman and Williams 1975). 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 after exposure of 100 ppm (Arito et al. 1994a). Based on the 50-ppm LOAEL identified in the Arito et al. (1994a) study, an intermediate-duration inhalation MRL of 0.1 ppm was calculated as described in the footnote in Table 2-l.

In a study involving 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 &hour exposure to 300 ppm of trichloroethylene, followed by exposure to 1,000 ppm for 8 hours 7 days later (Arito et al. 1994b). 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 per day, 5 days per 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 per day, 5 days per week for 30 days (Goldberg et al. 1964a). Changes in visually evoked potentials (Blain et al. 1992) and electroretinal responses to flash stimulation (Blain et al. 1994) were seen in rabbits exposed to 350 ppm trichloroethylene for 12 weeks (4 days/week, 4 hours/day). The study authors suggested that binding of trichloroethanol to blood proteins may enable it to reach the visual cortex.

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 for 4 days, 6 hours a day, to 200 ppm (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 deoxyribonucleic acid (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 2- 1 and plotted in Figure 2- 1.

2.2.1.5 Reproductive Effects

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.

Mice exposed to 2,000 ppm of trichloroethylene, 4 hours/day for a 5-day period, had a significant increase in abnormal sperm morphology of 1% 28 days after the exposure (Land et al. 1981). No effect was seen at 200 ppm. 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 per 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 these 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 2- 1 and plotted in Figure 2- 1.

2.2.1.6 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 (TCE). This risk increased further when women with less than l/2 hour of exposure to TCE 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 TCE. 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 analyze TCE exposures and most fetal growth would occur after the first 20 weeks of pregnancy.

Pregnant laboratory animals have been exposed to trichloroethylene vapors, but no conclusive studies have been encountered that clearly indicate teratogenic effects. Available data from animals suggest that the conceptus is not uniquely susceptible to trichloroethylene (EPA 1985c). No statistically significant increases in skeletal, visceral, or external malformations have been found in pups of rat dams exposed to 100-500 ppm of trichloroethylene (Beliles et al. 1980; 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 per day on gestation days 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 per day on gestation days 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 2-l or Figure 2-l.

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 2-1 and plotted in Figure 2- 1.

2.2.1.7 Genotoxic Effects

Investigations into the genotoxicity of trichloroethylene in humans have not been conclusive but are suggestive of clastogenic effects. A study of chromosomal aberrations among trichloroethylene-exposed workers detected an increase in hypodiploid cells but found no evidence of chromosomal breaks in lymphocytes (Konietzko et al. 1978). Another study showed an increase in sister chromatid exchange for workers exposed to trichloroethylene (Gu et al. 1981). In a more recent study, men using trichloroethylene as a degreasing agent were tested for lymphocyte chromosomal abnormalities- specifically, breaks, gaps, deletions, inversions, translocations, and hyperdiploidy. The same study also investigated the rate of nondisjunction for the Y chromosome in sperm. Positive results were observed for chromosomal aberrations and hyperdiploid cells, but the results were negative for chromosomal nondisjunction (Rasmussen et al. 1988). The frequency of sister chromatid exchange in the peripheral lymphocytes of trichloroethyleneexposed workers was the focus of another investigation (Seiji et al. 1990). Smokers and nonsmokers were included in this study. The only positive result obtained was for smokers who were also exposed to trichloroethylene. Since smoking itself is known to induce sister chromatid exchange, sister chromatid exchange comparisons were performed among smokers and nonsmokers irrespective of trichloroethylene exposure. This general comparison between smokers and nonsmokers showed no significant differences in the rate of sister chromatid exchange. Therefore, the study authors suggest that smoking and trichloroethylene exposure may act together to produce increased sister chromatid exchange frequencies (Seiji et al. 1990). The study authors point out that other compounds (i.e., toluene and styrene) show synergisms with smoking. This study is limited by a relatively small sample size (26 male and 25 female nonsmokers; 22 male and 16 female smokers). In addition, it was unclear whether exposure to other solvents also occurred. Finally, other researchers have found no significant increase in the rate of sister chromatid exchange among either smoking or nonsmoking workers exposed to trichloroethylene (Nagaya et al. 1989a).

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 tumor induction by trichloroethylene than rats. 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.

Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

Several retrospective cohort studies of workers exposed to unquantified levels of trichloroethylene have been conducted. All of these studies have limitations that restrict their usefulness for evaluating the carcinogenicity of trichloroethylene. None has shown clear, unequivocal, evidence that trichloroethylene exposure is linked to increased cancer risk.

A number of epidemiological studies have been conducted to investigate human exposure to trichloroethylene in the workplace and subsequent tumor development (Axelson 1986; Axelson et al. 1978, 1994; Malek et al. 1979; Shindell and Uhich 1985; Spirtas et al. 1991). These investigators did not find significant increases in incidence of cancer, but some studies were limited by relatively small numbers of subjects, lack of lengthy follow-up periods, and multiple chemical exposure. When all workers (14,457) at an aircraft maintenance facility were studied, significant increases in multiple myeloma in white women (standardized mortality ration [SMR] 236; 95% confidence interval [CI] 87-514), non-Hodgkin’s lymphoma in white women (SMR 2 12; 95% CI 102-390), and cancer of the biliary passages and liver in white men dying after 1980 (SMR 358; 95% CI 116-836) were observed. When only those exposed to trichloroethylene were examined (6,929) no

significant associations between several measures of trichloroethylene exposure and excess cancer risk were observed. For example, based on 4 cases of non-Hodgkin's lymphoma among white women exposed to trichloroethylene, the SMR was 286 with a 95% CI of 78-731. The study authors pointed out that the work histories of persons dying from multiple myeloma or non-Hodgkin's lymphoma indicated that many of the women who developed these diseases worked in fabric handling departments where a substance used to treat fabric ("dope") and solvents were used. The study authors concluded that "no significant or persuasive relationships were found between various measures of exposure to trichloroethylene and the risk of any specific malignancy."

An update of a previous study (Axelson et al. 1978), Axelson (1986) evaluated an expanded cohort of 1,424 men (levels of trichloroethylene exposure inferred from measured urinary metabolite concentrations) and found a significant increase in incidences of bladder cancer and lymphomas, and a lower than expected incidence of total cancer mortality. A further update of this work (Axelson et al. 1994) expanded the cohort to include 249 women, tracking cancer morbidity over 30 years, and found no correlation between exposure concentration or exposure time and cancer incidence at any site. The highest standardized incidence ratio noted in this study was 1.56 (95% CI of 0.51-3.64) for 5 cases of non-Hodgkin's lymphoma observed in men. Although four of these cases occurred in persons exposed for at least 2 years, and 3 cases had a latency of 10 years or more, urinary levels of TCA showed that 4 of the 5 cases were exposed to the lowest levels of trichloroetbylene (urinary levels of TCA 0 - 49 mgL). The study authors mentioned that a urinary TCA level below 50 mg/L corresponds to a trichloroethylene exposure concentration of about 20 ppm. The study authors concluded that "this study provides no evidence that trichloroethylene is a human carcinogen, i.e., when the exposure is as low as for this study population."

In contrast, three European studies have found slight but statistically significant increases in cancer in workers exposed to trichloroethylene. A survey of Finnish workers exposed to primarily trichloroethylene found an association of limited statistical significance between exposure and incidence of stomach, liver, prostate, and lymphohematopoietic cancers (Antilla et al. 1995). However, the study did not reliably separate the effects of individual solvents, so attributing these cancers to trichloroethylene exposure alone was not possible. A significant association between workplace exposure to trichloroethylene and kidney cancer was found in a retrospective cohort study of German cardboard factory workers (Henschler et al. 1995). The

association was based on five cases of kidney cancer among 169 workers who had been exposed to trichloroethylene for at least 1 year (mean exposure period = 17.8 years) between 1956 and 1975, relative to no cases among the unexposed control group. Exposure levels were not provided in this study. In a study of Swedish workers, a statistically significant increase in non-Hodgkin's lymphoma was observed (Hardell et al. 1994). This study utilized univariate analysis of 105 confirmed cases of non-Hodgkin's lymphoma and found an increased risk of non-Hodgkin's lymphoma associated with occupational exposure to trichloroethylene. These workers were exposed to solvents in addition to trichloroethylene, and exposures were self-reported. A study of dry cleaners found a significant increase in the incidence of all malignant neoplasms combined as well as increased incidences of cancer at several sites (lung/bronchus/trachea, cervix, and skin) (Blair et al. 1979). Exposure to trichloroethylene, however, was not well documented; evidence indicates that exposures were primarily to tetrachloroethylene and other dry-cleaning chemicals (e.g., carbon tetrachloride, petroleum solvents). Thus, the human studies that did show increases in cancer are limited by uncertainties in the exposure data, small sample sizes, and likely exposure to other chemicals. In other studies, associations between liver cancer (Novotna et al. 1979; Paddle 1983) and trichloroethylene exposure have not been observed.

Some laboratory studies with rats and mice have linked trichloroethylene exposure to various types of cancers. Several of these studies, however, should be viewed cautiously, since the tumorigenic activity might be influenced by the presence of direct-acting compounds, namely the epoxides (e.g., epichlorohydrin) added as stabilizers in trichloroethylene. Epoxides are known to be very reactive, and some, such as epichlorohydrin, are potent carcinogens themselves.

Increased incidence of hepatomas (specific type of neoplasm not specified) occurred in male Swiss mice and in $B6C3F_1$ 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 (Maltoni et al. 1986, 1988). In a retest with male $B6C3F_1$ mice, a decrease in leukemias was seen, 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 $B6C3F_1$ mice but not among the males. Incidences were significantly increased over controls at 600 ppm for lung tumors in the female $B6C3F_1$ mice and at 600 ppm for liver tumors in both sexes of $B6C3F_1$ mice. The incidence data

for lung tumors in female Swiss mice together with other tumor incidence data from other studies were used by EPA (1987a) to derive a carcinogenic potency estimate; a classification of B2 (probable human carcinogen) was assigned to trichloroethylene. In 1988, EPA's Scientific Advisory Board offered an opinion that the weight of evidence was on a C-B2 continuum (possible-probable human carcinogen). The agency has not restated a more current position on the weight-of-evidence classification and is reflecting this by posting an "under review" status in the Integrated Risk Information System (IRIS) (IRIS 1996).

In male Sprague-Dawley rats, there was a dose-related increase in testicular Leydig cell tumors and a slight increase in tubular renal adenocarcinoma at the 600-ppm exposure level after exposure for 104 weeks (Maltoni et al. 1986, 1988). EPA and other groups regard such increases as indicative of a hazard potential unless there are reasons to rule this out. However, other authorities believe testicular tumors are common in rats that are not exposed to toxic substances.

There are several problems in interpreting these studies. First, males and females responded differently; in some cases, the females were more sensitive, but in others, the males were more sensitive. In addition, there were lung and liver tumors in mice but not rats. An inconsistency was also observed in the two different studies with $B6C3F_1$ male mice. In one study, an increase in hepatomas was reported, whereas no significant increase was seen in the other. In addition, an inconsistent dose-response was observed, i.e., an increase in liver tumors at high levels, and a decrease compared to control levels at the low dose. Other problems were found in the study methodology: use of an unconventional technique of holding the animals until spontaneous death, use of an unorthodox method of reporting results (percentage of animals with tumors reported, but not the number of surviving animals), a lack of appropriate pathological data on the types of tumors observed, and a lack of a complete report on methodology. Finally, inadequate laboratory operation procedures were used; there was a lack of independent pathology reviewers; and the use of Good Laboratory Practices was not confirmed.

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. The amount of epichlorohydrin (approximately 0.019%) was extremely low in this

study. It should be recognized that some types of cells in the lung have the ability to metabolize trichloroethylene and that metabolic activation *in situ* may be responsible for the pulmonary injury and carcinogenicity seen following inhalation exposure (Bruckner et al. 1989).

Two other inhalation carcinogenicity studies were negative. Newborn rats were exposed to 2,000 ppm trichloroethylene for 10 weeks, but examination of the liver showed no signs of ATPase-deficient foci (Laib et al. 1979). This apparent preneoplastic change was seen in the liver of rats similarly exposed to vinyl chloride, a known hepatocarcinogen. NMRI mice, Wistar rats, and Syrian hamsters of both sexes were exposed to 100 or 500 ppm of trichloroethylene for 18 months (Henschler et al. 1980). The only statistically significant effect was an increase in the incidence and rate of development of malignant lymphomas in female mice over controls. 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 cancer effect levels (CELs) in Table 2- 1 and Figure 2- 1.

2.2.2 Oral Exposure

2.2.2.1 Death

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

Acute oral LD_{50}s 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 gestation days 6-152 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 (Met-rick et al. 1989). Further

explanation of these study results is included in Section 2.2.2.2, 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 2.2.2.8. LD_{50} values and the lowest doses causing death in rats and mice are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 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 2-2 and plotted in Figure 2-2.

Respiratory Effects. 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 Wobum, Massachusetts, were found to contain several solvents including trichloroethylene (267 ppb) and 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 2.2.2.8.

Rales and dyspnea were observed in pregnant rats treated by gavage with 1,500 mg/kg/day trichloroethylene in corn oil on gestation days 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.

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	Gd 6-15 (GO)				1125 F (2/13 died)	Narotsky et al. 1995
2	Rat (NS)	once (G)				7208 (LD_{50})	Smyth et al. 1969
3	Mouse (CD-1)	once (G)				2443 F (LD_{50}) 2402 M (LD_{50})	Tucker et al. 1982
Systemic							
4	Rat (Fischer-344)	14 d (GO)	Hepatic	500 F	1500 F (increased relative liver weights, hepatocellular hypertrophy)		Berman et al. 1995
			Renal		50 F (increased relative kidney weights)		
			Endocr	1500 F			

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
5	Rat (Wistar)	10 d 1 x/d (GO)	Hepatic	2000M			Elcombe 1985
6	Rat (Fischer-344)	10 d 1 x/d (GO)	Hepatic		1000M (122% increased liver weight, 180% increased palmitoyl CoA oxidation activity)		Goldsworthy and Popp 1987
			Renal	1000M			
			Bd Wt	1000M			
7	Rat (Fischer-344)	10 d 1 x/d (GO)	Renal	1000			Goldsworthy et al. 1988
8	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)	
9	Rat (Sprague-Dawley)	Gd 6-15 (GO)	Bd Wt			475 F (body weight gain 31% lower than controls)	Narotsky et al. 1995

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
10	Rat (Osborne-Mendel)	3 d 1 x/d (GO)	Hepatic	1100M			Stott et al. 1982
			Renal	1100M			
11	Mouse (Swiss-Webster)	10 d 1 x/d (GO)	Hepatic	50M	100M (200% increase in palmitoyl CoA oxidation)		Elcombe 1985
12	Mouse (B6C3F1)	10 d 1 x/d (GO)	Hepatic		1000M (150% increased liver weight, 625% increased palmitoyl CoA oxidation activity)		Goldsworthy and Popp 1987
			Renal	1000M			
			Bd Wt	1000M			
13	Mouse (B6C3F1)	3 d 1 x/d (GO)	Hepatic		2400M (hepatic hypertrophy, centrilobular swelling)		Stott et al. 1982
			Renal	2400M			

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
14	Mouse (CD-1)	14 d 1 x/d (G)	Hemato	240M			Tucker et al. 1982
			Hepatic	240M			
			Renal	240M			
			Bd Wt	240M			
Neurological							
15	Rat (Fischer-344)	14 d (GO)		150 F	500 F (increased rearing)		Moser et al. 1995
16	Rat (Sprague-Dawley)	Gd 6-15 (GO)		475 F		633 F (transient ataxia)	Narotsky et al. 1995
Developmental							
17	Rat (Sprague-Dawley)	Gd 6-15 (GO)		844		1125 (increased prenatal loss, micro- or anophthalmia)	Narotsky et al. 1995
18	Mouse (B6D2F1)	Gd 1-5 Gd 6-10 Gd 1-15 1 x/d (GO)		240			Cosby and Dukelow 1992

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
19	Mouse (NMRI)	7 d 1 x/d (GO)			50[b] M (reduced rearing rate at 60 days of age)		Fredriksson et al. 1993
INTERMEDIATE EXPOSURE							
Death							
20	Rat (Osborne-Mendel)	6 wk 5 d/wk 1 x/d (GO)				5620 (10/10 died)	NCI 1976
21	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
22	Mouse (B6C3F1)	6 wk 5 d/wk 1 x/d (GO)				5620 M (4/5 deaths) 3160 F (2/5 deaths)	NCI 1976
23	Mouse (B6C3F1)	13 wk 5 d/wk 1 x/d (GO)				1500 M (2/10 died) 3000 F (1/10 died)	NTP 1990

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Systemic							
24	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	2000M			
			Gastro	2000M			
			Musc/skel	2000M			
			Hepatic	2000M			
			Renal		1000 F (minimal or mild cytomegaly, karyomegaly of renal tubular epithelial cells in 5/10)		
			Endocr	2000M			
			Derm	2000M			
			Bd Wt	1000M		2000 M (body weights 24% less than controls)	
25	Rat (Osborne-Mendel)	3 wk 5 d/wk 1 x/d (GO)	Hepatic	1100M			Stott et al. 1982
			Renal	1100M			
			Bd Wt	1100M			
26	Mouse (Swiss-Cox)	6 wk 5 d/wk 1 x/d (GO)	Hepatic	100M	400M (enlarged hepatocytes)	1600 M (central lobular necrosis)	Buben and O'Flaherty 1985
			Bd Wt	3200			

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
27	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	2400M			
28	Mouse (B6C3F1)	3 wk 5 d/wk 1 x/d (GO)	Hepatic	250M	500M (liver enlargement, increased DNA content per gram tissue)	1200 M (liver enlargement, increased DNA content, centrilobular hepatocyte swelling)	Stott et al. 1982
			Renal	2400M			
			Bd Wt	2400M			
29	Mouse (CD-1)	6 mo ad libitum (W)	Gastro	18 M 793 F	217M (gas pockets in the intestinal coating, blood in the intestines in 5)		Tucker et al. 1982
			Hemato	393 M 793 F	660M (red blood cell counts 16% lower than controls)		
			Hepatic	793 F			
			Renal	217 M 437 F	393 M (elevated urinary 793 F protein and ketones)		
			Bd Wt	393M	660M (body weights 11% lower than controls, associated with decreased water intake)		

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Immunological/Lymphoreticular							
30	Mouse (CD-1)	4 or 6 mo ad libitum (W)		200 F	400 F (suppressed humoral and cellular response)		Sanders et al. 1982
Neurological							
31	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
32	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
Reproductive							
33	Rat (Fischer-344)	18 wk ad libidum (F)		300			NTP 1986

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
34	Rat (Long-Evans)	6 wk 5 d/wk 1 x/d (GO)		100M		1000 M (impaired copulatory behavior, mount/ ejaculation latency, intromissions)	Zenick et al. 1984
35	Mouse (CD-1)	17 wk ad libitum (F)		375M 750 F	750M (18-45% decreased sperm motility)		NTP 1985
Developmental							
36	Rat (Sprague-Dawley)	3 mo before Gd 0-21 ad libitum (W)				0.18 (5% increased fetal heart abnormalities)	Dawson et al. 1993
37	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

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)		Reference
38	Rat (Long-Evans)	2 wk 5 d/wk Gd 0-21 7 d/wk (GO)		100		1000	(decreased neonatal survival)	Manson et al. 1984
39	Rat (Fischer-344)	18 wk ad libidum (F)		300				NTP 1986
40	Rat (Sprague-Dawley)	14 d before mating Gd 0-21 -weaning ad libitum (W)			37M (increased exploratory behavior)			Taylor et al. 1985
41	Mouse (CD-1)	17 wk ad libitum (F)		375M		750	(increased perinatal mortality)	NTP 1985

CHRONIC EXPOSURE

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Death							
42	Rat (Osborne-Mendel)	78 wk 5 d/wk 1 x/d (GO)				1097 M (47/50 died) 549 F (35/48 died)	NCI 1976
43	Rat (Fischer-344)	103 wk 5 d/wk 1 x/d (GO)				500 M (30/50 died) 500 F (17/50 died)	NTP 1990
44	Mouse (B6C3F1)	78 wk 5 d/wk 1 x/d (GO)				869 F (8/50 died)	NCI 1976
45	Mouse (B6C3F1)	103 wk 5 d/wk 1 x/d (GO)				1000 M (34/50 died)	NTP 1990

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Systemic							
46	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	50M	250M		
			Endocr	250			
			Derm	250			
			Ocular	250			
			Bd Wt	250			

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
47	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			
			Derm		549 (alopecia, roughening of hair coat, sores)		
			Ocular		549 (squinting, red discharge)		
			Bd Wt	549M	1097M (body weights 18% lower than controls at 78 weeks)		
					549 F (body weights 15% lower than controls at 78 weeks)		

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
48	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			
			Derm	1000			
			Ocular	1000			
			Bd Wt		500M (body weights 11% lower than controls)		
49	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			
			Derm	1000			
			Ocular	1000			
			Bd Wt	500M	1000M (body weights 11.6% lower than controls)		

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
50	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			
			Derm	1000			
			Ocular	1000			
			Bd Wt	500M	1000M (body weights 12.3% lower than controls)		
51	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			
			Derm	1000			
			Ocular	1000			
			Bd Wt	500 F	1000 F (body weights 10.1% lower than controls)		

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
52	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			
			Derm	1000			
			Bd Wt	500M	1000M (body weights 13% lower than controls) 500 F (body weights 12% lower than controls)		
53	Mouse (B6C3F1)	78 wk 5 d/wk 1 x/d (GO)	Resp	2239M			NCI 1976
			Cardio	2239M			
			Gastro	2339M			
			Musc/skel	2239M			
			Hepatic	2239M			
			Renal		1160 M (toxic nephrosis) 869 F		
			Endocr	2239M			
			Derm		869 F (alopecia, skin sores)		
			Ocular	2239M			
			Bd Wt	2239M			

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

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
54	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			
			Derm	1000			
			Bd Wt		1000 M (body weights 10% lower than controls)		
Cancer							
55	Rat (Fischer-344)	103 wk 5 d/wk 1 x/d (GO)				1000 M (CEL: renal tubular cell adenocarcinomas)	NTP 1990
56	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 2-2. Differences in levels of health effects and cancer effects between males and femalse are not indicated in Figure 2-2. Where such differences exist, only the levels for the most sensitive gender are presented.

[b]Used to derive an acute-duration oral Minimal Risk Level (MRL) of 0.2 mg/kg/day for trichloroethylene; 50 mg/kg/day divided by an uncertainty factor of 300 (10 for using a LOAEL, 10 for extrapolation from animals to humans, and 3 for human variability, to account for differences in metabolism, and considering pups as a sensitive subpopulation) .

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; CoA = coenzyme A; d = day(s); Derm = dermal; DNA = deoxyribonucleic acid; Endocr = endocrine; F = female; (F) = food; Gastro = gastrointestinal; (G) = gavage (type unspecified); Gd = gestation day(s); (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; LD_{50} = lethal dose, 50% kill; M = male; mo = months; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s)

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

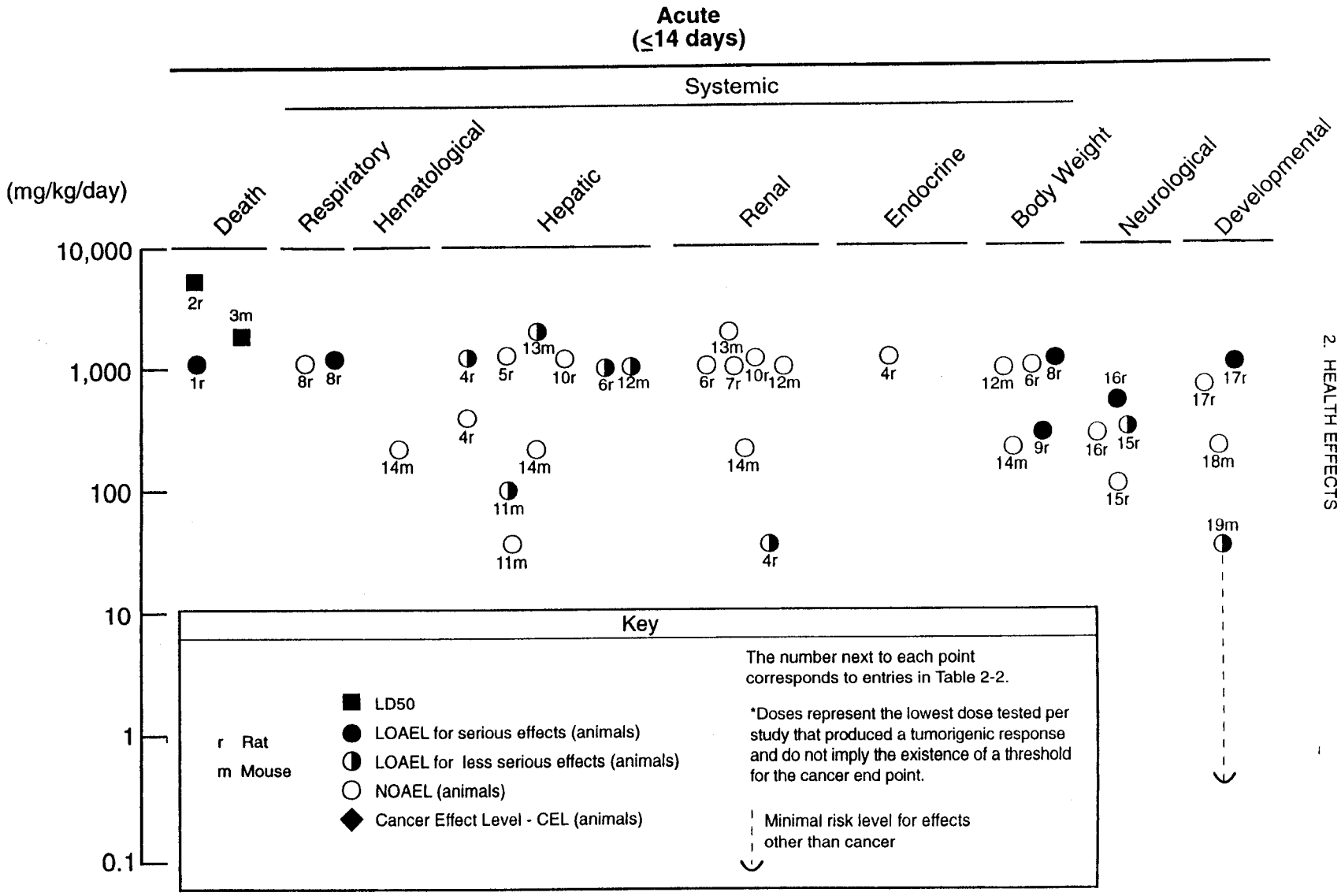


Figure 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

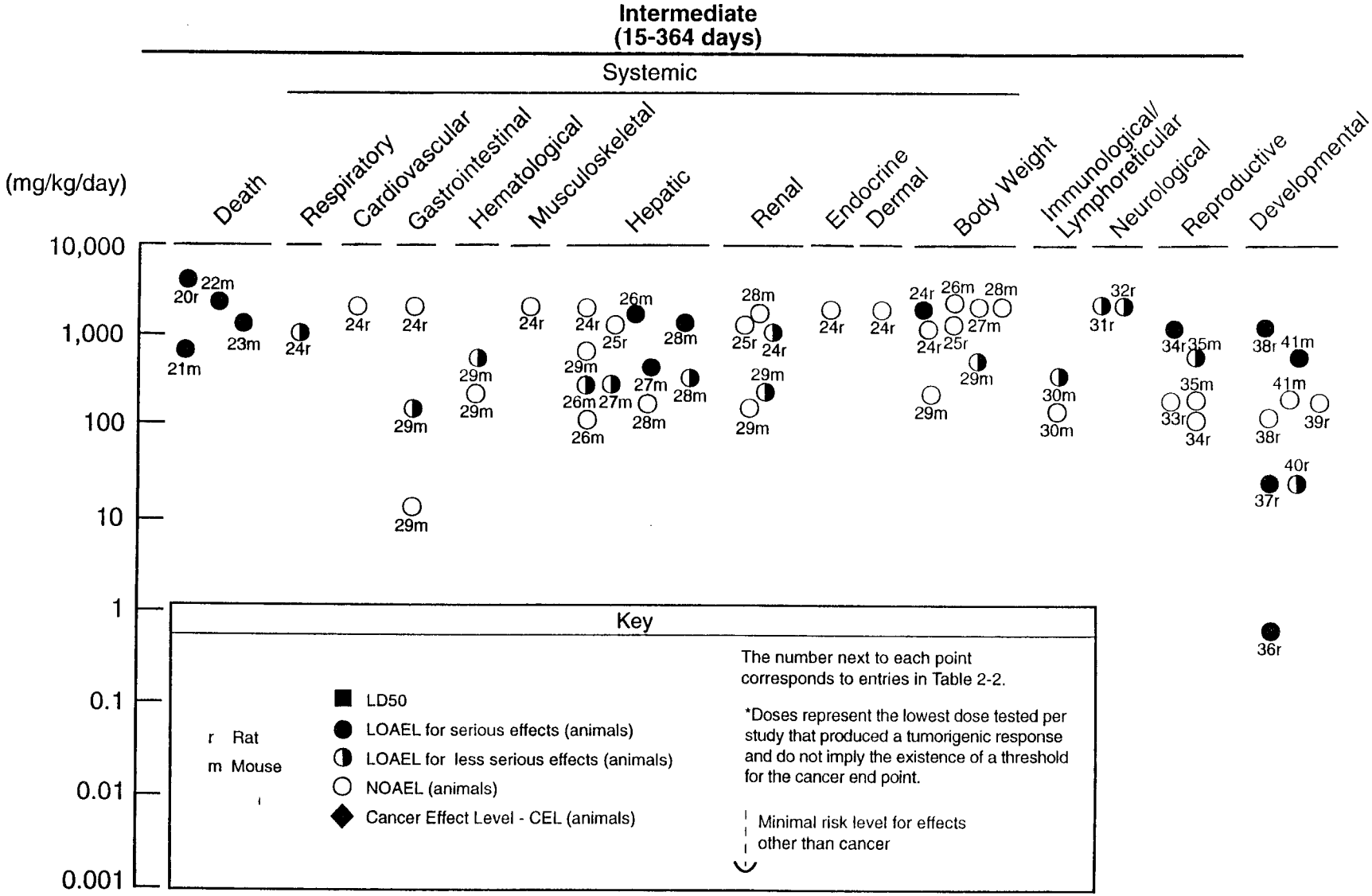


Figure 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

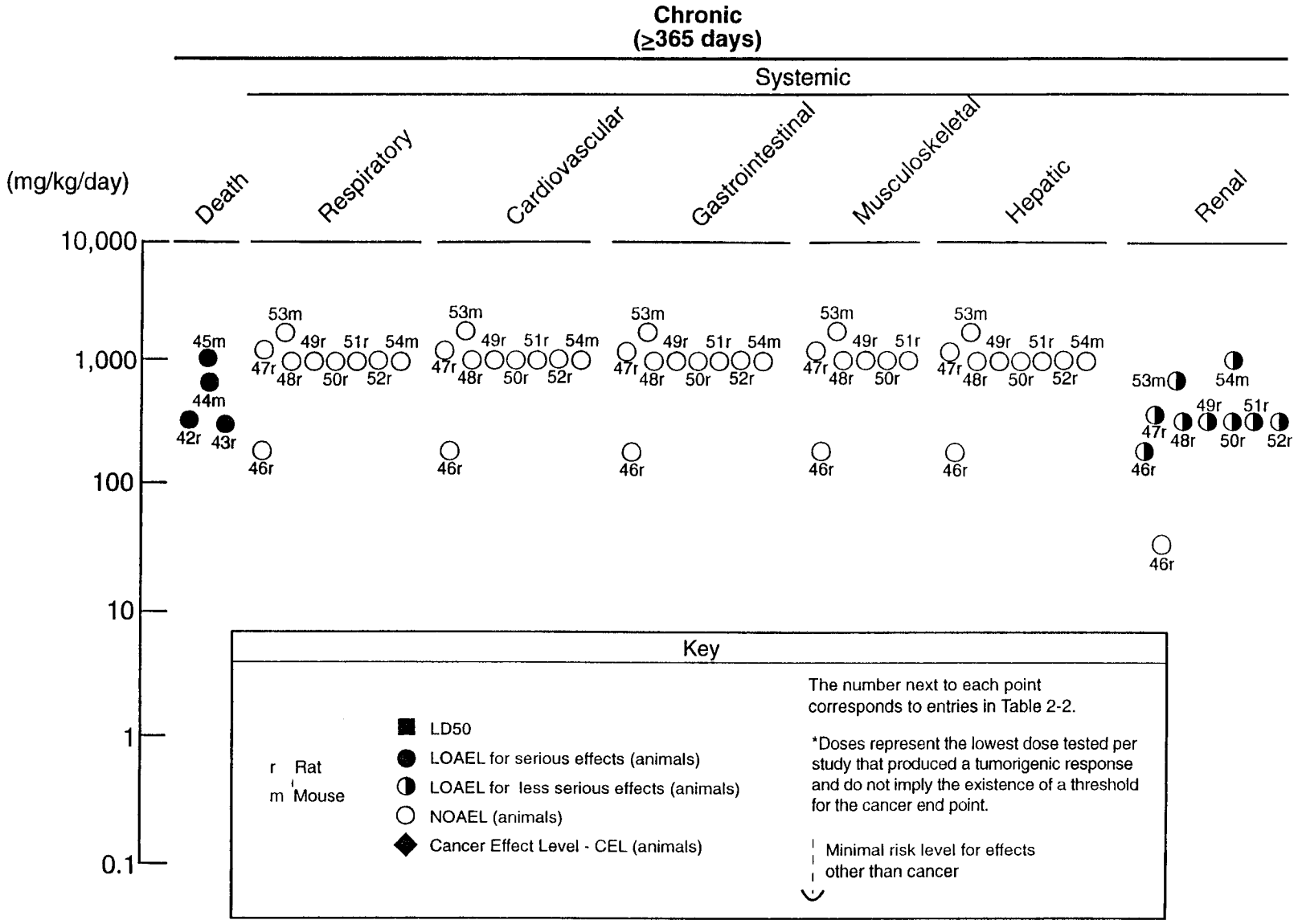
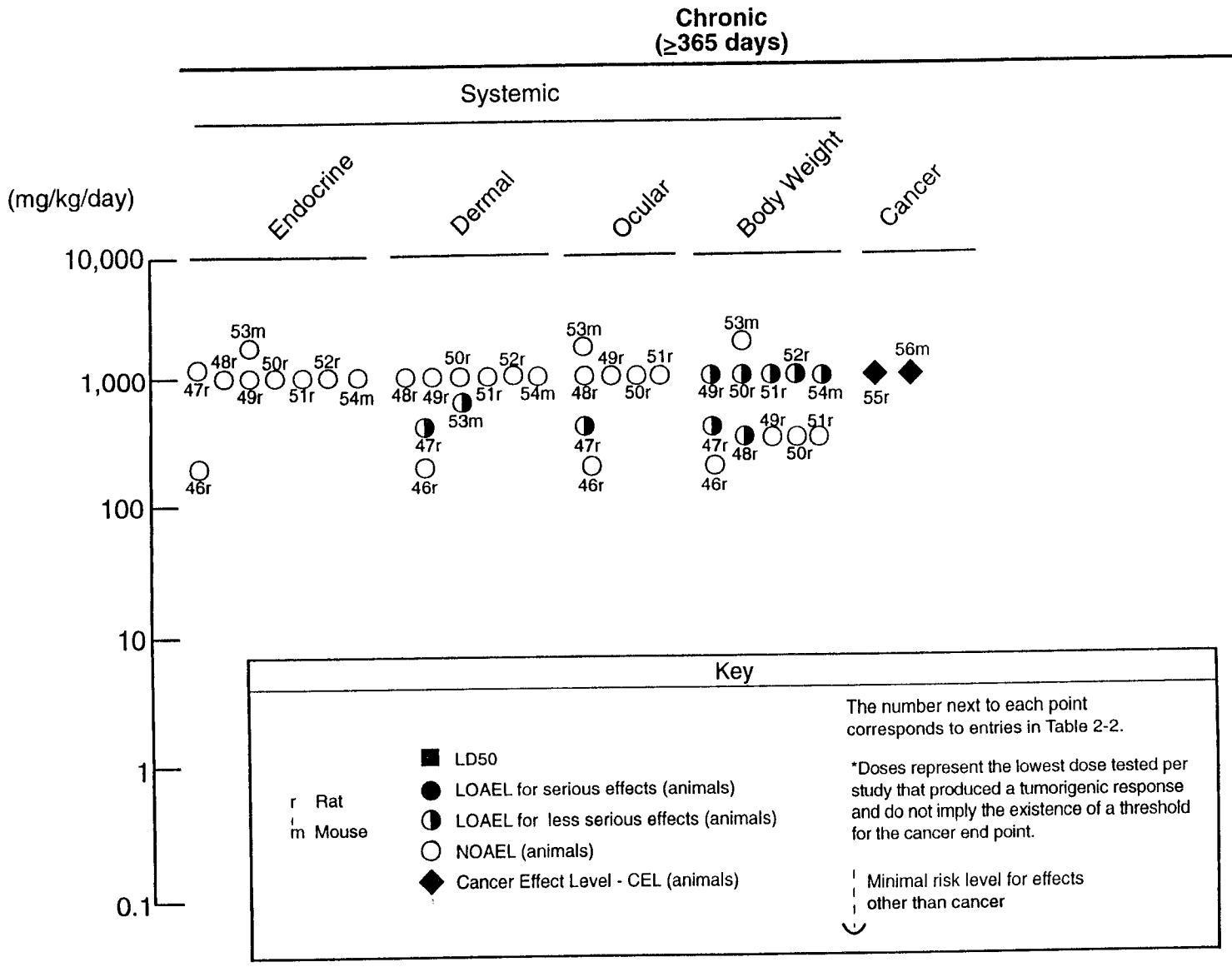


Figure 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)



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 a women who drank an unknown amount of trichloroethylene (Perbellini et al. 1991).

Cardiovascular effects of trichloroethylene were investigated in families from Wobum, Massachusetts, that included at least one child with leukemia (Byers et al. 1988). Medical and laboratory tests were conducted on 25 family members. There were 14 surviving parents, all of whom 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 2.2.2.8. Excesses of anemia, stroke, blood disorders, and death from heart disease were reported in the ATSDR subregistry of persons environmentally exposed to trichloroethylene (ATSDR 1994; Burg et al. 1995). However, the data were gathered by questionnaire and may be limited by reporting bias.

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. 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 2.2.2.8. Self-reported gastrointestinal problems were not increased among persons in the trichloroethylene subregistry who were exposed to trichloroethylene in their drinking water (ATSDR 1994; Burg et al. 1995).

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 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 a 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 2.2.1.2).

Histopathological changes in the gastrointestinal tract have not been observed in intermediate- or chronic-duration studies in which rats and mice were treated by gavage to 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 mgLkg/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. The trichloroethylene subregistry, which has compiled information on 4,280 people exposed to trichloroethylene through their drinking water, found significantly increased incidences of anemia in selected age groups when compared with corresponding national data (ATSDR 1994; Burg et al. 1995). The excess rates did not show a pattern with respect to age or sex. Therefore, no conclusion regarding the association between trichloroethylene and hematological effects can be drawn from this study.

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).

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. No 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). Self-reported liver problems were not increased among persons in the trichloroethylene subregistry who were exposed to trichloroethylene in their drinking water (ATSDR 1994; Burg et al. 1995).

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 (Stott et al. 1982). Liver effects were not observed in rats treated with three daily gavage doses of 1,100 mg/kg trichloroethylene in corn oil (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 (Elcombe 1985). Significant dose-related effects on peroxisomal β-oxidation activity were not observed in rats treated for 10 days by gavage with trichloroethylene in corn oil at doses up to 2,000 mg/kg/day (Elcombe 1985). A second lo-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 p-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 (Dees and Travis 1993). The study authors suggest that trichloroethylene induces mitosis and DNA proliferation in mature hepatocytes.

Several studies did show 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 glutamic-pyruvic transaminase (SGPT) 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. Liver effects were not observed in rats treated by gavage with trichloroethylene in corn oil at 1,100 mg/kg/day for 3 weeks (Stott et

al. 1982). 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). 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).

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 793 mg/kg/day) for 6 months, showed no treatment-related effects other than increased liver weights without accompanying macroscopic lesions (Tucker et al. 1982). This may be indicative of differences in absorption efficiencies of the lipophilic trichloroethylene administered in water versus oil.

In contrast to mice, 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). 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). Except for enlarged livers, liver effects were not reported in mice treated by gavage with trichloroethylene in corn oil for 18 months at a dose of 1,978 mg/kg/day for males and 1,483 mg/kg/day for females (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).

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 is available that 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, three communities in Michigan that were exposed to trichloroethylene and other solvents in drinking water had no increase in kidney disease (Freni and Bloomer 1988).

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 pahnitoyl 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-2_u-globulin in the kidneys of male rats when 1,000 mg/kg/day trichloroethylene was similarly administered to male and female Fischer-344 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). Increased kidney weights, but no histopathological changes were observed in rats treated by gavage with 1,500 but not 500 mg/kg/day trichloroethylene in corn oil (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 Osbome-Mendel rats (approximately 550-1,100 mg/kg/day) and B6C3F_1 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 AC1 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 2.2.2.8.

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to trichloroethylene.

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; NIT 1988, 1990).

Dermal Effects. Some of the people in Wobum, 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 24 weeks. These skin conditions generally ceased l-2 years after cessation of exposure to contaminated water. The limitations of this study are discussed in Section 2.2.2.8. 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 fascitis, 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 improved symptoms.

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 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 trichlorethylene.

Squinting and a red discharge from the eyes were reported with increasing frequency in rats treated by gavage with trichloroethylene in corn oil at time-weighted average 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 chronicduration 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. No effects on body weight were observed in rats or mice treated by gavage with trichloroethylene in corn oil at a dose of 1,000 mg/kg/day for 10 days (Goldsworthy and Popp 1987). In pregnant rats treated by gavage with trichloroethylene in corn oil, body weight gain was 45% lower than controls in rats treated with 1,125 mg/kg/day on gestation days 6-19 (Narotsky and Kavlock 1995) and 31% lower than controls in rats treated with 475 mg/kg/day on gestation days 6-15 (Narotsky et al. 1995).

Body weight effects were not observed in mice treated with trichloroethylene by gavage at a dose of 240 mg/kg/day for 14 days or in drinking water at a dose of 660 mg/kg/day for 6 months (Tucker et al. 1982). Body weight effects were also not observed in mice following gavage treatment at a dose of 2,400 mg/kg/day for 3 (Stott et al. 1982) or 4 weeks (Merrick et al. 1989) or a dose of 3,200 mg/kg/day for 6 weeks (Buben and O'Flaherty 1985). No effect on body weight was observed in rats treated by gavage with a dose of 1,100 mg/kg/day for 3 weeks (Stott et al. 1982) or a dose of 1,000 mg/kg/day for 13 weeks (NTP 1990). Body weights were 24% less than controls in rats treated by gavage with trichloroethylene in corn oil at a dose of 2,000 mg/kg/day for 13 weeks (NTP 1990).

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 tricbloroethylene 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).

2.2.2.3 Immunological and Lymphoreticular Effects

Immunological abnormalities were reported in 23 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 2.2.2.8. 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 (arthritis, Raynaud's phenomenon, malar rash, skin lesions related to sun exposure, seizure or convulsions) of which were statistically significant (Kilbum and Warshaw 1992). Diffuse fascitis 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).

The immunotoxic effects of trichloroethylene were evaluated in CD- 1 mice following sensitization to sheep red blood cells during exposure to trichloroemylene for 14 days by gavage (at 24 or 240 mg/kg) or for 4 and 6 months in drinking water (at doses of 18-800 mg/kg) (Sanders et al. 1982). The parameters assessed included humoral and cell-mediated immunity, lymphocyte responsiveness to mitogens, bone marrow function, and macrophage function. A significant inhibition of cell-mediated immunity of males exposed via gavage was noted, while the antibody-mediated immune response remained similar to vehicle-treated controls; no females were involved in this phase of the study. In the drinking water study, observed effects

included depression of delayed type hypersensitivity in males (67% depression at the high dose of 660 mg/kg). Antibody-mediated immunity was significantly inhibited in females only, and significant only at 400 and 700 mg/kg, in a dose-response fashion. Overall, females were seen to be more sensitive. The effects seen were consistent with effects of other chlorinated hydrocarbons on the immune system. 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 investigators concluded that, although the effects observed were not remarkable, the immune system does appear to be sensitive to the chemical. The NOAEL and LOAEL for immunological effects in mice identified in the Sanders et al. (1982) study are recorded in Table 2-2 and plotted in Figure 2-2.

Histopathological changes in the spleen and thymus have not been 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).

2.2.2.4 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).

The epidemiological studies of the people exposed to trichloroethylene, as well as other chemicals, from well water in Wobum, Massachusetts, did not reveal neurological complaints (study limitations described in Section 2.2.2.8) (Byers et al. 1988; Lagakos et al. 1986a). Some of the people from this population did show 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). However, this study is limited by 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, POMS), 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 (Kilburn and Warshaw 1993). However, 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 exposure subregistry, a statistically significant increase in impairment of hearing was reported in children age 9 years or younger (ATSDR 1994; Burg et al. 1995). The relative risk in this group was 2.13 with a 95% confidence interval of 1.12-4.06. The study authors caution that their study does not identify a causal relationship between trichloroethylene and effects but does suggest areas for further research.

In animal studies, signs of neurotoxicity and neuropathology have been observed in response to oral doses of trichloroethylene. 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 gestation days 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 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). The rats were exposed to a dose of approximately 23.3 mg/kg/day.

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 (Bat-ret 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 2-2 and plotted in Figure 2-2.

2.2.2.5 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). In three communities in Michigan exposed to trichloroethylene and other solvents in drinking water, there was no increase in adverse pregnancy outcomes (Freni and Bloomer 1988).

A continuous breeding fertility study was conducted in which male and female Fischer-344 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 F_2 generation (NTP 1986). There was an increase in the relative left testis/epididymis weight in the F_0, generation and a decrease in absolute left testis/epididymis weight in the F_1 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-l 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 F_0 or F_1 mice, but sperm motility was reduced by 45% in F_0 males and 18% in F_1 males.

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.

Behavioral effects were noted when reproductive function was assessed in male Long-Evans rats that were given trichloroethylene in corn oil by gavage for 6 weeks (Zenick et al. 1984). Copulatory behavior was decreased at 1,000 ppm, and the study authors attributed this to the narcotic properties of trichloroethylene. Sperm count, motility, or morphology were not affected in these rats. The time between dosing and observation of copulatory behavior was not stated.

Histopathological changes in reproductive organs have not been 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 time-weighted average 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 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

There is some evidence that exposure to trichloroethylene in drinking water may cause certain types of birth defects. However, this body of research is still far from conclusive and there is insufficient evidence to determine whether or not there is an association between exposure to TCE and developmental effects. Two recent studies reported an association between exposure to TCE and neural tube defects and oral clefts. 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) found an association between trichloroethylene levels of >10 ppb and oral clefts, central nervous system defects, neural tube defects, and major cardiac defects (Bove et al. 1995). Uncertainty regarding exposure classification and small numbers of cases were the main limitations of this study. In a study of residents exposed to drinking water contaminated with solvents (including 267 ppb trichloroethylene) in Wobum, 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 2.2.2.8.

Additional studies of the Wobum population have been completed (MDPH 1994). The final report indicated that there was an increased prevalence in choanal atresia, a rare respiratory effect, and hypospadias/congenital chordee. A small increase in eye defects was observed, but there was no association between TCE exposure and heart defects. There was no statistically significant associations between exposure concentrations and birth defects, although analyses was limited by the small number of cases observed. Based on four cases in the Wobum population, a rate of 0.88 was observed in the exposed population, compared to rates of 0.11 and 0.13 in the Atlanta and California comparison populations, respectively. In a prospective study completed after well closure, the rate of choanal atresia was 0.88 (based on 1 case) in Wobum, 0.11 in the surrounding communities, and 0.2 and 0.13 in Atlanta and California, respectively. 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.

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 TCE contaminated water during the first trimester of pregnancy, the rate of congenital heart defects was approximately 2 l/2 times higher than among children of mothers who were not exposed to TCE 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. The mosi: significant limitation of this report is that the exposure was ill-defined. Exposures for individuals was not quantifiable, the areas that received TCE-contaminated water were not clearly delineated, the first year of exposure was unknown, the amount of TCE 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, although concentrations of TCE were highest.

Among persons in the ATSDR exposure subregistry, a statistically significant increase in impairment of hearing was reported in children age 9 years or younger (ATSDR 1994; Burg et al. 1995). The relative risk in this group was 2.13 with a 95% confidence interval of 1.12-4.06. Because the time of onset for hearing loss is not available, it is not known if this effect may be a result of *in utero* exposure or exposure after birth. The study authors caution that their study does not identify a causal relationship between trichloroethylene and effects but does suggest areas for further research.

Both Bove et al. (1995) and MDPH (1994) examined effects of trichloroethylene exposure on fetal birth weights. Neither study saw a conclusive effect on birth weight, although birth weights did tend to be lower in exposed infants compared to controls in the MDPH (1994) study. A small effect on birth weight in male infants was noted in preliminary findings in an interim report on adverse birth outcomes for a population (n=31) living at Camp LeJeune, North Carolina (ATSDR 1997). The women were exposed some time during gestation. The study authors cautioned that the small group size weakens the causal association. Further analyses are ongoing.

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, making statistically significant associations more difficult to identify.

Studies in animals indicate that trichloroethylene can act as a developmental toxicant, especially at doses also resulting 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 gestation days 6-19 in Fischer-344 rats (Narotsky and Kavlock 1995) or gestation days 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 l%, 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 (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 B6C3F_1mice treated by gavage with 240 mg/kg/day trichloroethylene in corn oil on gestation days l-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 F_1offspring of CD-l mice exposed to 750 mg/kg/day from conception through weaning (NIT 1986). Decreased maternal body weight gain and reduced fetal body weights were also observed, but there were no skeletal or visceral anomalies. Fischer-344 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).

In rats, 1,000 mg/kg/day trichloroethylene by gavage in corn oil increased several indicators of maternal toxicity and caused significant fetal mortality and decreased fetal body weight, but no significant teratogenic effects (Manson et al. 1984). Dawson et al. (1993) exposed groups of 9-39 female rats to trichloroethylene in drinking water (1.5 or 1,100 ppm) either before pregnancy (for 3 months prior to mating), before and during pregnancy (2 months prior plus 21 days into gestation), or during pregnancy only (21-day gestation). 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% in controls; 8.2% at 0.18 mg/kg/day; 9.2% at 132 mg/kg/day). This was based on examination of 2,037 hearts from litters of l-20 live fetuses (Johnson 1996). In dams exposed only during pregnancy, fetal heart defects were observed only at the higher dose (10.4% versus 3% in controls). While it is not known whether these effects were caused by trichloroethylene or its metabolites, the results provide qualitative support for human epidemiological studies that have found

higher incidences of congenital heart defects in children born to mothers exposed during pregnancy to trichloroethylene and dichloroethylene in drinking water (Goldberg et al. 1990). The study is limited in that only two widely spaced exposure concentrations were used and that a significant dose-response was not observed for several exposure scenarios.

Developmental neurotoxicity has been studied in very young animals exposed to trichloroethylene. 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 (Fredriksson et al. 1993). This study suggests that trichloroethylene affects brain maturation. Based on the 50-mg/kg/day LOAEL identified in the Fredriksson et al. (1993) study, an acute-duration oral MRL, of 0.2 mg/kg/day was calculated as described in the footnote in Table 2-2.

Open-field activity, a parameter in which hippocampal involvement has been implicated, was evaluated in 21- and 45-day-old F_1 rats that had been continuously exposed to trichloroethylene, *in utero* and throughout lactation via maternal dietary exposure (microcapsules), at doses ranging from approximately 75 to 300 mg/kg/day (NTP 1986). There was a significant dose-related trend toward an increase in the time required for grid traversal in the 21-day-old pups, but effects on other measures of open-field locomotor activity or miscellaneous behavior were not observed. Evaluation at 45 days was unremarkable, suggesting that trichloroethylene had a transient effect. Therefore, the 300-mg/kg/day dose is considered a NOAEL for this study. However, another series of studies has been completed in which female rats were exposed to trichloroethylene in drinking water for 14 days before mating, throughout gestation to weaning. Morphological (Isaacson and Taylor 1989), and functional neurological (Noland-Gerbec et al. 1986; Taylor et al. 1985) effects were assessed in the offspring. A 40% decrease in the number of myelinated fibers was observed in 21 -day-old offspring of rats provided with 312 mg/L trichloroethylene (about 37 mg/kg/day) (Isaacson and Taylor 1989). The magnitude of the effect was similar at the higher concentration (625 mg/L, 75 mg/kg/day). A decrease in myelinated fibers is considered a serious LOAEL. Glucose uptake by the brains 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 completed in 60-day-old rats showed increases in the offspring of rats provided with 312 mg/L trichloroethylene (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 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to trichloroethylene.

The data regarding the genotoxicity of trichloroethylene in animals are conflicting with both positive and negative results reported. One study reported that both male $B6C3F_1$ mice and Sprague-Dawley rats exhibited hepatic cell DNA damage in the form of single-strand breaks after oral exposure to trichloroethylene (Nelson and Bull 1988). The mice were much more sensitive to trichloroethylene than the rats; a single dose of 1.5 g/kg produced breaks in mouse DNA, compared to 3 g/kg in rats. Other groups of rats were pretreated 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 trichloroetbylene 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.

Other investigations using unscheduled DNA synthesis (UDS) assays reported that single gavage doses of trichloroethylene apparently caused no liver cell DNA damage in CD-1 mice (Doolittle et al. 1987), $B6C3F_1$ mice, or Fischer-344 rats (Mirsalis et al. 1989). Single doses of up to 1,000 mg/kg trichloroethylene did, on the other hand, cause an increase in the rate of DNA replication in both the CD-l mouse (Doohttle et al. 1987) and the $B6C3F_1$ mouse, but not in the Fischer-344 rat (Mirsalis et al. 1989). Increased DNA synthesis in hepatocytes and renal cells was observed in male but not female $B6C3F_1$ mice treated by gavage with 500 mg/kg/day trichloroethylene in corn oil for 7 days (Klaunig et al. 1991). In Fischer 344 rats treated by gavage with 500 mg/kg/day trichloroethylene in corn oil for up to 14 days, no effect on hepatocyte DNA

synthesis was observed, but renal DNA synthesis was increased in male but not female rats (Klaunig et al. 1991). Trichloroacetaldehyde (chloral), a major metabolite of trichloroethylene in humans and rodents, was tested for its ability to form hepatocyte DNA-protein cross-links *in vivo* in the $B6C3F_1$ mouse following oral doses of trichloroethylene. The results were negative (Keller and Heck 1988).

There is evidence that commercially available trichloroethylene may be weakly mutagenic to bacteria after metabolic activation (EPA 1985c), although the data are not conclusive. Concerning the mutagenicity of commercial trichloroethylene, it is probable that the responses were due to the presence of epoxide stabilizers, which are direct-acting mutagens. Data for purified samples were not conclusive, however, and a weak mutagenic effect was noted at high doses. Therefore, mutagenic potential for purified trichloroethylene cannot be disregarded; the data suggest that it could be a very weak indirect mutagen.

Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

The link between oral exposure to trichloroethylene and the incidence of cancer in humans is controversial. Support for an association comes from a New Jersey study in which cancer registry data were correlated to data on drinking water contaminated with trichloroethylene (and other volatile organic hydrocarbon) (Fagliano et al. 1990). In this study, the standardized incidence ratio for leukemia was increased for females in towns with the highest exposure category (estimated volatile organic hydrocarbon levels ranged from 37 to 72 ppb). Shortcomings of this type of study include the lack of information on individual exposure levels, variations in the routes of exposure, and the presence of other volatile organic compounds. A subsequent study expanded the cohort size to about 1.5 million residents in 75 towns monitored between 1979 and 1987, and the results included a significant elevation of total leukemias, childhood leukemias, acute lymphatic leukemias, and non-Hodgkin's lymphoma in.groups of females exposed to >5.0 ppb trichloroethylene (Cohn et al. 1994). Diffuse large cell/reticulosarcoma non-Hodgkin's lymphoma was significantly elevated in males as well. In contrast, a survey of total cancer, liver cancer, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and leukemia incidences from 1953 to 1991 in two Finnish villages with drinking water

contaminated with up to 220 ppb trichloroethylene and/or up to 180 ppb tetrachloroethylene found no significant increase in standardized incidence ratios for these diseases (Vartiainen et al. 1993).

Two investigations involving the review of mortality statistics for 1969-1979 concluded that there was a significantly elevated rate of childhood leukemia in Wobum, Massachusetts (Kotelchuck and Parker 1979; Parker and Rosen 1981). Two of the eight municipal wells servicing Woburn were known to be contaminated with trichloroethylene and several other chlorinated organic compounds, but etiologic factors for the leukemia were not identified in these studies. Two controversial studies found potential associations between ingestion of drinking water contaminated with solvents and increased risk of childhood leukemia, particularly acute lymphocytic leukemia (Byers et al. 1988; Lagakos et al. 1986a). Not all of the leukemia cases could be explained by the contaminated wells because several cases occurred in children with no access to these wells.

The studies performed at the Woburn site have several limitations (MacMahon 1986; Prentice 1986; Rogan 1986; Swan and Robins 1986; Whittemore 1986), including the presence of other contaminants and small sample size. One important difficulty is the poorly defined exposure conditions. The extent and duration of the contamination in the wells of concern are not known. Geophysical modeling has suggested that the contamination had probably been present earlier than the initial measurements that had identified the problem. This possibility makes the analyses of period-specific rates of effects incomplete since no time can be specified for the initiation of exposures. Two approaches were used in classifying exposures in the study by Lagakos et al. (1986a). The use of a continuous measurement based on estimates of the use and distribution of water from the contaminated wells actually showed less significance than the cruder measurement which grouped exposure into four categories. In addition, no attempt was made to account for water consumed from other sources, such as schools or workplaces. The contamination of the two wells at Woburn involved more than one measurable contaminant; thus, the adverse effects reported may not be attributable to trichloroethylene exposure alone.

A more recent study at Woburn was conducted by the Massachusetts Department of Health. Investigators found that the risk of leukemia in the group exposed to TCE in utero was about 8 times higher than that found in the unexposed group (MDPH 1996). It was concluded that these results were consistently in the direction of an association and support the hypothesis that childhood leukemia in this population may be

related to the mother's exposure to contaminated drinking water during pregnancy. Findings in this study are limited by the small numbers of cases and the limited information on exposures.

A study of three Michigan communities in which people were exposed to chlorinated solvents including trichloroethylene in drinking water showed no significant increases in cancers among the exposed population, including leukemia (Freni and Bloomer 1988). However, the cohort size in this study was only 223.

A health survey of 4,280 people exposed to trichloroethylene and other contaminants through drinking water in three states (Illinois, Indiana, and Michigan) has been completed (ATSDR 1994). An increase in respiratory tract cancers was observed in males. The study authors concluded that based on the incidence of smoking in the population "it would be inappropriate to relate this excess solely to trichloroethylene exposure."

Various types of cancers have been found in animals after trichloroethylene exposure by the oral route. There are problems, however, in interpreting the animal studies. Contamination of trichloroethylene with other potential carcinogens is one difficulty. For example, epoxides are often used to stabilize 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, $B6C3F_1$ 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 Fischer-344 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, this study has numerous limitations because of unusual reporting methods, such as failure to indicate the number of surviving animals and the absence of Good Laboratory Practices. 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.

In contrast to rats, $B6C3F_1$ mice developed hepatocellular carcinomas and hepatocellular adenomas following exposure to epoxide-free trichloroethylene (NTP 1990). The view of trichloroethylene as a hepatic carcinogen in mice but not rats was rienforced by a study in which rats were given trichloroethylene at 500 mg/kg/day by oil gavage for up to 14 days, 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.

Cancer effect levels (CELs) from all reliable studies are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 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 more than 29 g/kg but did not report any other details (Smyth et al. 1969). No other dermal lethality dam were available.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, renal, 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 riduals occupationally exposed to trichloth dermal and(Bauer and Rabens 1974; Phoon et al. 1984).

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

Dermal Effects. Because of the high volatility of trichloroethylene, human occupational exposure by dermal routes usually incudes 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, bums, 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 comeum (Goldsmith et al. 1988). The study indicates that lipid extraction is the reason for whitened skin following exposure to 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 three times a day for 3 days (Anderson et al. 1986).

2.2.3.3 Immunological and Lymphoreticular Effects

As discussed under dermal effects, people can develop hypersensitivity to trichloroethylene. The effects observed in hypersensitive individuals include skin effects (Conde-Salazar et al. 1983; Nakayama et al. 1988; Phoon et al. 1984; Waller et al. 1994) and liver effects (Phoon et al. 1984). Dermal sensitivity was confirmed with patch testing in only two cases (Conde-Salazar et al. 1983; Nakayama et al. 1988). The woman described by Conde-Salazaer et al. (1983) reacted positively to both vapor exposure and a dermal application of 5% trichloroethylene in olive oil.

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

2.2.3.4 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; Kohhnuller and Kochen 1994).

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

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

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

The combined incidence of stomach, liver, prostate, and lymphohematopoeitic cancers was increased among 2,050 male and 1,924 female Finnish workers occupationally exposed primarily to trichloroethylene (Antilla et al. 1995). The workers were exposed principally through 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 three times per 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.

2.3 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. Metabolism occurs fairly rapidly, and it may be that the resulting metabolites are responsible for much of the toxic effect 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 done for both animal and human systems (see Section 2.3.5), and predictions about target organ toxicity 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 2.4.3).

2.3.1 Absorption

2.3.1 .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 much 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 (Pernandez 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 (Mtiller 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 less than 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 mgkg 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).

2.3.1.2 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 (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 for clearance was found to be 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 mgkg in 50% aqueous polyethylene glycol400 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 from two to three 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 levels of up to 90% have been observed in rats dosed by this method (Prout et al. 1985).

Absorption kinetic studies on 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 have been due to trichloroethylene metabolites rather than the parent compound.

2.3.1.3 Dermal Exposure

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 a solution of unspecified trichloroethylene concentration for 30 minutes (Sato and Nakajima 1978). 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 comeum, 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 withnormal 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.

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 pure 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) increased rapidly, peaking at 0.5 hours (0.8 μg/rnL 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 in 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 liter of the water used for bathing. Thus, dermal absorption may be a significant route of human exposure to trichloroethylene from water-related sources.

Sex differences in uptake and metabolism of trichloroethylene have been seen in both humans and animals (see Section 2.8). 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). The mechanism behind this effect is still unclear.

2.3.2 Distribution

2.3.2.1 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; Mtiller et al. 1974). Once in the bloodstream, trichloroethylene may be transported rapidly to various tissues where it will likely be metabolized. Trichloroethylene was detected in the blood of babies at birth 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). Post-mortem analyses of human tissue from persons with unspecified exposure revealed detectable levels of trichloroethylene (< l-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.

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 may increase 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).

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.

2.3.2.2 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).

Limited data on tissue distribution following oral exposure in animals suggest that trichloroethylene is metabolized in the liver. Trichloroethylene that bypasses the liver is taken up by other tissues and sequestered in fat (Pfaffenberger et al. 1980). Rats were dosed by gavage with 1 or 10 mg/day trichloroethylene for 25 days, and blood serum and adipose tissue levels were determined at nine intervals during the exposure period and twice after cessation of dosing. Blood serum trichloroethylene levels were not detectable (i.e., <l µg /L serum) during the dosing period. Adipose tissue levels during the 25day exposure averaged 280 and 20,000 ng/g trichloroethylene for the l- and 10-mg/day doses, respectively. The average adipose trichloroethylene level was 1 ng/g for both exposure concentrations 3-6 days after the end of exposure.

2.3.2.3 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.

2.3.3 Metabolism

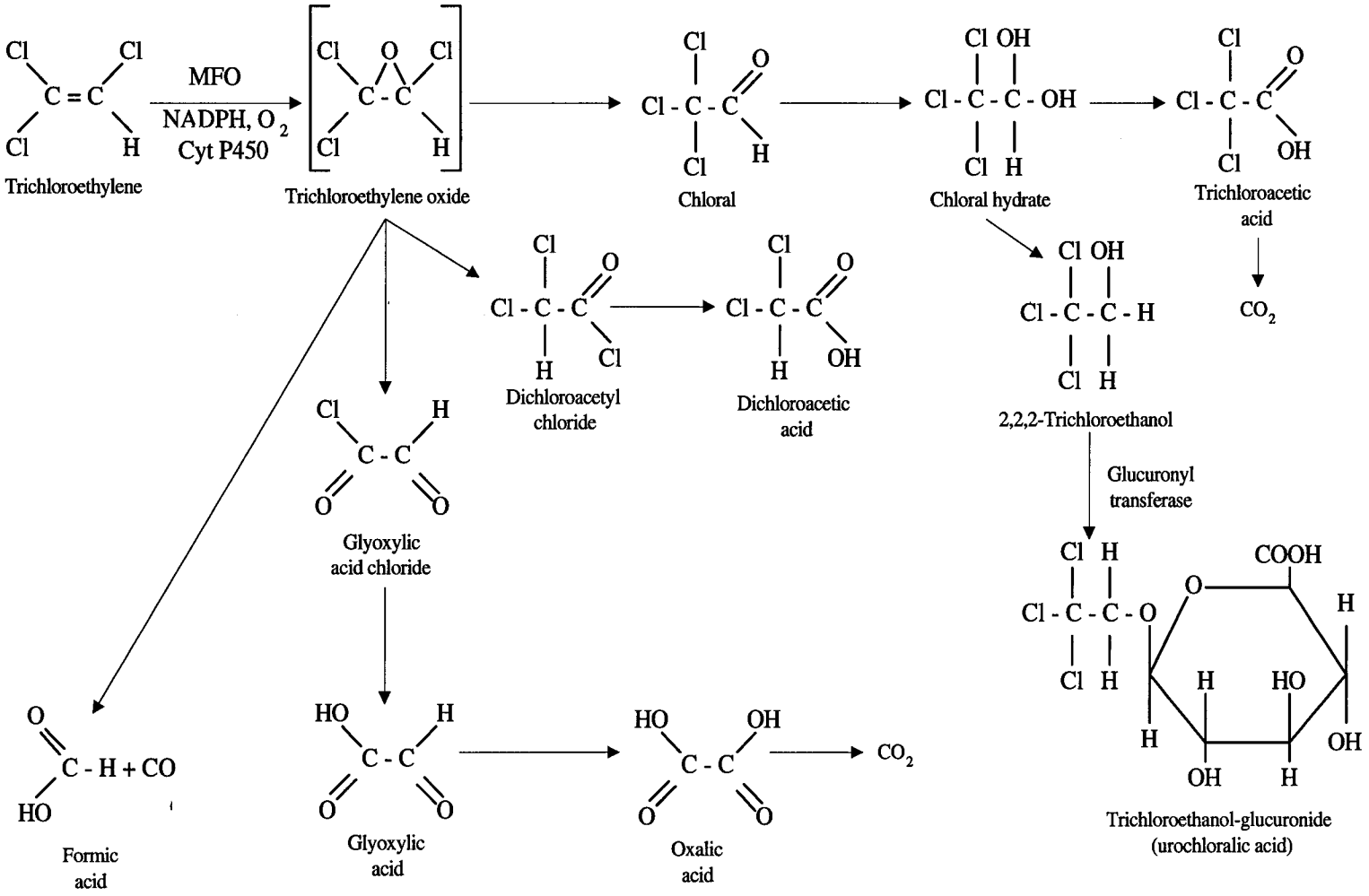
Inhaled doses of trichloroethylene are metabolized extensively in humans. The percentage of the dose metabolized has been reported to be between 40% and 75% of the retained dose (Bartonicek 1962; Ertle et al. 1972; Femandez et al. 1977; Kimmerle and Eben 1973a, 1973b; Monster et al. 1976, 1979; Mtiller 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. 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).

The principal metabolites of trichloroethylene in humans are trichloroethanol, trichloroethanol-glucuronide ("urochloralic acid"), and trichloroacetic acid (TCA) (Butler 1949; Cole et al. 1975; Mtiller 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). The major pathways of trichloroethylene metabolism in humans and animals are shown in Figure 2-3. Through an apparent epoxide intermediate, trichloroethylene oxide can form chloral, which rapidly converts to chloral hydrate. Chloral hydrate undergoes oxidation to TCA (Butler 1949). Alternatively, chloral hydrate can be metabolized to trichloroethanol, which undergoes Phase II glucuronidation to produce trichloroethanol-glucuronide (Miller and Guengerich 1983). Under certain conditions, the trichloroethylene-oxide intermediate can apparently form dichloroacetyl chloride and rearrange to dichloroacetic acid (DCA) (Dekant et al. 1984; Green and Prout 1985), or the oxide can hydrolyze to form formic acid, glyoxylic acid, oxalic acid, and carbon dioxide (Dekant et al. 1984; Green and Prout 1985). Minor urinary metabolites in trichloroethylene-exposed humans are monochloroacetic acid (Soucek and Vlachova 1960), N-(hydroxyacetyl)-aminoethanol, and DCA (Dekant et al. 1984).

The cytochrome P-450-dependent metabolism of trichloroethylene was studied in hepatic microsomal fractions from 23 different humans (Lipscomb et al. 1997). CYP2El was the predominant form of P-450 responsible for the metabolism of trichloroethylene in humans. Incubations of trichloroethylene with the microsomal preparations resulted in hyperbolic plots consistent with Michaelis-Menton 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/min/mg protein and were normally distributed. The study authors concluded that the human variability in metabolism of trichloroethylene via P-450-dependent pathways was within a 10-fold range.

FIGURE 2-3. The Metabolic Pathways of Trichloroethylene*



***Derived from Bogen et al. 1988**

Experiments demonstrate that oral absorption of trichloroethylene in animals is extensive and metabolism is rapid. A study of F344 rats which 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).

Urinary data in animals also show that the major metabolites of trichloroethylene are 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. It was also reported that chloroform is a minor metabolite of trichloroethylene (Mtiller et al. 1974; Pfaffenberger et al. 1980); however, this finding is questionable and needs further confirmation because chloroform may be an artifact of the analytical method used to identify metabolites. Other metabolites are the glutathione (GSH) conjugates of trichloroethylene and its metabolites (Miller and Guengerich 1983). GSH conjugation, although quantitatively not very important in trichloroethylene metabolism, may play an important role in the carcinogenicity/toxicity of trichloroethylene (see Section 2.4).

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 P-450 systems, evidence suggested the existence of a pre-epoxide transition state that involves the binding of

trichloroethylene to the activated oxygen of P-450, leading to chloral formation (Miller and Guengerich 1982, 1983).

Phenobarbital, an inducer of some forms of cytochrome P-450, has been shown to stimulate binding and metabolism of trichloroethylene by P-450 enzymes in rat liver microsome preparations (Costa et al. 1980). Similar stimulation of P-450-mediated trichloroethylene metabolism by phenobarbital has been demonstrated *in vivo* (Carlson 1974; Moslen et al. 1977). Using monoclonal antibodies against specific ethanol- and phenobarbital-induced P-450 enzymes in rat liver, Nakajima et al. (1992a) found that CYP2El was the most important isozyme involved in metabolizing trichloroethylene to chloral hydrate. The induction of these enzymes was also 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 CYP2El levels were lower in mature rats relative to immature rats. At puberty, the level of CYP2El 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 lo- and 600-ppm exposure concentrations, and there was no evidence of metabolic saturation. In rats, however, 98% of the net trichloroethylene uptake from the lo-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 high gavage doses of trichloroethylene, male mice metabolized trichloroethylene at a faster rate than male rats (Larson and Bull 1992b; Prout et al. 1985). The net metabolism of trichloroethylene to TCA and trichloroethanol was similar in rats and mice given single oral gavage doses of 1.5-23 mmol/kg (197-3,022 mg/kg) (Larson and Bull 1992b). However, 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 1992b). 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 1992b). This has been further validated by studies in which rats and mice had greater liver tumor induction with direct exposure to trichloroethylene metabolites such as DCA, TCA, chloral hydrate, or 2-chloroacetaldehyde (Bull et al. 1993; Daniel et al. 1992; DeAngelo et al. 1991; Larson and Bull 1992a).

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 &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. *In vitro* and *in vivo* data suggest that the cytochrome P-450 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). Isolated rabbit pulmonary cells (Clara, Type II, and alveolar macrophages) also demonstrated non-P-450-mediated bioactivation of trichloroethylene (Nichols et al. 1992). Trichloroethylene metabolism also appears to be important in trichloroethylene-induced nephrotoxicity (Dekant et al. 1986a; Elfarra and Anders 1984).

2.3.4 Elimination and Excretion

2.3.4.1 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). 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).

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 halftime 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 urinary excretion of TCA is much slower, and data from several studies indicate that the halftime of urinary TCA is approximately 52 hours because the metabolite is very tightly and extensively bound to plasma proteins (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 trichloro compounds and 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). In mice, 75% of the radioactivity was excreted in the

urine. Another 9% was exhaled as carbon dioxide. Rats excreted slightly less radioactivity in the urine and breath and more in the feces.

2.3.4.2 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.

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., less than 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 were given drinking water containing 4.8 ppm of [^{14}C]-trichloroethylene and that consumed 0.4 mg/kg 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).

2.3.4.3 Dermal Exposure

Elevated trichloroethylene levels in expired air were measured in subjects who immersed one hand in an unspecified concentration of trichloroethylene for 30 minutes (Sato and Nakajima 1978). Guinea pigs, exposed to dilute concentrations of aqueous trichloroethylene (≈ 0.020 to 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; 95% of the metabolized dose was excreted in 8.6 days (Bogen et al. 1992). No other studies were located for humans or animals regarding excretion after dermal exposure to trichloroethylene.

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

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

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic

behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

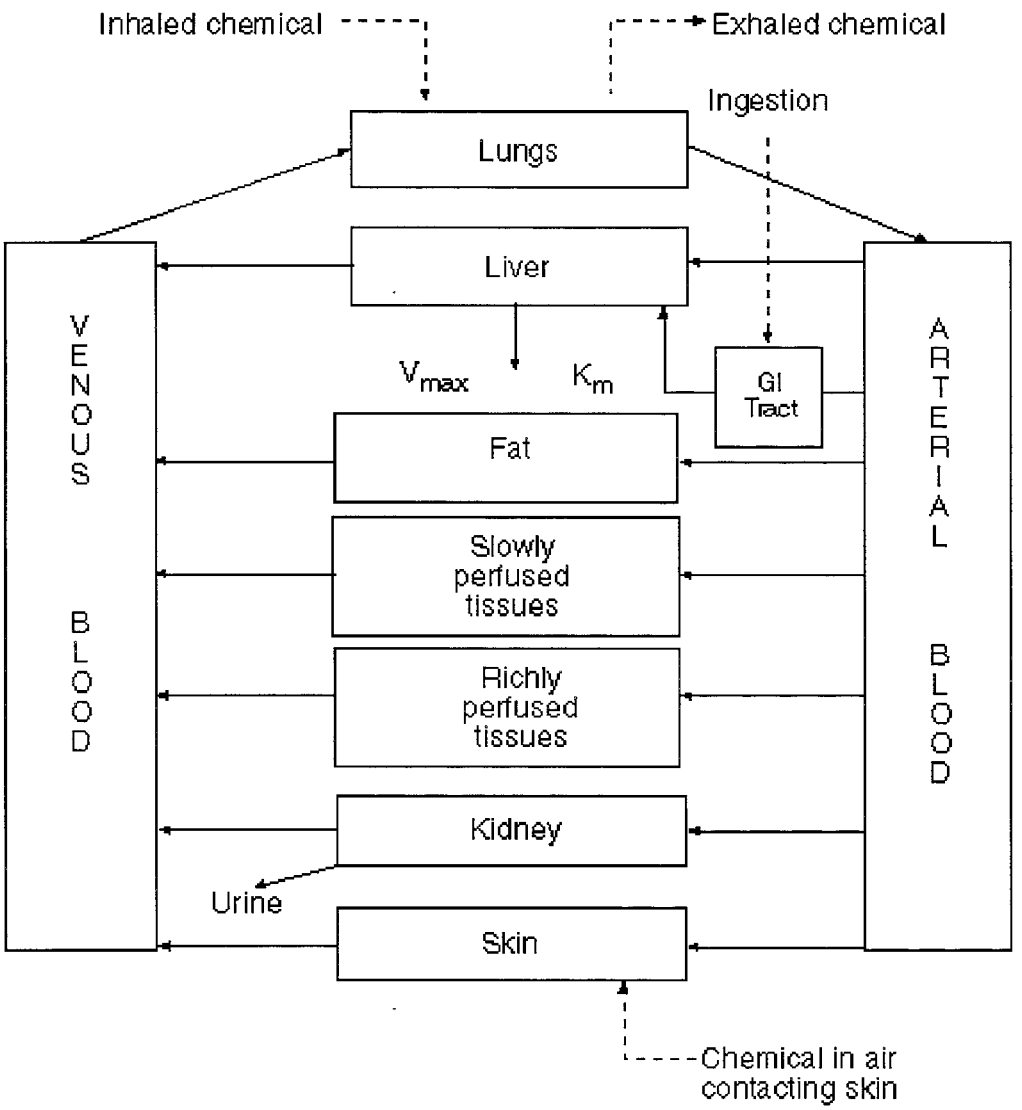
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s validated PBPK models were developed for a number of toxicologically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

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identity the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

The overall results and individual PBPK models for trichloroethylene are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations. Several PBPK models have been developed for inhaled trichloroethylene. In au early model by Femandez et al. (1977), the human body was divided into three major compartments or tissue groups: the vessel-rich group (VRG), muscle group (MG), and adipose tissue (fat) group (FG). The distribution of trichloroethylene in these

Figure 2-4. 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.

compartments was predicted for an 8-hour inhalation exposure of 100 ppm. The model suggested that for short exposures to high concentrations, the absorbed dose will distribute to the VRG and be rapidly eliminated before significant accumulation in the MG and FG takes place. Although the model also predicted that the concentration of trichloroethylene in-the FG will increase very slowly even after the end of the exposure period, the FG was predicted to accumulate substantially higher concentrations of trichloroethylene than any other tissue in the body. Another model by Droz et al. (1989a, 1989b) expanded this model in an attempt to account for individual differences including body build, liver and renal function, exposure, and physical workload.

PBPK models have also been used to explain the rate of excretion of inhaled trichloroethylene and its major metabolites (Bogen 1988; Fisher et al. 1989, 1990, 1991; Ikeda et al. 1972; Ramsey and Anderson 1984; Sato et al. 1977). One model was based on the results of trichloroethylene inhalation studies using volunteers who inhaled 100 ppm trichloroethylene for 4 hours (Sato et al. 1977). The model used first-order kinetics to describe the major metabolic pathways for trichloroethylene in vessel-rich tissues (brain, liver, kidney), low perfused muscle tissue, and poorly perfused fat tissue and assumed that the compartments were at equilibrium. A value of 104 L/hour for whole-body metabolic clearance of trichloroethylene was predicted. Another PBPK model was developed to fit human metabolism data to urinary metabolites measured in chronically exposed workers (Bogen 1988). ‘This model assumed that pulmonary uptake is continuous, so that the alveolar concentration is in equilibrium with that in the blood and all tissue compartments, and was an expansion of a model developed to predict the behavior of styrene (another volatile organic compound) in four tissue groups (Ramsey and Andersen 1984).

Sato et al. (1991) expanded their earlier PBPK model to account for differences in body weight, body fat content, and sex and applied it to predicting the effect of these factors on trichloroethylene metabolism and excretion. Their model consisted of seven compartments (lung, vessel rich tissue, vessel poor tissue, muscle, fat tissue, gastrointestinal system, and hepatic system) and made various assumptions about the metabolic pathways considered. First-order Michaelis-Menten kinetics were assumed for simplicity, and the first metabolic product was assumed to be chloral hydrate, which was then converted to TCA and trichloroethanol. Further assumptions were that metabolism was limited to the hepatic compartment and that tissue and organ volumes were related to body weight. The metabolic parameters, V_{max} (the scaling constant for the maximum rate of metabolism) and K_m (the Michaelis constant), were those determined for trichloroethylene in a study by Koizumi (1989) and are presented in Table 2-3.

TABLE 2-3. Parameters Used in Two Human PBPK Models

Parameter	Sato et al. 1991	Fisher and Allen 1993
V_{max}	$10.2(BW)^{0.7}$	$14.9(BW)^{0.7}$
K_m	1.5	2.5
Alveolar ventilation (L/hour)	$17.8(BW)^{0.7}$	$12.6(BW)^{0.74}$
Cardiac output (L/hour)	$17.8(BW)^{0.7}$	$14.9(BW)^{0.74}$
Compartment		
Lung		
% Body weight	V_L[a]	-
% Cardiac output	100	-
Partition coefficient	-	-
Vessel rich		
% Body weight	3.0 (M), 3.0 (F)	-
% Cardiac output	37.9 (M), 37.9 (F)	-
Partition coefficient	3.4	-
Vessel poor		
% Body weight	8.5 (M), 8.5 (F)	-
% Cardiac output	6.3 (M), 6.3 (F)	-
Partition coefficient	1.6	-
Muscle		
% Body weight	41.5 (M), 31.5 (F)	-
% Cardiac output	11.4 (M), 8.7 (F)	-
Partition coefficient	1.6	-
Gastrointestinal		
% Body weight	1.9 (M), 1.9 (F)	-
% Cardiac output	17.1 (M), 17.1 (F)	-
Partition coefficient	2.8	-
Hepatic		
% Body weight	2.3 (M), 2.3 (F)	-
% Cardiac output	6.9 (M), 6.9 (F)	-
Partition coefficient	4.4	-
Arteriovenous shunt		
% Body weight	–	-
% Cardiac output	15.1 (M), 13.9 (F)	-
Partition coefficient	–	-
Fat		
% Body weight	21.1 (M), 36.5 (F)	19.0
% Cardiac output	5.3 (M), 9.2 (F)	5.0
Partition coefficient	68.0	73.3

TABLE 2-3 (*continued*)

Parameter	Sato et al. 1991	Fisher and Allen 1993
Liver		
% Body weight	–	2.6
% Cardiac output	–	26.0
Partition coefficient	–	6.8
Richly perfused		
% Body weight	–	5.0
% Cardiac output	–	44.0
Partition coefficient	–	6.8
Slow perfused		
% Body weight	–	62.0
% Cardiac output	–	25.0
Partition coefficient	–	2.4

[a]V_L = volume of lung compartment based on tidal volume, residual capacity, lung/air partition coefficient, and arterial blood volume

– = information not used in the model; BW = body weight (kg); F = female; M = male

This model accurately predicted the time curves for blood concentration and urinary excretion of metabolites by male volunteers exposed to 100 ppm trichloroethylene (Sato et al. 1991). It was found that, while the amount of metabolite excretion increases with body weight, the concentration does not, because of a corresponding increase in urinary volume. Also, women and obese people, compared with slim men, have lower concentrations but longer residence times of blood trichloroethylene because of their higher fat content (Sato et al. 1991). As a comequence, the model predicted that 16 hours after exposure to trichloroethylene, one could expect a woman's blood level to be 30% higher and an obese man's level to be twofold higher than that of a slim man (Sato 1993).

PBPK modeling has also been applied to the assessment of human cancer risk from trichloroethylene inhalation by considering the kinetics of its carcinogenic metabolite, TCA (Allen and Fisher 1993). This model was based on a previous model which explored trichloroethylene/TCA dynamics in rodents (Fisher et al. 1991). Four compartments were considered (rapidly perfused tissue, slowly perfused tissue, fat, and liver), and it was assumed that only the liver was involved in metabolism. Kinetic parameters were optimized by matching model predictions to results from published studies. Estimates obtained in this manner for TCA kinetics were as follows: the fraction of trichloroethylene metabolized to TCA was estimated as 0.33, the rate constant for elimination of TCA from the plasma was 0.028 h^{-1}, and the scaling constant for the TCA volume of distribution was found to be dependent on body weight (BW) and ranged from 0.34(BW) to 0.0034(BW) (Allen and Fisher 1993). The parameters used by the model for trichloroethylene metabolism (V_{max} and K_m) are presented in Table 2-3. The authors set the scaling constant for the trichloroethylene first-order metabolism rate at zero, citing a lack of evidence for a first-order pathway in humans (Allen and Fisher 1993).

A comparison of results indicated that the capacity for oxidation of trichloroethylene in humans is less than in $B6C3F_1$ mice but greater than in Fischer-344 rats (Allen and Fisher 1993; Fisher et al. 1991). In addition, the systemic concentration of TCA in mice was greater than in humans and rats. The increased body burden of TCA in mice may be related to the formation of hepatocellular carcinomas in mice exposed to trichloroethylene (Fisher et al. 1991); the significance of the predicted human body burden is as yet unclear. This model was also applied toward estimating liver and lung cancer risk from environmental exposure to trichloroethylene, using a linearized multistage model, and the results indicated that concentrations of

7.0 µg /L in water and 10.0 ppb in air each correspond to a cancer risk of 1 in 1 million (Fisher 1993; Fisher and Allen 1993).

Monte Carlo simulation, an iterative technique which derives a range of risk estimates, was incorporated into a trichloroethylene risk assessment using the PBPK model developed by Fisher and Allen (1993). The results of this study (Cronin et al. 1995), which used the kinetics of TCA production and trichloroethylene elimination as the dose metrics relevant to carcinogenic risk, indicated that concentrations of 0.09-l .0 µg /L, (men) and 0.29-5.3 µg /L (women) in drinking water correspond to a cancer risk in humans of 1 in 1 million. For inhalation exposure, a similar risk was obtained from intermittent exposure to 0.07-13.3 ppb (men) and 0.1643 ppb (women), or continuous exposure to 0.01-2.6 ppb (men) and 0.0343 ppb (women) (Cronin et al. 1995).

This study, like that of Fisher and Allen (1993), incorporated a linear multistage model. However, the mechanism of trichloroethylene carcinogenicity appears to be non-genotoxic, and a non-linear model (as opposed to the linearized multistage model) has been proposed for use along with PBPK modeling for cancer risk assessment. The use of this non-linear model has resulted in a 100-fold increase in the virtually safe lifetime exposure estimates (Clewell et al. 1995).

A PBPK model for acute and subchronic inhalation and drinking water exposures was developed for the kinetics of trichloroethylene and TCA in pregnant rats (Fisher et al. 1989) and in lactating rats and nursing pups (Fisher et al. 1990). Following maternal inhalation exposure to trichloroethylene, the parent compound and TCA were detected in both pregnant rats and the fetuses (Fisher et al. 1989,1990), whereas the metabolite was the major compound measured in nursing pups (Fisher et al. 1990). The PBPK model accurately predicted the time-course of these two compounds in the blood and the rate of metabolism of dams and pups following trichloroethylene inhalation or ingestion in drinking water (Fisher et al. 1990).

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Absorption. Trichloroethylene, like other volatile hydrocarbons, causes generalized disruption of 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). Many observed neurotoxic effects of trichloroethylene have been attributed to demyelination resulting from such membrane disruption (Feldman et al. 1970, 1992). Experiments with muscle fibers have indicated that trichloroetbylene affects the dynamics of calcium ion transport across membranes (Kessler 1991), and a similar effect observed in cardiomyocytes has been offered as an explanation for trichloroethylene-induced cardiac arrhythmia (Hoffmann et al. 1994). Iron and trichloroethylene were found to synergistically promote lipid peroxidation in bovine pulmonary arterial endotbelial cells and rabbit aortic smooth muscle cells, suggesting a mechanism for the observed cardiac effects of trichloroethylene (Tse et al. 1990). Membrane interaction appears to be more pronounced at the interfacial region rather than the hydrocarbon core of the lipid bilayer (Bhakuni and Roy 1994). *In vitro* rabbit platelet activation, as measured by thrombin B, synthesis, was not inhibited by trichloroethylene, although inhibition by trichloroethanol was observed, thus implicating this metabolite in platelet membrane disruption (Yamazaki et al. 1992).

Distribution. Once inside the body, trichloroethylene is easily absorbed into and distributed through the circulatory system. The amount that is not absorbed initially on inhalation is expired unchanged (see Section 2.3.1.1). Absorption from the gastrointestinal tract often leads to a first pass through the liver, where toxic metabolites can form (see Section 2.3.3). Trichloroethylene and its metabolites may form adducts with blood proteins, and the metabolite glyoxylate may become incorporated into amino acids (Stevens et al. 1992), thus facilitating their distribution. The ability of these compounds to traverse membranes accounts for their generalized systemic effects.

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 (Femandez et al. 1977; Monster et al. 1979).

Excretion. Much of the initially inhaled trichloroethylene is expired unchanged, and trichloroethylene has been detected in the breath of people exposed orally and dermally as well. Once absorbed, trichloroethylene is rapidly metabolized by standard detoxification routes, such as the P-450 monooxidase and glutathione pathways, and many metabolic products are then excreted in the urine and feces. Differences among species in the primary metabolic pathways used may account for some differences seen in the toxic effect of trichloroethylene. For instance, high doses may saturate the P-450 pathway in rodents, causing a switch to glutathione conjugation, which may ultimately produce a metabolic product that is a renal carcinogen (Dekant et al. 1986a, 1986b; Miller and Guengerich 1982; Prout et al. 1985). However, no evidence exists for similar saturation in humans, which may partially account for the apparent absence of human renal cancer resulting from trichloroethylene exposure (Miller and%uengerich 1982; Steinberg and DeSesso 1993). No evidence exists for reabsorption, 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.

Effect of Dose and Duration of Exposure on Toxicity. Linearity of dose-response for trichloroethylene is often assumed, although this assumption has been challenged (Abelson 1993; Steinberg and DeSesso 1993). At low doses, the induction of detoxification pathways may be sufficient to minimize toxic effects, although saturation of these systems may occur at higher doses, potentially leading to the production of more toxic metabolites (see Section 2.3.3). Thus, a threshold effect may occur during chronic or high-dose exposure, leading to changes in the dose-response relationship.

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, and the liver, heart, and central nervous system are the primary targets for both routes (Candura and Faustman 199 l).- Renal toxicity results principally from oral exposure, and dermal exposure generally confines its toxic effects 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.

2.4.2 Mechanisms of Toxicity

Effects of Metabolism on Toxicity. Metabolism plays an important role in the toxicity of trichloroethylene because many of its metabolites are themselves toxic. Many differences among species in their responses to trichloroethylene exposure may be attributed to differences in the rates at which they metabolize the parent compound (Dekant et.al. 1986b; Prout et al. 1985).

An example is the rate by which the oxidative metabolism of trichloroethylene produces carcinogenic byproducts such as TCA. $B6C3F_1$ mice, which are far more prone to trichloroethylene-induced liver cancer, exhibit rapid metabolism of inhaled trichloroethylene, while F-34.4 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 its metabolites was greater in rats. 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).

Similarly, the metabolism of trichloroethylene to DCA, which may be important in the renal carcinogenic@ of trichloroethylene, appears to be a more commonly utilized pathway in rodents than in humans (Miller and Guengerich 1983; Steinberg and DeSesso 1993). The conjugation of DCA to GSH, followed by addition of L-cysteine, can eventually lead to the production of a reactive thiol group capable of binding to macromolecules (Dekant et al. 1986b). Several isomers of 1,2-dichlorovinyl-cysteine (DCVC), a product of trichloroethylene metabolism in the kidney, are mutagenic in the *in vitro* Ames assay (Commandeur et al. 1991; Dekant et al. 1986c). Production of of DCVC in humans is believed to occur by a minor pathway that is unlikely to become saturated and lead to kidney damage (Goeptar et al. 1995). However, N-acetylated

DCVC (a detoxification product of DCVC) has been identified in the urine of workers exposed to trichloroethylene (Bimer et al. 1993). 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, sexual differences due mainly to the effects of body fat content on trichloroethylene absorption are expected based on PBPK modeling (see Section 2.3.5).

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, heart, and kidneys. Central nervous system effects may also result in indirect toxic effects on heart, brain, and lung function. Retinal cell function appears to be targeted in rabbits at low exposures, based on electroretinogram changes following trichloroethylene injection (Blain et al. 1990) and visual evoked potential changes following trichloroethylene inhalation (Blain et al. 1992). Inhalation of trichloroethylene can produce toxic effects in rodent lungs, but the specific targeting of the lungs in exposed humans does not seem to be a major effect. Dermal contact with trichloroethylene can have effects on the skin as a result of defatting action and general irritation.

Species differences in the target organ specificity of trichloroethylene are exemplified by the case of the respiratory system. Mice exhibit greater susceptibility to trichloroethylene-induced lung tumors in chronic studies than do rats (Fukuda et al. 1983; Maltoni et al. 1986; NCI 1976), and short-term exposure studies have found that most cytotoxicity is specific to the Clara cells (Villaschi et al. 1991). Limited metabolism of trichloroethylene by cytochrome P-450 enzymes occurs in these cells, producing chloral (Miller and Guengerich 1983), a mutagen which may accumulate because of a limited ability of the cells to reduce it to trichloroethanol (Odum et al. 1992). Differences between rat and mouse pulmonary tumor induction may be thus attributed to differences in lung morphology: Clara cells are more abundant in mice and distributed in the bronchi and bronchioles, while those of the rat are located lower in the lung, where their exposure is reduced (Odum et al. 1992). The study authors further point out that, since trichloroethylene does not produce cancer in the rat lung and since Clara cell morphology of the rat lung is more similar to humans than mice, it is unlikely that the effect of trichloroethylene on the human lung would be like that of the mouse rather than like that of the rat. However, it is necessary to evaluate other potential mechanisms for lung toxicity and foci of activity that differ across species. When compared with national survey data, preliminary

data from the ATSDR Trichloroethylene Subregistry indicate an excess number of deaths from respiratory cancer in an older aged group exposed to TCE in the environment (ATSDR 1994). In addition, respiratory problems (including asthma and allergies) were moderately associated with cumulative TCE exposures. Although analyses of these data are ongoing, these findings suggest that adverse effects in the lung can occur in humans and may result from alternate mechanisms.

The liver is an organ that shows variable effects from trichloroethylene among species, and this can probably be attributed to interspecies differences in metabolism (see Section 2.4.2.1). Specifically, the apparent difference in susceptibility to trichloroethylene-induced hepatocelhtlar carcinoma between humans and rodents may be due to metabolic differences (see Section 2.4.2.3). Kidney effects are also variable among species. Humans and mice are less sensitive than rats. In rats exposed chronically to trichloroethylene, toxic nephrosis characterized as cytomegaly has been reported (NTP 1988). The kidney effects in rats do not seem to be related to an increase in alpha-2μ-globulin (Goldsworthy et al. 1988). Effects on the nervous system appear to be widespread among species, presumably due to interactions between trichloroethylene and neuronal membranes.

Carcinogenesis. The comparative carcinogenic potency of trichloroethylene and its metabolites, TCA and DCA, in the mouse liver was studied with the chemicals administered in drinking water (Herren-Freund et al. 1987). DCA and TCA, but not trichloroethylene, caused a significantly increased incidence of liver tumors with and without prior initiation with ethyhritrosourea. Although trichloroethylene was not shown to be a hepatocarcinogen in mice in this study, the amount of trichloroethylene that could be solubilized in the drinking water was quite low (40 mg/L) compared to DCA or TCA (5,000 mg/L). Other studies have shown that direct exposure to the trichloroethylene metabolites DCA, TCA, chloral hydrate, 2-chloroacetaldehyde) induces liver tumors, providing support to the theoretical mechanism of toxic metabolites in trichloroethylene-induced tumors in animals (Bull et al. 1993; Daniel et al. 1992; DeAngelo et al. 1991; Larson and Bull 1992a; Templin et al. 1993).

Hepatic peroxisome proliferation, characterized by liver enlargement due to hyperplasia and hypertrophy, has been proposed as a basis for differences in species susceptibility to trichloroethylene carcinogenicity. Peroxisomes are membrane-bound organelles which contain enzymes generally involved in lipid metabolism,

and their proliferation may be a response to perturbations in this metabolism (Bentley et al. 1993). Mechanisms by which peroxisome proliferation may induce cancer are unclear, although it has been speculated that the generation of increased levels of reactive oxygen species in peroxisomes may cause indirect DNA damage (Bentley et al. 1993). In addition, the general background of chronic cellular injury, necrosis, and regenerative cell growth common to peroxisome proliferation may result in sustained DNA synthesis, hyperplasia, and eventually cancer (Bentley et al. 1993; Steinberg and DeSesso 1993). Recent evidence of selective mutations in several codons of the H-ras oncogene in $B6C3F_1$ mice treated with trichloroethylene suggests this as a possible mechanism (but not the only one) of carcinogenicity as well (Anna et al. 1994).

Trichloroethylene exposure in male rats and .mice resulted in elevated cyanide-insensitive palmitoyl CoA oxidase levels, indicative of peroxisome proliferation (Goldsworthy and Popp 1987). In a similar experiment, exposure of mice and rats to high levels of trichloroethylene produced increased peroxisomal proliferation in mice but not rats (Elcombe et al. 1985). However, when mice and rats were exposed in the same study to the trichloroethylene metabolite TCA, both species responded with dramatic increases in peroxisome proliferation. Thus it seems that TCA is the agent of peroxisome proliferation induction, and differences among species in responses to trichloroethylene exposure may actually reflect differences in their metabolic pathways and hence their production of TCA. It is noteworthy that, at trichloroethylene dose levels that produce a strong peroxisomal proliferation response in rodents, no such effect is seen in humans (Bentley et al. 1993). Likewise, chronic dosing of trichloroethylene, while hepatocarcinogenic in mice, does not seem to be so in humans (N'TP 1990). However, Bull et al. (1993) caution that the metabolite DCA, also hepatocarcinogenic in mice. does not seem to act through peroxisome proliferation and thus may itself pose a risk for human cancer. More research needs to be done to resolve this issue.

Klaunig et al. (1991) found that hepatocyte DNA synthesis increased significantly in male mice exposed to trichloroethylene by gavage for up to 14 days, but no such increase was seen in female mice or in renal DNA synthesis in either sex. Similar exposures in rats produced increases in renal DNA synthesis in males, but no such increase in females, 01 .1n hepatic DNA synthesis in either sex. These results correlate well with observed species- and gender-specific trichloroethylene carcinogenicity, and the study authors suggest that trichloroethylene acts as a tumor promoter to induce proliferation of previously initiated cells.

Renal tubular cancer has been seen in rats following trichloroethylene exposure (NIP 1990). One possible explanation involves hyalin protein droplet induction associated with alpha-2_u-globulin accumulation in lysosomes, with cell proliferation in the P2 segment of the kidney, as seen when male rats are exposed to certain solvents (Goldsworthy et al. 1988). The increased cell proliferation associated with alpha-2_u-globulin, which is a male rat-specific protein (synthesized in the liver and excreted by the kidney glomemlus with reabsorption by the proximal convoluted tubular cell), may increase the possibility of spontaneous mutations, leading to tumor formation (Doolittle et al. 1987; Mirsalis et al. 1989). This histopathological alteration is not likely to be relevant for trichloroethylene toxicity in humans. However, for a number of chlorinated hydrocarbons, the development of renal tumors in male rats has been associated with alpha-2_u-globulin and hyaline droplet formation. In male Fischer-344 rats, no increase was noted in renal alpha-2_u-globulin concentration after exposure to trichloroethylene (Goldsworthy et al. 1988). Protein droplet accumulation and cell replication did not differ from controls in trichloroethylene-treated male or female rats (Goldsworthy et al. 1988).

Another possible mechanism for renal tumor development involves glutathione (GSH) conjugation of trichloroethylene and its metabolites; the quantitative significance of this route of metabolism is not clear, but it may play an important role when the oxidative P-450 pathway becomes saturated at high doses of trichloroethylene (Dekant et al. 1987). After administration of high doses of trichloroethylene, the conjugation product N-acetyl-dichlorovinyl-cysteine (DCVC) was found in the urine of the treated animals (Dekant et al. 1986a). Urinary dichlorovinyl-cysteine has also been identified in workers exposed to unspecified levels of trichloroethylene (Birner et al. 1993). It has been shown that cleavage of this conjugation product by β-lyase, an enzyme present in the renal tubule, leads to the formation of potentially nephrocarcinogenic metabolites (Dekant et al. 1986b).

Rats appear to be more sensitive to the nephrocarcinogenic effects of trichloroethylene (NTP 1990). This may be due to pathways other than glutathione conjugation and subsequent β-lyase cleavage,since the extent of trichloroethylene activation through this pathway, as measured by production of acid-labile adducts to renal proteins, was greater ir, mice than in rats (Eyre et al. 1995a). The amount of DCVC found in rat kidneys after oral exposure to trichloroethylene was four to six times greater than that found in mouse kidneys after an equivalent exposure, suggesting more efficient glutathione conjugation, and subsequent

DCVC formation, in rats (Eyre et al. 1995b). However, this study also found renal activation of DCVC to nephrocarcinogenic byproducts in mice to be 12 times greater than in rats, resulting in the overall renal activation of trichloroethylene by the cysteine S-conjugate pathway in mice being double that of rats. Agents which inhibit P-lyase protect against DCVC nephrotoxicity in rats (Elfarra et al. 1986). Additional insight into the role of dichlorovinyl-cysteine in nephrocarcinogenicity was provided by McLaren et al. (1994), who noted that it induces DNA double-strand breaks and poly(ADP-ribosyl)ation (a post-translational modification which affects DNA repair enzymes) in the rat renal cortex.

2.4.3 Animal-to-Human Extrapolations

Extrapolating animal toxicity data to predict human risk is often controversial and is especially so in the case of trichloroethylene since some of the mechanisms implicated in its animal effects do not apparently exist in humans. For instance, trichloroethylene-induced peroxisome proliferation, a potential precursor to hepatocarcinoma induction, is common in rodents but not in humans (Bentley et al. 1993; Elcombe 1985). Abelson (1993) has pointed out that, while the metabolism of trichloroethylene to TCA is rapid and linear in mice, leading to peroxisome proliferation and carcinogenesis, the same metabolic pathway in rats and humans is limited, as is the evidence for peroxisome proliferation and carcinogenesis. However, the metabolite DCA is also hepatocarcinogenic in mice, though it is not an effective peroxisome proliferator, so the implications for human hepatocarcinogenicity are still unclear (Bull et al. 1993). Differences in lung morphology among rodents and humans may help explain species differences in susceptibility to respiratory tumors resulting from trichloroethylene inhalation (see Section 2.4.2.2).

On the other hand, chloral, a metabolite of trichloroethylene, which is also a mutagen and inducer of aneuploidy, is produced via a pathway which is more predominant in rats and humans than in mice (Kimbrough et al. 1985). A study using identical trichloroethylene concentrations in rats and mice, and which found increased aneuploidy in rats but no effect in mice, offered this mechanism as a possibleexplanation (Khgerman et al. 1994). An implication from this would be that humans are similarly more susceptible to chloral-mediated effects of trichloroethylene exposure.

It thus appears that, as models for predicting human susceptibility to trichloroethylene-induced cancer, mice may be less than satisfactory, while rats may be slightly better. Much of the available epidemiological evidence for exposed humans does not seem to indicate that trichloroethylene is a prominent carcinogen at concentrations usually found at worksites or in the environment (Abelson 1993). However, the database also includes limited evidence that suggests carcinogenic effects, such as leukemias, may be linked to trichloroethylene exposure (Fagliano et al. 1990; Lagakos et al. 1986a). These studies are limited by exposure to multiple chemicals.

Developmental effects of trichloroethylene exposure have been demonstrated with the FETAX (Frog Embryo Teratogenesis Assay Xenopus) bioassay, an *in vitro* method using whole frog embryos (Fort et al. 1991, 1993; Raybum et al. 1991). Observed defects included gut m&coiling, skeletal kinking, and heart malformations; heart malformations have also been observed in rat developmental assays (Dawson et al. 1993).

2.5 RELEVANCE TO PUBLIC HEALTH

Exposure to trichloroethylene can occur via the inhalation, oral, and dermal routes in people living in areas surrounding hazardous waste sites if evaporation occurs from contaminated soils or spill sites, or if contaminated water is ingested or used in bathing. Individuals who work in the vicinity of industries that use this substance may breathe trichloroethylene vapors or come into physical contact with spilled trichloroethylene. The group with the greatest likelihood for substantial exposure to trichloroethylene consists of those exposed to trichloroethylene in the workplace.

In the past, trichloroethylene was used as a human anesthetic. Trichloroethylene has also been used by individuals who intentionally inhale it for its narcotic properties. Therefore, most of the information regarding the effects of trichloroethylene in humans comes from case studies and experiments describing effects of trichloroethylene after inhalation exposure. These studies indicate that the primary effect of exposure to trichloroethylene is on the central nervous system. Effects include headache, vertigo, fatigue, short-term memory loss, decreased word associations, central nervous system depression, and anesthesia.

Minimal Risk Levels for Trichloroethylene

Inhulution MRLs

- An MRL of 2 ppm was derived for acute inhalation exposure (14 days or less) to trichloroethylene. This MRL was based on a study by Stewart et al. (1970) in which volunteers were exposed to 200 ppm trichloroethylene for 5 days, 7 hours/day. A LOAEL was observed for mild subjective neurological effects, such as fatigue and drowsiness. Support for this end point is provided by human case studies of cardiac arrhythmia after unspecified trichloroethylene exposure (Dhuner et al. 1957; Milby 1968; Thierstein et al. 1960), and by decreased wakefulness and post-exposure heart rate in rats exposed to 1,000 ppm (Arito et al. 1993). Kishi et al. (1993) observed decreased shock avoidance and Skinner box lever press in rats after exposure to 250 ppm trichloroethylene, although performance was variable among individuals. Other human studies, while not acceptable for MRL derivation because of shortcomings in experimental design, nevertheless reported decreased reaction time at 110 ppm after 8 hours (Salvini et al. 1971); studies involving exposures of 300 ppm or less for fewer than 4 hours found no effects in several neurological tests (Ettema et al. 1975; Konietzko et al. 1975a; Windemuller and Ettema 1978). These studies generally support the LOAEL of 200 ppm used for the MRL derivation.

- An MRL of 0.1 ppm was derived for intermediate inhalation exposure (15-364 days) to trichloroethylene. This MRL was based on a study by Arito et al. (1994a) in which male JCL-Wistar rats were exposed to 0, 50, 100, or 300 ppm trichloroethylene for 6 weeks, 5 days/week, 8 hours/day. A LOAEL of 50 ppm was observed for decreased wakefulness during exposure, and decreased post-exposure heart rate and slow wave sleep. Another study with rats found an increase in sleep-apneic episodes and cardiac arrhythmias after exposure to trichloroethylene (Arito et al. 1993). These results corroborate similar effects observed in humans exposed to trichloroethylene, as described in the previous paragraph, as well as evidence of organic solvent-induced sleep apnea in humans (Edling et al. 1993; Monstad et al. 1987, 1992; Wise et al. 1983).

No chronic inhalation exposure (365 or more days) MRL was derived for trichloroethylene because the available chronic-duration data were limited by lack of adequate characterization of exposure conditions or quantitation of results, or because the existing studies had end points that were not suitable for derivation of anMRL.

Oral MRLs

- An MRL of 0.2 mg/kg/day was derived for acute oral exposure (14 days or less) to trichloroethylene. This MRL was based on the study by Fredriksson et al. (1993) in which mouse pups were dosed by gavage with 0, 50, or 290 mg/kg/day trichloroethylene in a 20% peanut oil emulsion between the ages of 10 and 16 days. Behavioral changes (reduced rearing rate) were noted during tests performed at

60 days of age. Support for this developmental end point was provided by similar studies involving dose-related but transient changes in open field behavior (NT.P 1986) and changes in exploratory behavior (Taylor et al. 1985) in rat pups from dams exposed to trichloroethylene during gestation, as well as reports of decreased myelination of brain neurons (Isaacson and Taylor 1989) and decreased uptake of 2-deoxy-D-glucose in the brain (Noland-Gerbec et al. 1986) in rat pups from exposed dams.

No intermediate oral exposure MRL was derived for trichloroethylene because of a lack of adequately designed studies examining suitable end points. No chronic oral exposure MRL was derived for trichloroethylene because the existing studies had end points that were not suitable for derivation of an MRL.

Death. Humans have died after breathing (Bell 1951; Buxton and Hayward 1967; Clearfield 1970; DeFalque 1961; Ford et al. 1995; James 1963; Kleinfeld and Tabershaw 1954; McCarthy and Jones 1983; Smith 1966; Troutman 1988) or drinking (Kleinfeld and Tabershaw 1954; Secchi et al. 1968) very large amounts of trichloroethylene. This occurred during acute accidental workplace atmospheric exposures, or by intentional ingestion or inhalation of large doses of the substance in order to commit suicide or become intoxicated. The deaths following acute inhalation exposure were generally attributed to ventricular fibrillation or central nervous system depression, while the deaths following acute oral exposure were attributed to hepatorenal failure. Death associated with liver failure has 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). Reports regarding the death of humans following dermal exposure to trichloroethylene were not located.

Animals have also died following large inhalation (Kylin et al. 1962; Siegel et al. 1971) or oral exposures (Merrick et al. 1989; Smyth et al. 1969; Tucker et al. 1982). Deaths in animals have also been reported following chronic-duration inhalation exposure (Henschler et al. 1980) and following intermediate- and chronic-duration oral exposure (Henschler et al. 1984; NCI 1976; NTP 1990). No deaths due to dermal exposure have been reported. Death is not likely to result from exposure to low levels of trichloroethylene at hazardous waste sites.

Systemic Effects

Respiratory Effects. Labored breathing and respiratory edema were reported in a worker after welding steel that had been washed with trichloroethylene (Sjogren et al. 1991). These effects may be a result of the trichloroethylene decomposition products phosgene and dichloroacetyl acid.

Some members of a community that were exposed to trichloroethylene along with a variety of other solvents in their drinking water complained of respiratory disorders, but the complaints could not be attributed specifically to trichloroethylene (Byers et al. 1988). This effect may have been due to imrnune system impairment resulting in increased susceptibility to infection. A study in mice in which inhalation exposure to trichloroethylene increased the susceptibility to pulmonary infection with *Streptococcus zooepidemicus* (Aranyi et al. 1986) provides evidence that trichloroethylene may result in adverse respiratory effects through effects on the immune system.

Vacuole formation and endoplasmic reticulum dilation in the Clara cells have been observed in mice (Odum et al. 1992; Vilaschi et al. 1991) but not rats (Odum et al. 1992) exposed to trichloroethylene by inhalation. The increased sensitivity of mice to this effect is thought to result from the greater abundance of these cells in mice and the difference in the distribution of these cells in mice compared to rats (Odum et al. 1992). Rales and dyspnea have been reported in pregnant rats treated by gavage with high doses of trichloroethylene (Narotsky and Kavlock 1995). Following intermediate-duration oral exposure to high doses of trichloroethylene, pulmonary vasculitis has been reported in rats (NTP 1990). Although exposure to trichloroethylene at levels found in the environment or at hazardous waste sites is unlikely to result in direct respiratory effects, the data suggest that increased susceptibility to respiratory infection secondary to immune system effects may occur.

Cardiovascular Effects. Chronic cardiovascular disease has not been reported in workers occupationally exposed to low levels of trichloroethylene (El Ghawabi et al. 1973), although deaths following acute highlevel inhalation exposures to trichloroethylene have been attributed to cardiac arrhythmias. Case studies have described cardiac arrhythmias that in some instances led to death after occupational exposure (Bell 1951; Kleinfeld and Tabershaw 1954; Smith 1966), poisoning (Dhuner et al. 1957; Gutch et al. 1965), or

anesthesia (Pembleton 1974; Thierstein et al. 1960). Accidental oral exposure to trichloroethylene has resulted in cardiac arrymmias (Dhuner et al. 1957; Morreale 1976; Perbellini et al. 1991). Cardiac arrhythmias reported in a small number of people who drank from contaminated wells could not be attributed to trichloroethylene alone (Byers at al. 1988). Increased congenital heart defects were noted in another population exposed to trichloroethylene in their drinking water, but a cause-and-effect relationship could not be established (Goldberg et al. 1990). When compared with a national sample, the ATSDR subregistry of persons environmentally exposed to trichloroethylene reports excesses of anemia, stroke, blood disorders, and death from heart disease (ATSDR 1994; Burg et al. 1995). However, the data were gathered by questionnaire and may be limited by self-reporting bias.

Studies in laboratory animals have indicated that trichloroethylene-induced cardiac sensitization to catecholamines may explain the arrhythmias that have been documented in humans exposed to this agent (Morris et al. 1953; Reinhardt et al. 1971; White and Carlson 1979,1981). Cardiac arrhythmias were reported in rats exposed to trichloroethylene (Arito et al. 1993), and an intermediate-duration inhalation exposure MRL of 0.1 ppm was derived from another study in which this effect was found in rats (Arito et al. 1994a). Exposure to trichlc roethylene has been correlated with cardiac abnormalities in developing chick embryos (Loeber et al. 1988) as well as rat fetuses (Dawson et al. 1990). Histopathological changes in the heart have not been observed in animals exposed to trichlorethylene following intermediate-duration exposure periods (Prendergast et al. 1967; Reinhardt et al. 1973; White and Carlson 1979,1981,1982). Changes in serum polyunsaturated fatty acid ratios, which are implicated in cardiovascular disease, have been observed in rats exposed to 300 ppm trichloroethylene vapor for 12 weeks (Okamoto and Shiwaku 1994). The evidence is suggestive that cardiovascular effects could be a concern for persons exposed to trichloroethylene near hazardous waste sites.

Gastrointestinal Effects. Case reports indicate that acute inhalation exposure to trichloroethylene results in nausea and vomiting (Buxton and Hayward 1967; Clear-field 1970; David et al. 1989; DeFalque 1961; Gutch et al. 1965; Milby 1968). Anorexia, nausea, vomiting, and intolerance to fatty foods have also been reported after chronic occupational exposure to trichloroethylene (El Ghawabi et al. 1973; Schattner and Mahrick 1990; Smith 1966). Trichlcroethylene-induced effects on the autonomic nervous system may contribute to these effects (Grandjean et al. 1955). Some of the people exposed to trichloroethylene and other chlorinated

hydrocarbons in the drinking water in Woburn, Massachusetts, occasionally complained of chronic nausea, episodic diarrhea, and constipation (Byers et al. 1988). Pneumatosis cystoides intestinalis has been described in workers exposed by inhalation to >50 ppm trichloroethylene as well as other solvents (Nakajima et al. 1990a). Self-reported gastrointestinal problems were not increased among persons in the trichloroethylene subregistry who were exposed to trichloroethylene in their drinking water (ATSDR 1994; Burg et al. 1995).

In a chronic inhalation study, histological changes in the gastrointestinal tract were not observed in rats (Maltoni et al. 1988). Gas pockets in the intestinal coating and blood in the intestines were observed in mice treated with trichloroethylene in drinking water (Tucker et al. 1982). The effect was not dose-related, and statistical analysis was not reported. Histopathological changes in the gastrointestinal tract have not 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).

Based on the limited human and animal data, it is not possible to predict whether or not trichloroethylene exposure at levels found in the environment and at hazardous waste sites can result in gastrointestinal effects.

Hematological Effects. The limited number of studies of humans exposed to trichloroethylene for an acute period (7 hours/day for 1 or 5 days) revealed no adverse effects on blood cell counts, sedimentation rates, serum lipid levels, serum proteins, or serum enzymes (Stewart et al. 1970). Blood cell counts were not affected in volunteers exposed to trichloroethylene for 2 hours (Vernon and Ferguson 1969). Volunteers inhaling 95 ppm trichloroethylene for 4 hours showed only an increase in neutrophil enzyme levels, with no change in serum enzyme levels (Konietzko and Reilll980). Effects on hemoglobin levels or red blood cell counts were not observed in persons occupationally exposed to trichloroethylene (Konietzko and Reilll980). Hematological effects have not been reported in cases of accidental oral exposure to trichloroethylene (perbellini et al. 1991; Todd 1954). The trichloroethylene subregistry, which has compiled information on 4,280 people exposed to trichloroethylene through their drinking water, found a significantly increased incidence of anemia among selected age groups when compared with corresponding national data (ATSDR 1994; Burg et al. 1995).

Changes in hematology end points were not observed in rats following intermediate-duration inhalation exposures to trichloroethylene (Prendergast et al. 1967). 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 (Pujita et al. 1984; Koizumi et al. 1984). Related effects included increased ALA synthetase activity and reduced heme saturation of tryptophan pyrrolase in the liver, increased urinary excretion of ALA and coproporphyrin, and reduced cytochrome P-450 levels in me liver. Hemoglobin concentration in erythrocytes did not change, and 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). Oral ingestion of trichloroethylene in drinking water for 6 months resulted in minor hematological changes in mice, 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). The effects were not dose related, and some effects were transient. Although available evidence suggests only minor hematological effects in humans, animal studies show hematological effects. Thus, hematological effects in humans exposed to environmental levels of trichloroethylene from hazardous waste sites may be a concern.

Musculoskeletal Effects. No studies were located regarding direct musculoskeletal effects in humans following any route of exposure. Trichloroethylene can result in nervous system effects that result in secondary effects on muscle strength, especially in the face (Leandri et al. 1995).

Histopathological changes in muscles have not been observed in rats following chronic-duration inhalation exposure to trichloroethylene (Maltoni et al. 1988), or in rats or mice following intermediate-duration or chronic-duration oral exposure to trichloroethylene (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990). Histopathological changes in bone have also not been observed in rats or mice following oral exposure to trichloroethylene (NTP 1988, 1990). Based on the available data, direct musculoskeletal effects are unlikely in humans following exposure to trichloroethylene at levels found in the environment, or at hazardous waste sites. Effects on muscle strength secondary to neurological effects may be a concern.

Heputie Effects. There is some evidence for trichloroethylene-induced hepatic effects in humans. This evidence is primarily from case reports of persons accidently or intentionally exposed to relatively high levels.

Hepatic necrosis has been observed in persons that died following inhalation (Joron et al. 1955; Priest and Horn 1965) or oral (Kleinfeld and Tabershaw 1954) exposure to high levels of trichloroethylene. Although death resulting from hepatic failure in eclamptic pregnant women has been reported following trichlorethylene anesthesia (DeFalque 1961), controlled trichloroethylene anesthesia generally produces minimal effects on the liver indicated by increased serum levels of SGGT (Pembleton 1974). Other studies of humans following trichloroethylene anesthesia have not reported adverse effects (Brittain 1948; Crawford and Davies 1975). A significant increase in the metabolism of the drug paracetamol was observed in patients anesthetized with trichloroethylene, indicating subtle effects on liver function may make determining the proper dosage more difficult (Ray et al. 1993). Liver effects were not reported in acute-duration human exposure studies (Konietzko and Reill 1980; Stewart et al. 1970).

Liver effects including blood and urine indices of liver function, and enlarged livers, have been reported in persons occupationally exposed to trichloroethylene (Bauer and Rabens 1974; Capellini and Grisler 1958; Graovac-Leposavic et al. 1964; Phoon et al. 1984; Schattner and Malnick 1990; Schuttmann 1970). Exposure concentrations in these studies were not reported. In contrast no evidence of hepatoxicity was observed in workers who had neurological effects from trichloroethylene (McCarthy and Jones 1983).

Several cases of accidental oral exposure to trichloroethylene have not reported hepatic effects (Morreale 1976; Perbellini et al. 1991; Todd 1954). Self-reported liver problems were not increased among persons in the ATSDR trichloroethylene subregistry who were exposed to trichloroethylene in their drinking water (ATSDR 1994; Burg et al. 1995).

Liver enlargement is the primary hepatic effect seen in trichloroethylene-exposed animals after oral or inhalation exposure, indicating that trichloroethylene is not as potent a liver toxin as are a number of other chlorinated hydrocarbons. However, many of the studies were limited by lack or inadequate scope of pathological examinations, lack of measurement of hepatic enzymes, and/or failure to evaluate liver function indices. Histological alterations characterized by cellular hypertrophy were associated with liver enlargement in some of the studies of mice exposed to trichloroethylene in the air (Kjellstrand et al. 1981,1983a, 1983b) or via the oral route (Buben and O'Flaherty 1985; Elcombe 1985; Goldsworthy and Popp 1987; Stott et al.

1982; Tucker et al. 1982). Increasing severity of liver necrosis with dose was also seen in the studies by Buben and O'Flaherty (1985) and Stott et al. (1982).

Increased liver weight and hypertrophy may be due to the induction of peroxisomal P-oxidation. Mice, especially males, appear to be particularly sensitive to the hepatic effects of trichloroethylene (Kjellstrand et al. 1983b). Differences in the hepatic effects of trichloroethylene between mice, rats, and humans are attributable to the greater metabolism of high doses of trichloroethylene by mice compared to rats and humans (Dekant et al. 1986b; Larson and Bull 1992b; Stott et al. 1982), as well as a much greater induction in peroxisomes following exposure to trichloroacetic acid (Bentley et al. 1993). A study in male mice showed increased liver weight at a dose of 100 mg/kg/day trichloroethylene and enlarged hepatocytes at 400 mg/kg/day (Buben and O'Flaherty 1985). Histopathological changes of the liver (including necrosis) were seen at higher doses. Although there are conflicting reports in humans and limitations in animal studies, these data together suggest that hepatic effects may be a concern for some persons exposed to trichloroethylene; however, it is unknown whether exposure to levels of trichloroethylene found in and around hazardous waste sites may result in hepatic injury.

Renal Effects. People who have been acutely exposed to high vapor levels during surgical anesthesia (Brittain 1948; Crawford and Davies 1975) have not exhibited renal toxicity. However, minor changes in urinary and serum indicators of renal function have been found in some workers occupationally exposed to trichloroethylene (Brogren et al. 1986; Clearfield 1970; David et al. 1989; Gulch et al. 1965; Nagaya et al. 1989b; Selden et al. 1993). Acute accidental oral exposure to trichloroethylene has not resulted in effects on renal function (Morreale 1976; Perbellini et al. 1991; Todd 1954). No clear evidence of kidney effects has been reported in studies examining the association of long-term exposure to trichloroethylene in drinking water and adverse health effects (Freni and Bloomer 1988; Lagakos et al. 1986a).

Acute inhalation exposure of rats to high concentrations of trichloroethylene has resulted in increases in urinary glucose, proteins, glucosaminidase, gamma glutamyl transpeptidase, and serum urea nitrogen (Chakrabarti and Tcuhweber 1988). Following intermediate-duration inhalation exposure of animals to trichloroethylene, increased kidney weights have been observed (Adams et al. 1951; Kimmerle and Eben 1973a; Kjellstrand et al. 1981, 1983a, 1983b; Prendergast et al. 1967). Chronic-duration inhalation exposure

of rats to trichloroethylene has resulted in renal tubular meganucleocytosis in males but not females (Maltoni et al. 1986,1988). With the exception of mild to moderate cytomegaly and karyomegaly in the renal tubular epithelial cells observed in an intermediate-duration oral study in mice (NTP 1990), acute- and intermediate-duration oral studies of trichloroethylene in mice have not reported significant renal effects (Goldsworthy et al. 1988; Stott et al. 1982; Tucker et al. 1982). Rats are more sensitive to the renal effects of trichloroethylene than mice. Following intermediate-duration oral exposure, the effects noted included increased kidney weights, elevated urinary protein and ketones (Tucker et al. 1982), minimal to mild cytomegaly, and karyomegaly of the renal tubular epithelial cells (NTP 1990). Treatment-related chronic nephropathy has been observed in rats (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990) and mice (NCI 1976) following chronic oral exposure to trichloroethylene. Although there are few data in humans and limitations in animal studies, the data suggest that kidney effects may be a concern for some persons exposed to trichloroethylene; however, it is unknown whether exposure to levels of trichloroethylene found in and around hazardous waste sites may result in renal injury.

Endocrine Effects. No studies were located regarding endocrine effects in humans following any route of exposure. Adrenal gland weight was not affected following acute-duration oral exposure of rats to trichloroethylene (Berman et al. 1995). Histopathological changes have not been reported in endocrine glands following inhalation (Maltoni et al. 1988) or oral (Maltoni et al. 1986; NCI 1976; NTP 1988,1990) exposure to trichloroethylene for intermediate- or chronic-durations. Based on the limited data, histopathological changes are unlikely in humans exposed to trichloroethylene at levels found in the environment or at hazardous waste sites. The data are not sufficient to predict if subtle changes in endocrine gland function may occur in humans exposed to trichloroethylene at levels found in the environment or at hazardous waste sites.

Dermal Effects. Some humans experienced dry throats following acute inhalation exposure to trichloroethylene at 200 ppm (Stewart et al. 1970). Persons working with trichloroethylene for intermediate periods sometimes develop skin rashes and dermatitis (Bauer and Rabens 1974; El Ghawabi et al. 1973). It is reported that some people may be particularly sensitive to trichloroethylene and develop allergies when exposed to high levels in the air or on their skin during occupational exposures of intermediate duration (Czirjak et al. 1993; Goh and Ng 1988; Nakayama et al. 1988; Phoon et al. 1984). Exposure to

trichloroethylene and other substances in drinking water has been associated with an increase in maculopapular rashes (Byers et al. 1988). Diffuse fascitis has been reported in a woman, but not her husband, although both were exposed to trichloroethylene and other chlorinated hydrocarbons in well water (Wailer et al. 1994). Substitution of bottled water for drinking resulted in improved symptoms. Dermal effects of trichloroethylene are usually the result of direct skin contact with trichloroethylene, which results in desiccation due to the defatting action of the solvent. It is also possible that adverse dermatological effects may be mediated by immunological responses in some persons.

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 for intermediate durations (NCI 1976). Histopathological changes in the skin were not observed in rats following chronic inhalation exposure (Maltoni et al. 1988) or in rats or mice following intermediate or chronic oral exposure (Maltoni et al. 1986; NTP 1988, 1990). Erythema, edema, and increased epidermal thickness were noted in guinea pigs following acute dermal exposure to trichloroethylene (Anderson et al. 1986).

Although human data are not extensive, the data suggest that dermal effects may be a concern for some humans exposed to trichloroethylene, particularly through bathing with contaminated water; however, it is unlikely that exposure to trichloroethylene in the air or soil at hazardous waste sites would be irritating to human skin. Some people may develop immunological sensitivity to trichloroethylene which may manifest as a dermal response following inhalation, oral, or dermal exposure to trichloroethylene.

Ocular Effects. Some humans experienced mild eye irritation following acute inhalation exposure to trichloroethylene at 200 ppm (Stewart et al. 1970). Itchy watery eyes (Baure and Rabens 1974; El Ghawabi et al. 1973) and inflamed eyes (Schattner and Malmck 1990) have been reported following contact with trichloroethylene vapor.

In a chronic oral study in rats, observation of squinting and red discharge from the eyes were reported more frequently in trichloroethylene exposed rats as the study progressed (NCI 1976). Histopathological changes in the eyes were not repotted in rats following chronic inhalation exposure (Maltoni et al. 1988) or in rats or mice following chronic oral exposure (Maltoni et al. 1986; NCI 1976; NTP 1988). Based on the limited data,

it is unknown whether exposure to the trichloroethylene levels found at hazardous waste sites would be harmful to human eyes.

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). In intermediate- and chronic-duration studies body weights less than controls have been reported in animals following inhalation (Adams et al. 1951; Kjellstrand et al. 1983a) and oral exposure (NCI 1976; NTP 1988, 1990) to high levels of trichloroethylene. Body weight effects have not been studied following dermal exposure of animals. Effects on body weight are unlikely to occur in humans exposed to trichloroethylene at levels found in the environment or at hazardous waste sites.

Immunological and Lymphoreticular Effects. It has been suggested that in some cases dermal effects in persons occupationally exposed to trichloroethylene may be sensitivity reactions (Czirjak et al. 1993; Goh and Ng 1988; Phoon et al. 1984). A case study involving excessive skin contact showed that 1 of 11 exposed individuals studied may have had an allergic response to trichloroethylene (Nakayama et al. 1988). People who drank trichloroethylene-contaminated water in Wobum, Massachusetts, had immunological abnormalities, but these people were also exposed to other volatile chlorinated hydrocarbons in the water (Byers et al. 1988; Lagakos et al. 1986b). Symptoms of systemic lupus erythematosus were increased in residents of Tucson, Arizona, exposed to trichloroethylene and other chemicals in drinking water (Kilburn and Warshaw 1992). Diffuse fascitis with eosinophilia was reported in a woman who used well water contaminated with trichloroethylene (Wailer et al. 1994).

There is one animal study indicating that trichloroethylene via the inhalation route alters immune function and resistance to *Streptococcus zooepidemicus* (Aranyi et al. 1986). Another animal study, in which mice were exposed to trichloroethylene in the drinking water, showed treatment-related effects on both cellular- and antibody-mediated immunity; however, the effects did not occur consistently or in a dose-dependent manner (Sanders et al. 1982). Histopathological changes in the spleen have not been reported in animals following intermediate-duration inhalation exposure (Prendegast et al. 1967), or in the spleen or thymus following

acute- (Berman et al. 1995), intermediate-, or chronic-duration (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990) oral exposure to trichloroethylene.

A study in which MRL +/+ mice were treated with trichloroethylene (1,314 mg/kg/treatment) or dichloroacetyl chloride (29.5 mg/kg/treatment) by intraperitoneal injection every 4 days for 6 weeks suggests that these chemicals may accelerate the autoimmune response (Khan et al. 1995). This strain of mice is genetically predisposed to develop systemic lupus erythematosus in the second year of life. Trichloroethylene and dichloroacetyl chloride induced significant increases (45% and 322%, respectively) in serum IgG levels. Significant increases in serum anti-nuclear antibodies, and nonsignificant increases in anti-ssDNA, and anti-cardiolipin were also observed. The study authors suggested that dichloroacetic acid may be the principal metabolite of trichloroethylene responsible for the induction of an autoimmune response, as a dose of trichloroethylene 50-fold greater than the dose of dichloroacetyl chloride was required to induce a response. The limited human data and the limited animal data suggest that in some sensitive people, especially those predisposed to develop autoimmune responses, there may be a concern for immune system effects from exposure to trichloroethylene. However, it is unknown whether exposure to levels of trichloroethylene found in and around hazardous waste sites may result in immune system effects.

Neurological Effects. In the past, trichloroethylene was used as an anesthetic, so it obviously can cause acute central nervous system depression in humans. Also, people have become unconscious after acute exposure to very high levels occasionally present in the workplace (Kohlmuller and Kochen 1994; La&nit and Pietschmann 1960; Longley and Jones 1963; McCarthy and Jones 1983; Steinberg 1981). Human experimental studies revealed mild effects on motor coordination, visual perception, and cognition (Feldman et al. 1985; Rasmussen et al. 1993a, 1993c, 1993d; Vernon and Ferguson 1969). Workers acutely exposed to relatively high levels of trichloroethylene have also complained of adverse effects similar to those seen in the experimental subjects. Nonspecific neurological effects from trichloroethylene exposure in the workplace have been reported and include dizziness and drowsiness, which are similar to the effects of acute inhalation exposure. These effects are generally reversible. An acute-duration inhalation MRL of 2 ppm was derived based on a study in which these subjective neurological effects were noted in exposed humans (Stewart et al. 1970). Evidence from acute and chronic exposures suggest that trichloroethylene causes adverse neurological effects such as dysfunction of cranial nerves (Barret et al. 1987; Buxton and Hayward 1967; Dogui et al.

1991; Feldman et al. 1970, 1985, 1988, 1992; Kilbum and Warshaw 1993; Rasmussen et al. 1993a; Ruijten et al. 1991). Accidental ingestion of trichloroethylene has resulted in delirium and loss of consciousness (Morreale 1976; Perbellini et al. 1991; Stephens 1945; Todd 1954). Studies of persons exposed to trichloroethylene and other chemicals in drinking water do not show conclusive evidence of neurological effects. Neurological complaints were not increased in the Wobum, Massachusetts, population (Byers et al. 1988; Lagakos et al. 1986a). Further examination of a subset of this population did reveal some evidence of cranial nerve damage (Feldman et al. 1988). In the Tucson, Arizona, population exposed to trichlorethylene, decrease in blinking reflex, eye closure, choice reaction time, and intelligence scores (Kilbum and Warshaw 1993), and impaired balance (Kilbum et al. 1994) were noted. Among persons in the ATSDR exposure subregistry, a statistically significant impairment in hearing was reported in children age 9 years or younger (ATSDR 1994; Burg et al. 1995). All of these studies are limited by exposure to multiple chemicals, and a lack of individual exposure data. Direct emersion of the hand (Sato and Nakajima 1978) or thumb (Stewart and Dodd 1964) into trichloroethylene has been reported to be painful.

It is not clear if the effects on cranial nerve dysfunction from inhalation exposure in humans are attributable to trichloroethylene alone or its decomposition products. For example, while a number of limited studies report neuropathies associated with exposure to trichloroethylene (Bardodej and Vyskocill956; Barret et al. 1987; Lawrence and Partyka 1981; McCunney 1988), there are studies which report that these effects resulted from exposure to the trichloroethylene decomposition product, dichloroacetylene (Buxton and Hayward 1967; Cavanagh and Buxton 1989; Feldman 1970; Humphrey and McClelland 1944). Barret et al. (1992) showed that neuropathies in animals resulted from treatment with both trichloroethylene and dichloroacetylene, though the effects from dichloroacetylene were more severe.

Neurological effects in animals exposed to trichloroethylene in the air include hearing loss (Albee et al. 1993; Crofton and Zhao 1993; Jaspers et al. 1993; Rebert et al. 1991), visual impairment (Blain et al. 1992; Kulig 1987; Niklasson et al. 1993), behavioral effects (Adams et al. 1951; Grandjean 1960; Silverman and Williams 1975), and cardiac arrhythmia (Arito et al. 1993, 1994a, 1994b). An intermediate-duration inhalation MRL of 0.1 ppm was derived based on a study in which effects on heart rate and sleep cycles were noted in exposed rats (Arito et al. 1994a). Neurological effects noted in animals following acute oral exposure include increased rearing activity (Moser et al. 1995), transient ataxia (Narotsky et al. 1995) increased performance in a swim test, and decreased brain myelination (Isaacson et al. 1990). Following

chronic-duration oral exposure of rats effects noted included ataxia, lethargy, convulsions, and hind limb paralysis (NTP 1988). In a chronic-duration oral study in mice, excitation followed by a subanaesthetic state was observed in mice shortly after daily gavage treatment with trichloroethylene (Henschler et al. 1984). The available evidence suggests that humans may be at risk for neurological effects from exposure to trichloroethylene at levels found in the environment and near waste sites.

Reproductive Effects. Operating room nurses exposed to trichloroethylene have been reported to have an increased incidence of miscarriages, but they were exposed to many other anesthetics as well (Corbett et al. 1974). Survey results of 1,926 women who had spontaneous abortions revealed a greater risk of abortion associated with trichloroethylene exposure (Windham et al. 1991). This study is limited by multiple chemical exposure. Humans exposed to trichloroethylene in the drinking water in certain areas of the country have not shown adverse reproductive effects (Byers et al. 1988; Freni and Bloomer 1988; Lagakos et al. 1986a).

Inhalation exposure of mice to trichloroethylene has resulted in an increase in abnormal sperm (Beliles et al. 1980; Land et al. 1981). No effects on spermatic micronuclei frequency were observed in mice exposed to trichloroethylene in air for 5 days (Allen et al. 1994). Treatment-related reproductive effects were not observed in female rats exposed to trichloroethylene in air for 2 weeks before mating (Dorfmueller et al. 1979). Mating behavior has been shown to be affected in mice exposed by gavage to high doses of trichloroethylene (Zenick et al. 1984). This effect was considered secondary to the narcotic effects of trichloroethylene. Except for increased testes weight (NTP 1986b) effects on reproductive performance have not been observed in continuous breeding studies of rats (NTP 1986b) or mice (NTP 1985) exposed orally to trichloroethylene. No effects on female fertility were noted in rats treated by gavage with trichloroethylene in corn oil for 2 weeks before mating (Mattson et al. 1984). Histopathological changes in reproductive organs have not been 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). Based on available evidence, exposure to trichloroethylene in air, water, or soil at hazardous wastes sites is not expected to adversely affect human reproduction.

Developmental Effects. There is limited evidence that oral exposure to trichloroethylene, in drinking water, may cause birth defects. However, the existing database contains limited positive as well as limited negative reports. Taken together, these data are inconclusive regarding teratogenic effects in humans exposed to TCE. Over 2,000 male and female workers who were exposed to unspecified concentrations of trichloroethylene and other solvents in the workplace were studied; an increase in malformations was not observed (Tola et al. 1980). An apparent doubling of risk was associated with effects on birth weight among the newborn of women exposed occupationally or nonoccupationally to unspecified concentrations of trichloroethylene (Windham et al. 1991). However, there was no association when general solvent exposure was examined. In both studies complete medical records were not provided. There is some evidence that exposure to trichloroethylene in drinking water may cause certain types of birth defects. However, this body of research is still far from conclusive. A survey of live births and fetal deaths in an area of New Jersey with contaminated public drinking water found an association between trichloroethylene and oral cleft, central nervous system, neural tube defects, and major cardiac defects (Bove et al. 1995). Uncertainty regarding exposure classification and small numbers of cases were the main limitations of this study. In a study of residents exposed to drinking water contaminated with solvents including trichloroethylene, in Wobum, 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). An additional study of the Wobum population has been completed (MDPH 1994). The study authors indicate that there were increased prevalence in choanal atresia, a rare respiratory defect, and hypospadias/congenital chordee among those ever exposed. However, these findings are limited by the small number of cases in which these effects were observed. The study authors cautioned that their study did not rule ;rut moderate increases in rates of the less common adverse reproductive outcomes. For these outcomes only large increases would have been detected. Overall, this study did not show any statistically significant associations between exposure concentration and birth defects. A study of Michigan residents exposed to trichloroethylene and other solvents in their drinking water found no significant excesses of congenital defects or adverse pregnancy outcomes. In this study, sample size was small and the period of exposure was ill-defined (Freni and Bloomer 1988). Another population, in Tucson,

Arizona, was exposed to trichloroethylene in drinking water and had increased numbers of congenital heart defects (Goldberg et al. 1990).

Among persons in the ATSDR exposure subregistry, a statistically significant impairment in hearing was reported in children age 9 years or younger (ATSDR 1994; Burg et al. 1995). Because the time of onset for hearing loss is not available, it is not known if this effect may be a result of *in utero* exposure or exposure after birth. The study authors cautioned that their study does not identify a causal relationship between trichloroethylene and effects but does suggest areas for further research.

Both Bove et al. (1995) and MDPH (1994) examined effects of trichloroethylene exposure on fetal birth weights. Neither study saw a conclusive effect on birth weight, although birth weights tended to be lower in exposed infants compared to controls in the MDPH (1994) study. A small effect on birth weight in male infants was noted in an interim report on adverse birth outcomes for a population living at Camp LeJeune, North Carolina (ATSDR 1997). The women were exposed sometime during gestation. The study authors cautioned that the small group size weakens the causal association and stated that further analyses are ongoing.

Several animal studies using both the inhalation (Beliles et al. 1980; Dorfmueller et al. 1979; Hardin et al. 1981; Schwetz et al. 1975) and oral (Cosby and Dukelow 1992; Manson et al. 1984; NTP 1985, 1986, 1990) routes of exposure did not reveal teratogenic effects on the developing fetus. Decreased litter size and increases in micro- or anophthalmia have been noted in the offspring of rats treated with trichloroethylene during gestation at maternally toxic (deaths, decreased body weight gain) doses (Narotsky and Kavlock 1995; Narotsky et al. 1995). Studies that looked at more sensitive neurological and neurobehavioral effects on developing pups and fetuses (changes in rearing open field activity, exploratory behavior) have found an effect from trichloroethylene exposure (Fredriksson et al. 1993; Isaacson and Taylor 1989; Taylor et al. 1985). The Fredriksson et al. (1993) study was used to derive an acute-duration oral exposure MRL of 0.2 mg/kg/day. A nonmammalian avian embryo model of cardiac teratogenesis was used to examine the question of whether trichloroethylene causes cardiac malformations (Loeber et al. 1988). White Leghorn chick eggs were exposed to 5-25 µM (2-28 µg /g body weight) trichloroethylene injected into the air space of the egg during various stages of incubation. Cardiac malformations, including septal defects, abnormal

cardiac muscle, and atrioventricular canal defects, were found in 7.3% of exposed hearts compared to 2.3% and 1.5% of saline-treated and mineral oil-treated controls. This was a well-conducted study with adequate controls and selection of doses. A study with rats found evidence of abnormal heart development in fetuses from exposed dams (Dawson et al. 1993). A study regarding the teratogenicity of trichloroacetic acid in rats indicates that this metabolite of trichloroethylene can also result in cardiac defects (Smith et al. 1989). In offspring of rats treated by gavage with 0, 330, 800, 1,200 or 1,800 mg/kg/day trichloroacetic acid in water on gestation days 6-15, l%, 5%, 24%, 47%, and 95% of the fetuses, respectively had cardiac defects. Maternal toxicity (decreased body weight gain, increased kidney and spleen weights) was observed at doses of 800 mg/kg/day and greater. Developmental effects may be a concern for some persons exposed to trichloroethylene; however, it is unknown whether exposure to levels of trichloroethylene found in and around hazardous waste sites may result in adverse developmental effects.

Genotoxic Effects. Data regarding the genotoxicity of trichloroetbylene suggest that it is a very weak, indirect mutagen (EPA 1985c). The potential for heritable gene mutations and the mechanisms of carcinogenicity are not known. 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 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

TABLE 2-4. Genotoxicity of Trichloroethylene *In Vivo*

Species (test system)	End point	Results	Reference
Drosophila melanogaster	Chromosomal aberrations	–	Beliles et al. 1980
Mammalian cells:			
Human (occupational exposure)	Chromosomal aberrations	+	Rasmussen et al. 1988
Mouse (spot test)	Gene mutation	(+)	Fahrig 1977
Mouse	Dominant lethal mutation	–	Slacik-Erben et al. 1980
Mouse	Micronucleus formation	+/–	Duprat and Gradiski 1980
Mouse	Micronucleus formation	–	Allen et al. 1994
Mouse	Micronucleus formation	–	Kligerman et al. 1994
Mouse	Chromosomal aberrations	–	Kligerman et al. 1994
Mouse	Sister chromatid exchange	–	Kligerman et al. 1994
Rat	Micronucleus formation	+	Kligerman et al. 1994
Rat	Chromosomal aberrations	–	Kligerman et al. 1994
Rat	Sister chromatid exchange	–	Kligerman et al. 1994
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 (alkaline unwinding assays)	DNA damage (single-strand breaks)	+	Nelson and Bull 1988
Mouse	DNA damage (single-strand breaks)	+	Walles 1986
Mouse (alkaline unwinding assay)	DNA damage (single-strand breaks)	+	Nelson and Bull 1988
Rat	DNA damage (single-strand breaks)	+	McLaren et al. 1994

TABLE 2-4 (*continued*)

Species (test system)	End point	Results	Reference
Rat (hepatocyte unscheduled DNA synthesis)	DNA damage (unspecified)	–	Mirsalis et al. 1989
Mouse (hepatocyte unscheduled DNA synthesis)	DNA damage (unspecified)	–	Mirsalis et al. 1989
Mouse (hepatocyte unscheduled DNA synthesis)	DNA damage (unspecified)	–	Doolittle et al. 1987
Human (occupational exposure)	Sister chromatid exchange	(+)	Gu et al. 1981
Human (smokers, occupational exposure)	Sister chromatid exchange	+	Seiji et al. 1990
Human (nonsmoker, occupational exposure)	Sister chromatid exchange	–	Seiji et al. 1990
Human (smokers and nonsmokers, occupational exposure)	Sister chromatid exchange	–	Nagaya et al. 1989a
Host-mediated assays:			
Schizosaccharomyces pombe (mouse host-mediated assay)	Gene mutation	–	Rossi et al. 1983[b]
Saccharomyces cerevisiae (mouse host-mediated assay)	Gene mutation	+	Bronzetti et al. 1978[b]

[a]Testing effects of chloral after p[r]etreatment with trichloroethylene
[b]Study involves use of metabolic activators.

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

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 per day. In addition, concomitant exposure to other solvents occurred. In a similar investigation of sister chromatid exchange, negative results tiere 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. 1981). Please refer to Table 2-4 for a further summary of the results of inhalation studies. There is no information on potential genotoxic effects in humans from oral exposure.

The results from *in vivo* animal studies are similarly inconclusive with regard to the genotoxicity of trichloroethylene. These studies have concentrated heavily on trichloroethylene's role in DNA damage, primarily in the form of single-strand breaks. High oral doses of trichloroethylene resulted in single-strand breaks in liver cells of $B6C3F_1$ mice and Sprague-Dawley rats (Nelson and Bull 1988). Differences in dose response and metabolite toxicity suggest differences in the mechanisms of single-strand break induction between the two species. 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). While no direct evidence exists for DNA adduct formation by trichloroethylene, covalent binding to DNA and RNA from various organs in rats and mice after intraperitoneal injection has been observed (Mazzullo et al. 1992).

Other investigators found no evidence for DNA damage in $B6C3F_1$ mice, Fischer-344 rats (Mirsalis et al. 1989), or CD-l mice (Doolittle et al. 1987) following oral trichloroethylene exposure or in male Sprague-Dawley rats following intraperitoneal injection (Parchman and Magee 1982). There was, however, evidence for an increased rate of DNA synthesis in $B6C3F_1$ and CD-l mice (Doolittle et al. 1987; Mirsalis et al. 1989), while no such effect was observed in Fischer-344 rats (Mirsalis et al. 1989). This observation indicates that different mechanisms may exist in different rodent species. In addition, the increased rate of

DNA synthesis, a nongenobxic effect, suggests that trichloroethylene may be carcinogenic without necessarily being genotoxic (Doolittle et al. 1987; Klaunig et al. 1991; Mirsalis et al. 1989). An inhalation study found no significant cytogenic or cell cycle progression effects in C57EW6J mice exposed to up to 5,000 ppm trichloroethylene, although evidence for aneuploidy and increased bone marrow micronuclei formation was found in similarly exposed CD rats (Kligerman et al. 1994). The study authors suggest that, although mice exhibit a greater ability than rats to metabolize trichloroethylene, the pathway involving production of the chloral intermediate (known to induce aneuploidy) is predominant in rats, and the observed effect may be due to formation of this metabolite. Results from these and other animal *in vivo* studies can be found in Table 2-4.

The results gathered from *in vitro* studies are no more conclusive than those from *in vivo* studies. A 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). Stuoies 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). A DNA-protein cross-link study produced negative results for chloral-treated liver nuclei from Fischer-344 rats (Keller and Heck 1988). The outcome was positive when D61 .M yeast was tested for mitotic aneuploidy following trichloroethylene treatment both with and without metabolic activation. The same researchers also assessed gene conversion and reverse mutation following treatment of D7 yeast with trichloroethylene (Koch et al. 1988). The results can be viewed in Table 2-5 but are difficult to evaluate because statistical comparisons were not reported. Finally, an interesting study comparing the effects of stabilized versus unstabilized trichloroethylene on the rate of gene mutation was performed on *Salmonella typhimurium.* As seen in Table 2-5, mixed results were found according to the purity of trichloroethylene and the type of assay performed (preincubation or vapor). However, the trichloroethylene stabilizers alone generated positive outcomes for both types of assay (McGregor et al. 1989). The results of other prokaryotic and fungal studies can be found in Table 2-5.

Although trichloroethylene itself may not be genotoxic, several of its metabolites are reactive and potentially genotoxic compounds (Miller and Guengerich 1982). Several isomers of 1,2-dichlorovinyl-cysteine, a product of trichloroethylene metabolism in the kidney, are mutagenic in the *in vitro* Ames assay

TABLE 2-5. Genotoxicity of Trichloroethylene *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium (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	+	+	McGregor et al. 1989
S. typhimurium (TCE stabilizers, preincubation assay)[a]	Gene mutation	No data	+	McGregor et al. 1989
S. typhimurium (TCE stabilizers, vapor assay)[a]	Gene mutation	No data	+	McGregor et al. 1989
S. typhimurium TA100 (reverse mutation)	Gene mutation	–	–	Waskell 1978
S. typhimurium TA100 (reverse mutation)	Gene mutation	(+)	–	Baden et al. 1979
S. typhimurium TA1535 (reverse mutation)	Gene mutation	+/–	+/–	Baden et al. 1979
S. typhimurium TA1535 (reverse mutation)	Gene mutation	–	–	Shimada et al. 1985
S. typhimurium TA98 (reverse mutation)	Gene mutation	–	–	Waskell 1978
Escherichia coli (forward and reverse mutation)	Gene mutation	+/–	No data	Greim et al. 1975

TABLE 2-5 (*continued*)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae D7 (stationary-phase/production of prototrophic colonies)	Gene conversion	–	–	Koch et al. 1988[b]
S. cerevisiae D7 (log-phase/ production of prototrophic colonies)	Gene conversion	–	–	Koch et al. 1988[b]
S. cerevisiae D7 (stationary-phase/production of prototrophic colonies)	Gene mutation	(+)	(+)	Koch et al. 1988[b]
S. cerevisiae D7 (log-phase/ production of prototrophic colonies)	Gene mutation	(+)	(+)	Koch et al. 1988[b]
S. cerevisiae (reverse mutation)	Gene mutation	No data	–	Callen et al. 1980
S. cerevisiae (reverse mutation)	Gene mutation	+	–	Bronzetti et al. 1980
Schizosaccharomyces pombe (forward mutation)	Gene mutation	–	–	Rossi et al. 1983
Aspergillus nidulans (forward mutation)	Gene mutation	No data	+	Crebelli et al. 1985
S. cerevisiae (gene conversion)	Recombination	No data	+	Callen et al. 1980
S. cerevisiae (gene conversion)	Recombination	+	–	Bronzetti et al. 1978
S. cerevisiae (homozygosis by recombination or gene conversion)	Recombination	No data	+	Callen et al. 1980
A. nidulans (gene cross over)	Recombination	No data	(+)	Crebelli et al. 1985

TABLE 2-5 (*continued*)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
S. cerevisiae D61.M (loss of dominant color homolog)	Mitotic aneuploidy	+	+	Koch et al. 1988
Mammalian cells:				
Rat liver nuclei (chromatographically separated DNA fractions)	DNA-protein cross-links	–	No data	Keller and Heck 1988[c]
Rat primary hepatocytes (unscheduled DNA synthesis)	DNA damage	No data	–	Shimada et al. 1985
C3T3 mouse cells (BALB cell transformation assay)	Cell transformation	No data	(+)	Tu et al. 1985
Rat embryo cells (transformation)	Cell transformation	No data	+	Price et al. 1978
Syrian hamster embryo cells (clonal assay)	Cell transformation	No data	–	Amacher and Zelljadt 1983
Human lymphocytes (unscheduled DNA synthesis)	DNA damage	+/–	+/–	Perocco and Prodi 1981
Human WI-38 (unscheduled DNA synthesis)	DNA damage	(+)	(+)	Beliles et al. 1980

[a]Stabilizers used were oxiranes (1,2-epoxybutane and epichlorohydrin).
[b]Results not statistically compared with others in the study
[c]Testing effects of chloral,, a metabolite of trichloroethylene

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

](Commandeur et al. 1991; Dekant et al. 1986c). These products have been identified in the urine of workers exposed to trichloroethylene (Bimer et al. 1993). Although trichloroethylene itself may not be genotoxic, the evidence that some of its metabolites are genotoxic suggests that genotoxic effects may be a concern for some persons exposed to trichloroethylene. However, it is unknown whether exposure to levels of trichloroethylene found in and around hazardous waste sites may result in genotoxic effects.

Cancer. Workers who have been exposed to trichloroethylene show no higher incidence of cancer than controls in numerous epidemiologic studies (Axelson et al. 1978; Hardell et al. 1981; Malek et al. 1979; Novotna et al. 1979; Paddle 1983; Spirtas et al. 1991; Tola et al. 1980). Studies that did show an increased incidence of specific cancers in exposed workers were complicated by exposures to other chemicals, including known human carcinogens (Antilla et al. 1995; Blair et al. 1979; Hardell et al. 1994; Henschler et al. 1995). A population that drank contaminated well water in Wobum, Massachusetts, was reported to have an increase in childhood leukemia (Lagakos et al. 1986a). This was supported by a second study of New Jersey communities, which were served by a community water system, where an increase in the standardized mortality ratio for leukemia was found in females exposed to trichloroethylene (Pagliano et al. 1990). Further expansion of the New Jersey population showed a significant elevation of total leukemias, childhood leukemias, acute lymphatic leukemias, and non-Hodgkin's lymphoma in females exposed to >5.0 ppb trichloroethylene (Cohn et al. 1994). Diffuse large celVreticulosarcoma non-Hodgkin's lymphoma was significantly elevated in males as well. A retationship between trichloroethylene exposure in drinking water and cancer including non-Hodgkin's lymphoma, multiple myeloma, and leukemia was not observed in a Finnish study (Vartianinen et al. 1993). Problems associated with these studies, including exposure to a mixture of chemical contaminants and, particularly in the Lagakos et al. (1986a) study, the use of statistical methods which have been questioned by others (MacMahon 1986; Prentice 1986; Rogan 1986; Swan and Robins 1986; Whittemore 1986). Thus, the associations drawn from these studies between the incidence of leukemia and other cancers and the oral exposure to trichloroethylene are suggestive yet inconclusive. Data in the ATSDR trichloroethylene subregistry indicate an excess number of deaths from respiratory cancer in men exposed environmentally to trichloroethylene when compared with national survey data (ATSDR 1994). The study authors concluded that based on the incidence of smoking in the population "it would be inappropriate to relate this excess solely to trichloroethylene exposure."

Animal studies have shown increases in various types of cancer following inhalation or oral exposure to trichloroethylene, including cancer of the liver in mice (NCI 1976; NTP 1990) and cancer of the kidney (NTP 1988, 1990) and testes (NTP 1988) in rats. A serious problem with many of the studies is poor survival rate (Maltoni et al. 1986; NTP 1988,1990). Also, some of the studies used trichloroethylene containing small amounts of epoxide stabilizers to preserve the trichloroethylene from rapid degradation. Since these epoxides form free radicals, they themselves may be carcinogens and may contribute to the carcinogenic potential of industrial trichloroethylene. An NTP study using epoxide-free trichloroethylene showed liver tumors in mice, some indication of renal tumors in male rats, and no evidence of carcinogenicity in female rats (NTP 1990). Acute oral exposure to trichloroethylene or its metabolites preferentially induces peroxisome proliferation in mouse liver, which may be related to the carcinogenic response in this species (Goldsworthy and Popp 1987).

In addition, it has been hypothesized that some of the potential for tumor induction may be related to formation of trichloroethylene metabolites such as DCA, TCA, chloral hydrate, and 2-chloroacetaldehyde (Daniel et al. 1992; DeAngelo et al. 1991; Larson and Bull 1992a). The greater trichloroethylene-induced carcinogenicity in mice compared to the rat is believed by some investigators to be related to the increased conversion of the parent compound by mice to the reactive metabolites and the saturation of metabolism at higher dose levels in rats (Dallas et al. 1991; Dekant et al. 1986b; Filser and Bolt 1979; Larson and Bull 1992a; Prout et al. 1985; Stott et al. 1982). Direct administration of DCA and TCA in the drinking water resulted in an increased incidence of liver tumors in the mouse, while administration of trichloroethylene did not (Herren-Freund et al. 1987).

Trichloroethylene has been nominated for listing in the National Toxicology Program's (NTP) 9th Report on Carcinogens. Evaluation of this substance by the NTP review committees is ongoing. Based on limited evidence in humans, and sufficient evidence in animals for carcinogen&city, IARC (1995) considers trichloroethylene probably carcinogenic to humans (2A). ACGIH has placed trichloroethylene in their group A5, not suspected as a human carcinogen (ACGIH 1996). This group is for chemicals not suspected to be human carcinogens on the basis of properly conducted epidemiologic studies in humans. The studies reviewed were considered to "have sufficiently long follow-up, reliable exposure histories, sufficiently high dose, and adequate statistical power to conclude that exposure to the agent does not convey a significant risk of cancer to humans."

The incidence data for lung tumors in female Swiss mice together with tumor incidence data from other studies were used by EPA (1987a) to derive a carcinogenic potency estimate; a classification of B2 (probable human carcinogen) was assigned to trichloroethylene. In 1988, the Scientific Advisory Board for the EPA offered an opinion that the weight-of-evidence was on a C-B2 continuum (possible-probable human carcinogen). The agency has not restated a more current position on the weight-of-evidence classification and is reflecting this by posting an "under review" status in IRIS (IRIS 1996).

It has been argued that occupational studies do not suggest that trichloroethylene is a potent carcinogen, given the enormous size of the workforce exposed to the chemical and the small number of persons experiencing carcinogenic effects (Abelson 1993; Kimbrough et al. 1985; Steinberg and DeSesso 1993). Kimbrough et al. (1985) further maintain that, although trichloroethylene has been shown to be a weak-to-moderate carcinogen in mice and rats, there are differences between low- and high-dose metabolism in animals and differences between species in susceptibility to cancer. They suggest the possibility that metabolism to a proximate carcinogen does not occur in humans at low doses. In general, the associations drawn from the limited epidemiological data in humans, as well as cancer studies in animals, are suggestive yet inconclusive. Based on the available data, cancer should be an effect of concern for people exposed to trichloroethylene in the environment and at hazardous waste sites.

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high

urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to trichloroethylene are discussed in Section 2.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by trichloroethylene are discussed in Section 2.6.2.

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

2.6.1 Biomarkers Used to Identify or Quantify Exposure to 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-l 1%) of the absorbed dose is exhaled as unchanged trichloroethylene

through the lungs, and 2% of the dose is eliminated by the lungs as trichloroethanol. A correlation was 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.

There are three biological exposure indices (BEIs) for exposure to trichloroethylene at the ACGIH threshold limit value time-weighted average (TLV-TWA) of 50 ppm (ACGIH 1996). When measured at the end of a 40-hour workweek, TCA in urine is approximately 100 mg/g creatinine; when measured at the end of an 8-hour shift at the end of a workweek TCA and trichloroethanol in urine is approximately 300 mg/g creatinine, and free trichloroethanol in blood is approximately 4 mg/L.

Monitoring for exposure to trichloroethylene has also been performed by measuring trichloroethylene and its principal metabolites (TCA, trichloroethanol, trichloroethanol glucuronide) in blood and urine (Ertle et al. 1972; Ikeda et al. 1972; Imamura and Ikeda 1973; Kimmerle and Eben 1973b; Monster et al. 1979; Mtiller 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).

The use of the methods for monitoring metabolites of trichloroethylene in blood and urine is, however, 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 men secrete more trichloroethanol than women (Inoue et al. 1989). The use of the level of trichloroethylene adduction to blood proteins as a quantitative measure of exposure is also possible, although obtaining accurate results may be complicated by the fact that several metabolites of trichloroethylene may also form adducts (Stevens et al. 1992).

Differences 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 tricbloroethylene will tend to decrease the amount exhaled after a workshift. Increased renal function 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.

Urinary concentration of the renal tubular enzyme N-acetyl-β-D-glucosaminidase (NAG) has been used as an indicator of renal damage resulting from trichloroethylene exposure, although part of this effect may have been age dependent (Brogren et al. 1986). Other studies specifically examining the influence of factors such as age or alcohol consumption on the association 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 dosedependent 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 recommending this assay as a sensitive indicator of low-level exposure (Bai and Stacey 1993; Hamdan and Stacey 1993). However, 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).

Ambient air monitoring remains the best predictor of external exposure to trichloroethylene. Based on results using a mathematical model, measurements of TCA levels are considered the best indicator oflong-term exposure to trichloroethylene; the level of TCA in urine before workshift exposure is regarded as a predictor of the average exposure over days (Femandez et al. 1977). Accordingly, the measurement of urine levels of trichloroethanol may give a better indication of recent exposure.

2.6.2 Biomarkers Used to Characterize Effects Caused by Trichloroethylene

The system that is most sensitive to acute toxicity from inhalation exposure to trichloroethylene is the nervous system. 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 decomposition product. Conclusive studies distinguishing the toxicity of trichloroethylene, its decomposition products, 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 trichloroetbylene exposure in the water (Feldman et al. 1988). Although this test has only been used in the past to differentiate group differences (because of the lack of individual exposure data), it is possible that further refinements of this technique may make it useful as a biomarker in the future. 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 (Amler et al. 1995; Arezzo et al. 1985; Baker et al. 1985; WHO 1990).

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 β_2-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 β_2-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 (β_2-microglobulin and N-acetyl-β-D-glucosaminidase) are used to indicate 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 protein levels have been used to assess exposure to trichloroethylene (Capellini and Grisler 1958; Konietzko and Reill 1980; Rasmussen et al. 1993b).

2.7 INTERACTIONS WITH OTHER SUBSTANCES

Alcohol can affect the metabolism of trichloroethylene. This is noted in both toxicity and pharmacokinetic studies. In toxicity studies, simultaneous exposure to ethanol and trichloroethylene increased the concentration of trichloroetitylene in the blood and breath of male volunteers (Stewart et al. 1974~). These people also showed “degreaser’s flush”-a transient vasodilation of superficial skin vessels. In rats, depressant effects in the central nervous system are exacerbated by coadministration of ethanol and trichloroethylene (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 a long time interval after ethanol administration, and subsequent enzyme induction, trichloroethylene metabolic rates would be expected to increase. This may be the explanation for 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, reflecting a more reduced state in the hepatocyte (Larson and Bull 1989).

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, these compounds increased the steady-state concentration of trichloroethylene in the venous blood (Jakobson et al. 1986). Treatment with disulfiiam 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 4064% and 72-87%, respectively. Pretreatment with phenobarbital and 3-methylcholanthrene, which, like ethanol, are inducers of the liver mixed-function oxidase system, increased the extent of liver injury following exposure to trichloroethylene (Carlson 1974). Similar results were found with other inducers of the hepatic mixed-function oxidase system (Allemand et al. 1978; Moslen et al. 1977; Nakajima et al. 1990b). By enhancing the metabolism of trichloroethylene to its cytotoxic metabolites, compounds that induce the hepatic mixed-function oxidase system can potentiate the hepatotoxicity of trichloroethylene.

Animal studies indicate that trichloroethylene can sensitize the heart to epinephrine-induced arrhythmias. 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 also been found to increase the incidence of epinephrine-induced arrhythmias in rabbits exposed to trichloroethylene (White and Carlson 1982).

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, 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 alanine aminotransferase 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 enzyme 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.

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. 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 pahnitoyl CoA oxidation activity (Goldsworthy and Popp 1987). Rats injected with mixtures of benzene and trichloroethylene generally showed inhibited benzene metabolism as measured by conjugated phenol excretion (Starek 1991). At higher doses of trichloroethylene (5 mmol/kg), conjugated phenol excretion was lower directly after exposure, but higher than in the rat exposed to benzene alone 2 days after exposure. Additional reports include potentiation of the hepatotoxicity of carbon tetrachloride by trichloroethylene in rats (Pessayre et al. 1982) and competitive inhibition of P-450 metabolism by mixtures of vinyl chloride and trichloroethylene in rats, as determined by PBPK modeling and *in vitro* studies (Barton et al. 1995).

In degreasing operations, there may be exposures to carbon monoxide, which may compound symptoms reported by workers (NIOSH 1973). Illnesses of certain employees, documented at a neighboring hospital, included headache, nausea, dizziness, and chest pain. The NIOSH report concluded that the first employee illness reports were due to toxic effects of carbon monoxide complicated by trichloroethylene exposure. The

source of carbon monoxide was propane for lifts, and the trichloroethylene source was a malfunctioning degreaser.

2.8 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 5.6, 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. If the metabolic products are more toxic than the parent compound, an individual with higher metabolic rates (such as some children and adolescents) would be expected to have greater 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. People who smoke may increase their risk of toxic effects from trichloroethylene. However, these data are equivocal and limited. People who consume alcohol or who are treated with disulf'ii may be at greater risk of trichloroethylene poisoning because ethanol and disulfii 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 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.

The metabolism of trichloroethylene, as measured by the levels of excreted urinary metabolites, differs significantly between men and women, although study results are inconsistent (Inoue et al. 1989; Kimmerle and Eben 1973b; Norniyama and Nomiyama 1971). It does appear, however, that women excrete more urinary TCA than do men (Kimmerle and Eben 1973b; Nomiyama and Nomiyama 1971). Testosterone has been implicated as a factor in the lower absorption of trichloroethylene in male rats compared with females (Kadry et al. 1991b; McCormick and Abdel-Rahman 1991), and the same effect may occur in humans.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to trichloroethylene. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to trichloroethylene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to trichloroethylene: Bronstein and Currance 1988; Ellenhom and Barceloux 1988; Stutz and Janusz 1988.

2.9.1 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. Externally, trichloroethylene can produce mild irritation; chronic exposure may produce a rash and chapped skin (HSDB 1994). Exposed skin should be washed thoroughly with soap and water. Exposed eyes should be flushed with a clean neutral solution such as water or normal saline for 15-20 minutes (HSDB 1994). One source recommends inducing emesis within 30 minutes of a substantial ingestion unless the patient is or could rapidly become intoxicated, comatose, or convulsive (HSDB 1994). Absorption of trichloroethylene in water was found to be more than three times greater than absorption after administration in corn oil (Withey et al. 1983). Use of an activated charcoal slurry, aqueous or mixed with saline cathartic or sorbitol, has also been advocated as a mitigation strategy to diminish absorption in persons who have ingested trichloroethylene (HSDB 1994). Researchers have found that the presence of food in the stomach decreases oral absorption of the chemical and that

gastrointestinal absorption from an aqueous vehicle occurs at a very rapid rate (D'Souza et al. 1985). Thus, any attempt to reduce absorption must be instituted very soon after ingestion has occurred.

2.9.2 Reducing Body Burden

Trichloroethylene is exhaled following inhalation and oral exposures (Dallas et al. 1991; Koizumi et al. 1986; Stewart et al. 1970), whereas metabolites are mainly excreted in the urine (Femandez et al. 1977; Koizumi et al. 1986; Monster et al. 1979; Sato et al. 1977). Based on the knowledge of trichloroethylene metabolism and excretion, potential methods for reducing the body burden are presented. These methods have not been used in persons or animals exposed to trichloroethylene and should be researched further before being applied.

Mitigation strategies to increase urinary output and dilute the trichloroethylene once it is in the bloodstream seem useful. One method for this may be increased hydration of the individual in order to stimulate diuresis. Although flushing the gastrointestinal system by gastric lavage is sometimes suggested, it is contraindicated in the case of trichloroethylene poisoning because it is cumbersome in cases of ingestion of a rapidly absorbed liquid like trichloroethylene and may result in serious compromise to the electrolyte balance of the individual.

Studies suggest that a large percentage of trichloroethylene absorbed upon inhalation or oral exposure is metabolized in the liver via the cytochrome P-450 system (Buben and CWlaherty 1985; Ertle et al. 1972; Femandez et al. 1977; Green and Prout 1985; Kimmerle and Eben 1973a, 1973b; Monster et al. 1976,1979; Mtiller et al. 1972; Prout et al. 1985; Sato et al. 1977; Soucek and Vlachova 1960; Stott et al. 1982; Vesterberg and Astrand 1976). The major metabolites for trichloroethylene are trichloroethanol, TCA, and trichloroethanol-glucuronide conjugate. Although GSH plays a relatively minor role in metabolism of moderate doses of trichloroethylene, GSH may be more important in reacting with trichloroethylene oxide in high-dose situations. Thus, it may aid in reducing cell injury by this reactive epoxide. Administration of drugs which lower GSH levels, such as acetaminophen, may therefore be inadvisable after trichloroethylene exposure. Other sulfhydryl containing compounds, such as cysteine or cysteamine, could also be given instead of GSH.

Attempts to diminish the overall metabolism of trichloroethylene might be useful (e.g., hypothermia, mixed-function oxidase inhibitors, competitive inhibitors of trichloroethylene metabolism [i.e., P-450 substrates]), if instituted soon enough after trichloroethylene exposure. Catecholamines (especially beta agonists) act in concert with trichloroethylene, increasing the risk of cardiac arrhythmias. Hence, catecholamines should be administered to patients only in the lowest efficacious doses and for certain limited presentations of trichloroethylene poisoning. 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.

Information on the distribution of trichloroethylene is limited and provides little insight on how distribution might be altered to facilitate any attempts at mitigation of effects. One study reported distribution of ^{14}C-trichloroethylene to the liver, skin, and kidney following drinking water exposure (Koizumi et al. 1986). These data were comparable to those reported by Stott et al. (1982) following inhalation exposure. Evidence for the redistribution of trichloroethylene to fat over time and some reports of significant accumulation (Savolainen et al. 1977) do not agree with other reports of negligible accumulation (Koizumi et al. 1986).

2.9.3 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 1354; Morreale 1976; Smith 1966). Propanolol is an example of an anti-adrenergic agent that may be useful after exposure to trichloroethylene. This agent acts by blocking β-adrenergic receptors, thus preventing catecholamines such as epinephrine from binding, and 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. Because physical activity appears to increase the chance of cardiac effects, reducing physical exertion after exposure to trichloroethylene may be useful.

2.10 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 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 health effects (and techniques for developing methods to determine such health effects) of trichloroethylene.

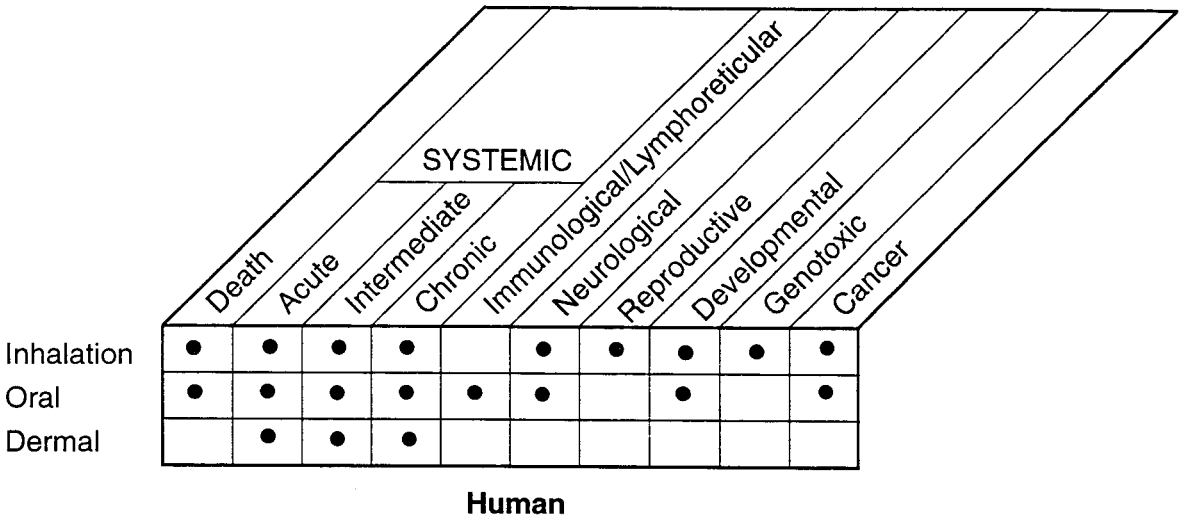
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

2.10.1 Existing Information on Health Effects of Trichloroethylene

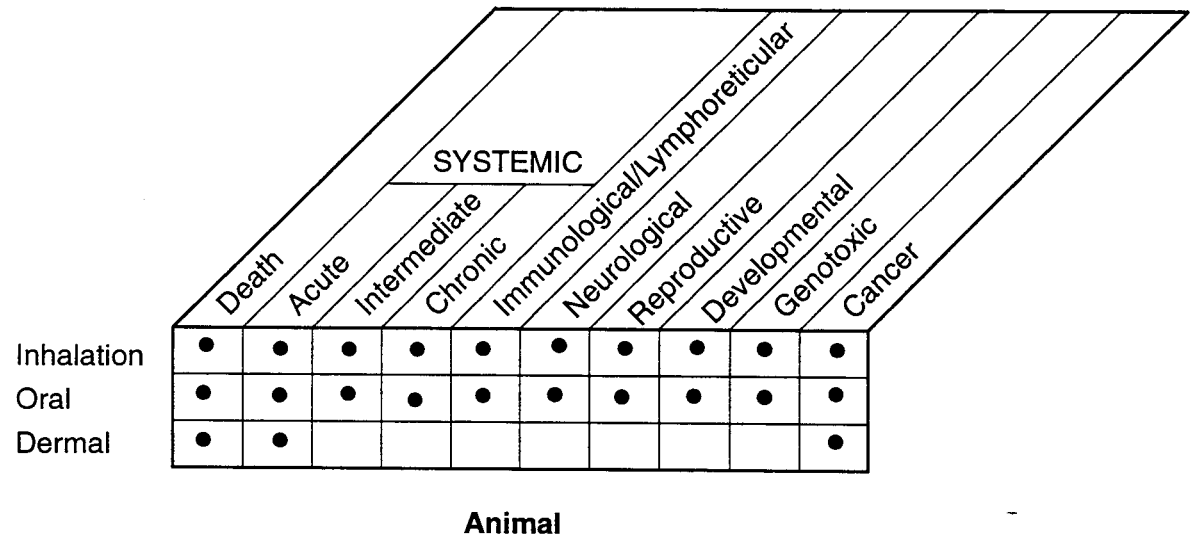
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to trichloroethylene are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of trichloroethylene. Each dot in the figure indicates that one or 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 Identifiing 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 in experiments have provided most of the data on health effects of inhaled tichloroethylene in humans. Most of the information on reported effects in humans following oral exposure

FIGURE 2-5. Existing Information on Health Effects of Trichloroethylene



Human



Animal

● Existing Studies

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 or unquantified. 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, but exposure/dose data are not available.

Studies have been performed in animals that cover all of the health effects areas listed in Figure 2-5 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 but do not fully characterize exposure/dose-effect relationships. Threshold doses are lacking for many of the toxic effects. Some of the effects (e.g., immunosuppression, hematologic effects) need additional characterization, and there is a paucity of data for effects resulting from acute and chronic exposures. One of the significant limitations to interpreting results from most 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 intermittent or continuous exposure to trichloroethylene in air or drinking water.

2.10.2 Identification of Data Needs

Acute-Duration Exposure. 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; Sidorin et al. 1992). 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 excretion. Acute inhalation studies in animals suggest that trichloroethylene sensitizes the heart to catecholamines (Reinhardt et al. 1973; White and Carlson 1979, 1981,1982). Sufficient human and animal information is available to identify the nervous system as the most 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. An acute-duration MRL of 2 ppm for inhalation exposure has been derived on the basis of subjective neurological effects (headache, fatigue, drowsiness) in humans exposed to 200 ppm

trichloroethylene for 5 days, 7 hours/day (Stewart et al. 1970). 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 (Cleat-field 1970; David et al. 1989; DeFalque 1961; Gutch et al. 1965; Lachnit and Pietschmann 1960), mild evidence of liver damage (Cleat-field 1970), and renal failure (David et al. 1989; Gutch et al. 1965). Additional adverse effects noted in animals following acute inhalation exposure to trichloroethylene include hrer damage (Carlson 1974; Fujita et al. 1984; Okino et al. 1991), kidney damage (Crofton and Zhao 1993), and respiratory effects in mice (Odum et al. 1992; Villas&i et al. 1991).

Acute oral LD_{50}s are available from animal studies (Smyth et al. 1969; Tucker et al. 1982). Following acute oral exposure to trichloroethylene effects noted in humans include cardiac effects (Dhuner et al. 1957; Morreale 1976; Perbellini et al. 1991) and neurological effects (Dhuner et al. 1957; Morreale 1976; Perbellini et al. 1991; Stephens 1945; Todd 1954). Effects noted in animals following acute oral exposure to trichloroethylene include hepatic (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 (Berman et al. 1995), and neurological effects (Coberly et al. 1992; Moser et al. 1995; Narotsky and Kavlock 1995; Narotsky et al. 1995). An acute-duration MRL of 0.2 mg/kg/day for oral exposure has been derived on the basis of developmental neurological effects in mice (Fredriksson et al. 1993). The weight of evidence supports nervous system development as a target of trichloroethylene (Isaacson and Taylor 1989; Nolaird-Gerbec et al. 1986; NTP 1986; Taylor et al. 1985), and thus justifies its use in deriving an MRL. However, further studies on the developmental neurological effects of trichloroethylene in both animals and humans are needed to more fully characterize these effects.

Pain and erythema have been reported by study subjects who stuck 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 is needed regarding doses/concentrations that result in cardiac effects and conditions that may make persons more sensitive to these effects.

Further information gained from accidental human exposures could be utilized in defining the lowest air level that affects humans. 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 available on neurological effects after acute inhalation exposure.

Intermediate-Duration Exposure. Intermediate-duration studies of tetrachloroethylene exposure of humans are limited to case reports of people who were occupationally exposed (Mitchell and Parsons-Smith 1969; Phoon et al. 1984; Priest and Horn 1965; Steinberg 1981; Wemisch et al. 1991). Neurological effects were the most consistent effects reported (Mitchell and Parsons-Smith 1969; Steinberg 1981; Wemisch et al. 1991). Trichloroethylene has been studied in animals following intermediate-duration inhalation exposure (Adams et al. 1951; Albee et al. 1993; Arito et al. 1994a; Baker 1958; Battig and Grandjean 1963; Blain et al. 1992,1994; Goldberg et al. 1964a; Haglid et al. 1981; Jaspers et al. 1993; Kimmerle and Eben 1973a; Kjellstrand et al. 1981, 1983a; Kulig 1987; Laib et al. 1979; Okamoto and Shiwaku 1994; Prendergast et al. 1967; Rebert et al. 1991; Silverman and Williams 1975). Effects noted in these studies included neurological effects (Adams et al. 1951; Arito et al. 1994a; Baker 1958; Battig and Grandjean 1963; Blain et al. 1992; Goldberg et al. 1964a; Haglid et al. 1981; Jaspers et al. 1993; Kulig 1987; Rebert et al. 1991; Silverman and Willams 1975), and hepatic effects (Adams et al. 1951; Kjellstrand et al. 1983a). An intermediate-duration inhalation MRL of 0.1 ppm has been derived based on neurological effects in rats (Arito et al. 1994a).

With the exception of studies examining reproductive outcome in people exposed to trichloroethylene in drinking water (ATSDR 1997; MDPH 1994), intermediate-duration studies in humans follow&g oral exposure were not available. Intermediate-duration oral studies of trichloroethylene in animals (Barret et al. 1991,1992; Buben and O'Flaherty 1985; Constan et al. 1995; Dawson et al. 1993; Goel et al. 1992; Isaacson et al. 1990; Mason et al. 1984; Merrick et al. 1989; NCI 1976; NTP 1988,1990; Stott et al. 1982; Tucker et al. 1982; Zenick et al. 1984) are available, but did not adequately provide exposure levels that could be

related to effects. Therefore, an intermediate-duration oral MRL has not been derived. Intermediate-duration dermal studies of trichloroethylene in humans or animals were not available.

Additional animal studies of trichloroethylene following intermediate-duration oral exposure are necessary to further define dose-response relationships. Because developmental neurotoxicity appears to be a sensitive end point, a focus on this end point would be useful. Animals studies following intermediate-duration dermal exposure are necessary. These studies would indicate whether targets following dermal exposure differ compared to inhalation and oral exposure.

Chronic-Duration Exposure and Cancer. Information on humans is available from studies of people exposed to trichloroethylene in the air for chronic periods in the workplace (Barododej and Vyskocil1956; Barret et al. 1987; Bauer and Rabens 1974; El Ghawabi et al. 1973; Kohhrmller and Kochen 1994; Rasmussen et al. 1993c; Ruitjen et al. 1991). These studies indicate that the nervous system may be the most sensitive target. other studies of workers occupationally exposed to trichloroethylene for chronic periods indicate that liver (Bauer and Rabens 1974; Capelliei and Grisler 1958; Schuttman 1970) and kidneys (Brogren et al. 1986) are targets of trichloroethylene. The liver effects noted included increases serum levels of liver enzymes (Bauer and Rabens 1974; Schuttman 1970), and liver enlargement (Capellini and Grisler 1958; Schuttman 1970). The kidney effects noted include increased N-acetyl-β-D-glucosaminidase (Brogren et al. 1986). Information on chronic human exposure to trichloroethylene via the oral route is largely from studies of people who consumed trichloroethylene and other solvents in their drinking water for several years (ATSDR 1994; Bove et al. 1995; Burg et al. 1995; Byers et al. 1988; Cohn et al. 1994; Fagliano et al. 1990; Feldman et al. 1988; Freni and Bloomer 1988; Goldberg et al. 1990; Kilbum 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; Kilbum and Warshaw 1992; Waller et al. 1994), neurological effects (Feldman et al. 1988), an increase in 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 has been established by ATSDR to monitor people living in areas wherethey were exposed to trichloroethylene in drinking water (ATSDR 1994; Burg et al. 1995). The data in the subregistry indicate excess numbers of heart disease and respiratory cancer deaths, as well as stroke, anemia, liver and kidney disease, and hearing and speech impairment. The greatest limitation to these studies is the difficulty in estimating dose, and exposure to multiple chemicals. Some workers who have had dermal contact with

tichloroethylene 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 inhalation MRL was not derived because of the lack of adequate measurement of exposure levels in some studies and/or the lack of effects that could be specifically related to the exposures. Chronic oral exposure studies in animals have focused on carcinogenicity and are not helpful in defining noncancer end points in humans following long-term exposure. Data were not sufficient for the development of a chronic-duration oral MRL. Further epidemiological studies in humans are necessary to help in assessing the risks to persons who live near hazardous waste sites. Additional chronic-duration oral and inhalation studies of trichloroethylene in animals are necessary to further define the thresholds of toxicity. A chronic-duration dermal study in animals may also be useful to identify targets following dermal exposure to trichloroethylene.

Humans exposed to trichloroethylene for chronic periods via the inhalation and dermal routes in the workplace apparently did not experience an increased incidence of cancer, as indicated by numerous epidemiological studies (Axelson 1986; Axelson et al. 1978, 1994; Malek et al. 1979; Shindell and Uhich 1985; Spirtas et al. 1991). I'hese studies are all limited, however, and may not be useful for detecting a weak carcinogen or carcinogens with a long latency period. A number of studies have also shown small but statistically significant associations betweencancer and occupational exposure to trichloroethylene (Antilla et al. 1995; Hat-dell et al. 1994; Henschler et al. 1995). The link between oral exposure to trichloroethylene and cancer in humans is controversial. A number of studies support an association (Byers et al. 1988; Fagliano et al. 1990; Kotelchuck and Parker 1979; Lagakos et al. 1986a; Parker and Rosen 1981), while a number of studies do not provide support for an association between cancer and exposure to trichloroethylene in drinking water (ATSDR 1994; Freni and Bloomer 1988; Vartiainen et al. 1993). These studies are all limited by multiple exposure and the lack of information regarding individual exposure information.

Animal studies have shown that tumors can result from both inhalation (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. Unfortunately, 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 and do not point to a particular target organ for increased tumor incidence. 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 but not female rats. Further studies are necessary to elucidate the mechanisms responsible for the sex and species differences in cancer incidence and to determine whether the processes that operate in the induction of mouse liver cancer by trichloroethylene also operate in the human liver.

Genotoxicity. The genotoxicity studies of trichloroethylene have produced mixed results. Human and *in vivo* animal data exist that suggest that trichloroethylene has genotoxic effects-specifically, sister chromatid exchange, chromosomal aberrations, single-strand breaks, and gene mutations (Gu et al. 1981; Nelson and Bull 1988; Rasmussen et al. 1988; Seiji et al. 1990; Walles 1986). In addition, *in vitro* studies show positive results for gene mutations, recombination, mitotic aneuploidy, and cell transformation (Bronzetti et al. 1978; Callen et al. 1980; Crebelli et al. 1985; Koch et al. 1988; McGregor et al. 1989; Tu et al. 1985). However, many additional studies testing these and other genotoxic effects have been negative (Amacher and Zelljadt 1983; Beliles et al. 1980; Nagaya et al. 1989a; Rossi et al. 1983; Shimada et al. 1985; Slacik-Erben et al. 1980). 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 an increased 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. 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 showed an approximate 3-fold increase in spontaneous abortion in women exposed to trichloroethylene and other solvents (Windham et al. 1991). Significant effects on sperm parameters were not observed in men occupationally exposed to trichloroethylene (Rasmussen et al. 1988). Adverse reproductive effects were not noted in humans that ingested water contaminated with trichloroethylene and other solvents (Byers et al. 1988; Freni and Bloomer 1988; Lagakos et al. 1986a). Available inhalation studies in animals do not fully characterize the reproductive effects following inhalation exposure. Only abnormal sperm morphology has been reported after inhalation exposure; however reproductive performance was not evaluated in these studies

(Beliles et al. 1980; Land et al. 1981). Studies for oral exposure indicate no adverse reproductive effects (NTP 1985, 1986). More research on the reproductive effects of inhalation exposure to trichloroethylene, especially effects on miscarriage in humans is needed. Additional animal studies via the inhalation and dermal routes are needed to further characterize reproductive effects.

Developmental Toxicity. Studies of female workers exposed to trichloroethylene found no correlation between fetal malformation and exposure (Tola et al. 1980) or birth weight and exposure (Windham et al. 1991). An increase in birth defects was observed in nurse-anesthetists who were exposed to trichloroethylene and other anesthetic gases during pregnancy (Corbett et al. 1974). Oral studies have suggested that exposure to trichloroethylene, along with other volatile hydrocarbons, may increase the risk of childhood leukemia (Lagakos et al. 1986b). Another study reported a possible increase in the risk of congenital heart defects (Goldberg et al. 1990) in children whose parents were exposed to trichloroethylene in the drinking water. Adverse developmental outcomes reported in more recent studies include decreased birth weights (Bove et al. 1995; MDPH 1994; ATSDR 1997); choanal atresia, and hypospadias/congenital chordee (MDPH 1994). An increase in hearing impairment in children aged 9 years or younger was reported among participants in the ATSDR exposure subregistry for tricholorehtylene. Though many studies have reported weak associations betweeen oral exposurse to trichloroethylene with other solvents and adverse birth outcomes, at least one report has found no increases in congenital defects from such exposures (Freni and Bloomer 1988). Limitations in the available reports include small numbers of cases, poorly characterized exposures, exposure to multiple solvents, and possible interviewer bias. 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 exisitng database. There are no known studies in humans of developmental effects from dermal exposure to trichloroethylene.

Animal studies regarding developmental effects have been completed using both inhalation (Beliles et al. 1980; Dorfmueller et al. 1979; Hardin et al. 1981; Healy et al. 1982; Schwetz et al. 1975) and oral exposure (Coberly et al. 1992; Cosby and Dukelow 1992; Dawson et al. 1993; Isaacson and Taylor 1989; Manson et al. 1984; Narotsky and Kavlock 1995; Narotsky et al. 1995; Noland-Gerbec et al. 1986; NTP1985, 1986). Following inhalation exposure, the effects noted at concentrations that were not overtly maternally toxic were decreased fetal weight and incomplete ossification (Dorfmueller et al. 1979; Healy et al. 1982). Following oral exposure at maternally toxic doses the effects observed included a significant decrease in litter size and micro- or anophthalmia (Narotsky and Kavlock 1995; Narotsky et al. 1995), increased perinatal mortality (Manson et al. 1984; NTP 1985), an increase in fetal heart abnormalities (Dawson et al. 1993), a decrease in

the number of myelinated fibers in the hippocampus (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). Trichloroacetic acid given to rats by gavage during gestation was also shown to increase heart defects (Smith et al. 1989). An acute-duration oral MRL of 0.2 mg/kg/day was derived based on behavioral changes observed in mice exposed from 10 to 16 days of age (Fredriksson et al. 1993).

Further monitoring for birth defects in humans exposed to trichloroethylene are needed, especially in populations in which exposure concentrations could be determined. Additional studies in animals that develop dose-response relationships for particular defects and trichloroethylene exposure, as well as exposure to metabolites of trichloroethylene, are needed.

Immunotoxicity. Immunological abnormalities were noted in adults who were exposed to contaminated well water and who were family members of children with leukemia (Byers et al. 1988). This was manifested by altered ratios of T-lymphocyte subpopulations, increased incidence of auto-antibodies, and increased infections. Interpretation of this study is limited by factors discussed in Sections 2.2.2.3 and 2.2.2.8. 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).

A limited study in animals also presents evidence for increased susceptibility to *Streptococcus zooepidomicus* (Aranyi et al. 1986). Immune system effects observed in mice exposed orally to trichloroethylene included 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. A study in which a susceptible strain of mice was treated with intraperitoneal injections of trichloroethylene suggests that trichloroethylene can accelerate the autoimmune response (Khan et al. 1995). The immune system may be a sensitive end point for toxic effects from low-level exposure to trichloroethylene; however, no firm conclusions can be drawn from the available information. Additional human and animal studies are needed to better characterize this end point and determine the potential for immunological effects for people exposed to trichloroethylene at hazardous waste sites.

Neurotoxicity. Sufficient human information exists to identify the nervous system as the primary target for acute inhalation trichloroethylene exposure in humans (Nomiyama and Nomiyama 1977; Salvini et al. 1971; Stewart et al. 1970,1974a; Vernon and Ferguson 1969). 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 Vyskocill 956; 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). Several studies of the population in Wobum, 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 did find possible residual cranial nerve damage when comparing the exposed and nonexposed population cohorts (Feldman et al. 1988).

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. Intermediate-duration animal studies via the inhalation route reveal behavioral changes (Albee et al. 1993; Battig and Grandjean 1963; Kulig 1987; Silverman and Williams 1975) and biochemical and histopathological alterations (Haglid et al. 1981). Caution should be used when interpreting the results of these studies, however, because the behavioral changes were not confirmed by biochemical measurements, and biochemical changes were not confirmed by behavioral measurements. Chronic oral animal studies reveal motor deficits (NTP 1988). Thus, the inhalation studies clearly indicate that the nervous system is a target organ, and there is suggestive evidence that exposure via the oral route would also damage this system. A complete battery of neurological tests performed on humans or animals exposed to trichloroethylene via the oral pathway is needed. There are few studies that examine the mechanisms of trichloroethylene-induced effects by the inhalation route; data in this area are needed.

Epidemiological and Human Dosimetry Studies. Several epidemiological studies have been conducted that showed little or no relationship between increased cancer risk and inhalation and dermal exposure to trichloroethylene in the workplace (Axelson 1986; Axelson et al. 1978, 1994; Malek et al. 1979; Shindell and Uhich 1985). There have also been studies of people exposed to a number of solvents including trichloroethylene in the drinking water (ATSDR 1994; Bove et al. 1995; Burg et al. 1995; Byers et al. 1988; Cohn et al. 1994; 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; Kilbum and Warshaw 1992; Waller et al. 1994), neurological effects (ATSDR 1994; Burg et al. 1995; Feldman et al. 1988), an increase in birth defects (Bove et al. 1995; Goldberg et al. 1990; Lagakos et al. 1986a), and cancer (Cohn et al. 1994; Fag&no et al. 1990; Lagakos et al. 1986a). The greatest limitations in these 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, 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 (trichloroethanol and TCA) in the urine and blood (Christensen et al. 1988; Monster and Boersma 1975; Pekari and Aitio 1985b; Wallace et al. 1986a, 1986b, 1986c, 1986d; Ziglio et al. 1984). 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 1996).

Effect. 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. Studies of workers occupationally exposed to trichloroethylene for chronic periods have reported increases in serum levels of liver enzymes (Bauer and Rabens 1974; Schuttman 1970), liver enlargement (Capellini and Grisler 1958; Schuttman 1970), and increased N-acetyl-β-D-glucosaminidase (Brogren et al. 1986). Although these effects are not specific for trichloroethylene exposure, additional research further defining the dose-response relationship 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; Femandez 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. Several investigators are working on PBPK models of trichloroethylene distribution in animals, and studies are under way 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 confiiation. 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. PBPK modeling efforts may help provide much of the needed information.

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 heath effects from animal data. Development and validation of PBPK models is one approach to inter-species comparisons of data.

Methods for Reducing Toxic Effects. The general recommendations for reducing the absorption of trichloroethylene following acute inhalation (HSDB 1994), oral (D'Souza et al. 1985; Withey et al. 1983), dermal, or ocular (HSDB 1994) exposure are well established and have a proven efficacy. No additional investigations are considered necessary at this time.

No clinical treatments other than supportive measures are currently available to enhance elimination of 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.

2.10.3 On-going Studies

The National Institute of Environmental Health Sciences is currently sponsoring substantial research into the health effects of trichloroethylene. The relationship between maternal trichloroethylene exposure birth weight is being studied in a human population in Tucson, Arizona. The study is being completed by Dr. S. Rodenbeck at Tulane University (Rodenbeck 1997). Continued research on the possible link between trichloroethylene exposure and human congenital heart defects is being conducted by Dr. S. Goldberg at the University of Arizona, using rat and avian model systems. Reproductive effects in rats, including cell-cell interactions, sperm motility, and myometrial gap junctional communication, are being investigated using both *in vivo* and *in vitro* systems by Dr. R. Loch-Caruso at the University of Michigan. Dr. B. Hoener of the University of California, Berkeley, is continuing development of PBPK models for the disposition and excretion of trichloroethylene and its metabolites in rats and children, while collaboration is on-going with Dr. C. Becker at the same university, with the goal of adapting lead kinetic models to the kinetics and neurotoxicity of trichloroethylene. Dr. M. Philbert of Rutgers University is exploring the effects of trichloroethylene on astrocyte function and fluid homeostasis in the rat brain during postnatal development, and Dr. G. Yost at the University of Utah is studying the mechanisms of trichloroethylene-induced pneumotoxicity in rabbits. Neurobehavioral effects of oral exposure to trichloroethylene in rats are being studied by Dr. Chandra Mehta at Texas Southern University.