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 of the toxicology of chloroethane. 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-adverseeffect 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 anattempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear LOAELs or NOAELs should also help in

determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of chloroethane are indicated in Table 2- 1 and Figure 2-l.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for chloroethane. 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 noncancerous health effects only and do not consider 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 are acquired following 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

Some of the data on the health effects of chloroethane following inhalation exposure were taken from a study by Troshina (1966). This report does not provide an adequate description of experimental methods or results. Consequently, the results of the study are not included in Table 2-l or plotted in Figure 2-l as levels of significant exposure.

2.2.1.2 Death

Use of chloroethane as a general anesthetic has occasionally resulted in the death of human patients (Konietzko 1984; Kuschinsky 1970; Lawson 1965; Lehman and Flury 1943). In the years between 1945 and 1964, there were 71 deaths attributed to chloroethane inhalation in the United Kingdom (Dawkins 1964). Only chloroform has been blamed for more anesthetic deaths than chloroethane (Lawson 1965). Death from respiratory paralysis (Kuschinsky 1970) and toxic injury to the heart (Lehman and Flury 1943) have been reported following anesthesia with chloroethane. Death of a man following abuse of chloroethane has also been reported (Yacoub et al. 1993). Although the blood concentration of chloroethane was 65 mg/dL in this man shortly after death, the study authors believed that because of resuscitation attempts for about 65 minutes, concentrations of chloroethane resulting in death were actually greater than the measured concentration. Levels of significant exposure are not reported in Table 2- 1 or plotted in Figure 2- 1 because concentrations of chloroethane lethal to humans are not known.

Mortality produced by inhalation of high concentrations of chloroethane vapor has been studied quantitatively in animals. The minimum lethal concentration of chloroethane in a 2-hour exposure study in mice was 56,860 ppm (Lazarew 1929). In another 2-hour exposure test, the minimum lethal concentration was 54,948 ppm in rats and mice (Troshina 1966). In this case, death was probably caused by asphyxiation. Exposure to 19,000 ppm chloroethane for 4 hours did not produce mortality in rats or mice (NTP 1989). The lethal concentration of chloroethane increased as the duration of exposure decreased in guinea pigs exposed to chloroethane concentrations ranging from 0 to 241,000 ppm for 5 minutes to 13.5 hours (Sayers et al.1929). Exposure to 20,000 ppm chloroethane for 9 hours was not lethal to guinea pigs in this study. Death was reported during or after exposure of guinea pigs to 40,000 ppm for 9 hours (2/6), 87,000 ppm for 4.5 hours (6/6), 76,000 ppm for 90 minutes (4/4), and 51,000 ppm for 40 minutes (l/3).

Table 2-1. Levels of Significant Exposure to Chloroethane - Inhalation

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
ACUTE EXPOSURE									
Death									
1	Mouse (NS)	2 hr					56860	(minimum lethal concentration)	Lazarew 1929
2	Gn Pig (NS)	540 min					40000	(2/6 died)	Sayers et al. 1929
Systemic									
3	Human	8.5 min	Gastro	25000	33600	(nausea, vomiting during recovery from anesthesia)			Davidson 1925
4	Human	2-4 breaths	Gastro		20000	(mild abdominal cramps)			Sayers et al. 1929
			Ocular	20000	40000	(slight eye irritation)			
5	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d	Resp	9980					Landry et al. 1982
			Cardio	9980					
			Gastro	9980					
			Hemato	9980					
			Musc/skel	9980					
			Hepatic	9980					
			Renal	9980					
			Endocr	9980					
			Dermal	9980					
			Ocular	9980					
			Bd Wt	9980					

Table 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
6	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d	Bd Wt	19000			NTP 1989
7	Mouse (B6C3F1)	11 d 23 hr/d	Resp	4843			Landry et al. 1987, 1989
			Cardio	4843			
			Gastro	4843			
			Hemato	4843			
			Musc/skel	4843			
			Hepatic	4843			
			Renal	4843			
			Endocr	4843			
			Dermal	4843			
			Ocular	4843			
			Bd Wt	4843			
8	Mouse (B6C3F1)	2 wk 5 d/wk 6 hr/d	Bd Wt	19000			NTP 1989
9	Mouse (CF-1)	Gd 6-15 6 hr/d	Hepatic	4946 F			Scortichini et al. 1986
			Bd Wt	4946 F			

Table 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
10	Gn Pig (NS)	90-540 min	Resp	20000	40000	(slight parabronchial pneumonia)			Sayers et al. 1929
			Cardio	20000			40000	(degeneration of heart muscle of guinea pigs that died)	
			Hepatic		20000	(liver pathology not further described)			
			Renal	20000			40000	(fatty or granular degeneration of the cortex)	
11	Dog (Beagle)	2 wk 5 d/wk 6 hr/d	Resp	9980 M					Landry et al. 1982
			Cardio	9980 M					
			Gastro	9980 M					
			Hemato	9980 M					
			Musc/skel	9980 M					
			Hepatic	9980 M					
			Renal	9980 M					
			Endocr	9980 M					
			Dermal	9980 M					
			Ocular	9980 M					
			Bd Wt	9980 M					
Immunological/Lymphoreticular									
12	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d		9980					Landry et al. 1982
13	Mouse (B6C3F1)	11 d 23 hr/d		4843					Landry et al. 1987, 1989

Table 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
14	Dog (Beagle)	2 wk 5 d/wk 6 hr/d		9980 M					Landry et al. 1982
	Neurological								
15	Human	up to 22 min			13000	(subjective feeling of intoxication, increased reaction times)	19000	(distinct intoxication, slight analgesia, decreased reaction times)	Davidson 1925
16	Human	8.5 min		25000	33600	(nausea, vomiting during recovery from anesthesia)			Davidson 1925
17	Human	2-4 breaths			20000	(marked dizziness)			Sayers et al. 1929
18	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d			9980	(slight lethargy)			Landry et al. 1982
19	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d		19000					NTP 1989
20	Mouse (B6C3F1)	11 d 23 hr/d		4843					Landry et al. 1987, 1989
21	Mouse (B6C3F1)	2 wk 5 d/wk 6 hr/d		19000					NTP 1989

Table 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
22	Gn Pig (NS)	540 min		10000	20000 (unsteady, sluggish, dizzy)		Sayers et al. 1929
23	Dog (Beagle)	2 wk 5 d/wk 6 hr/d			9980M (hyperactivity during exposure in 1/2 dogs)		Landry et al. 1982
	Reproductive						
24	Rat (Fischer- 344)	5d 6 h/day		15000			Fedtke et al. 1994a
25	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d		9980			Landry et al. 1982
26	Mouse (B6C3F1)	5 d 6 hr/day			15000F (approximately 35% decrease in uterine weight)		Fedtke et al. 1994a
27	Mouse (B6C3F1)	11 d 23 hr/d		4843			Landry et al. 1987, 1989
28	Mouse (CF-1)	Gd 6-15 6 hr/d		4946 F			Scortichini et al. 1986
29	Dog (Beagle)	2 wk 5 d/wk 6 hr/d		9980 M			Landry et al. 1982

Table 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Developmental							
30	Mouse (CF-1)	Gd 6-15 6 hr/d		1504[b]	4946 (increased incidence of small centers of unossified bone in the skull)		Scortichini et al. 1986
INTERMEDIATE EXPOSURE							
Systemic							
31	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Resp	19000			NTP 1989
			Cardio	19000			
			Gastro	19000			
			Hepatic	19000			
			Renal	19000			
			Endocr	19000			
			Dermal	19000			
			Bd Wt	19000			
32	Mouse (B6C3F1)	21 d 6 hr/d	Hepatic	15000			Bucher et al. 1995
			Endocr	15000			
			Bd Wt	15000			

Table 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
33	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d	Resp	19000			NTP 1989
			Cardio	19000			
			Gastro	19000			
			Hepatic	19000			
			Renal	19000			
			Endocr	19000			
			Dermal	19000			
			Bd Wt	19000			
Immunological/Lymphoreticular							
34	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		19000			NTP 1989
35	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		19000			NTP 1989
Neurological							
36	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		19000			NTP 1989
37	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		19000			NTP 1989

Table 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	Reproductive						
38	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		19000			NTP 1989
39	Mouse (B6C3F1)	21 d 6 hr/d			15000F (small increase in the average duration of the estrous cycle, no consistent changes in hormone levels)		Bucher et al. 1995
40	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		19000			NTP 1989
	CHRONIC EXPOSURE						
	Death						
41	Mouse (B6C3F1)	100 wk 5 d/wk 6 hr/d				15000 (decreased survival)	NTP 1989

Table 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Systemic							
42	Rat (Fischer- 344)	102 wk 5 d/wk 6 hr/d	Resp	15000			NTP 1989
			Cardio	15000			
			Gastro	15000			
			Musc/skel	15000			
			Hepatic	15000			
			Renal	15000			
			Endocr	15000			
			Dermal	15000			
			Bd Wt	15000			
43	Mouse (B6C3F1)	100 wk 5 d/wk 6 hr/d	Resp	15000			NTP 1989
			Cardio	15000			
			Gastro	15000			
			Musc/skel	15000			
			Hepatic	15000			
			Renal	15000 M	15000F	(scattered foci of tubular regeneration, minimal glomerulosclerosis)	
			Endocr	15000			
			Dermal	15000			
			Bd Wt	15000			
Immunological/Lymphoreticular							
44	Rat (Fischer- 344)	102 wk 5 d/wk 6 hr/d		15000			NTP 1989

Table 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
45	Mouse (B6C3F1)	100 wk 5 d/wk 6 hr/d		15000			NTP 1989
	Neurological						
46	Rat (Fischer- 344)	102 wk 5 d/wk 6 hr/d		15000			NTP 1989
47	Mouse (B6C3F1)	100 wk 5 d/wk 6 hr/d		15000 M	15000F (hyperactivity during exposure)		NTP 1989
	Reproductive						
48	Rat (Fischer- 344)	102 wk 5 d/wk 6 hr/d		15000			NTP 1989
49	Mouse (B6C3F1)	100 wk 5 d/wk 6 hr/d		15000			NTP 1989

Table 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL			Reference
					Less serious (ppm)	Serious (ppm)		
Cancer								
50	Rat (Fischer- 344)	102 wk 5 d/wk 6 hr/d				15000 M	(CEL: 5/50 skin trichoepithelioma, sebaceous gland adenoma, or basal cell carcinoma)	NTP 1989
						15000 F	(CEL: 3/50 malignant astrocytomas in the brain significantly different from historical but not concurrent controls)	
51	Mouse (B6C3F1)	100 wk 5 d/wk 6 hr/d				15000 F	(CEL: 43/50 uterine carcinomas; 8/48 hepatocellular carcinomas or adenomas)	NTP 1989
						15000 M	(CEL: 10/48 lung adenomas or carcinomas)	

[a] The numbers correspond 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] The acute-duration inhalation minimal risk level (MRL) of 15 ppm was derived by dividing the 1,504-ppm NOAEL by an uncertainty factor of 100 (10 for interspecies extrapolation, 10 for human variability).

Bd Wt = body weight; Cardio = cadiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; ppm = parts per million; Resp = respiratory; wk = week(s)

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

Acute (≤14 days)

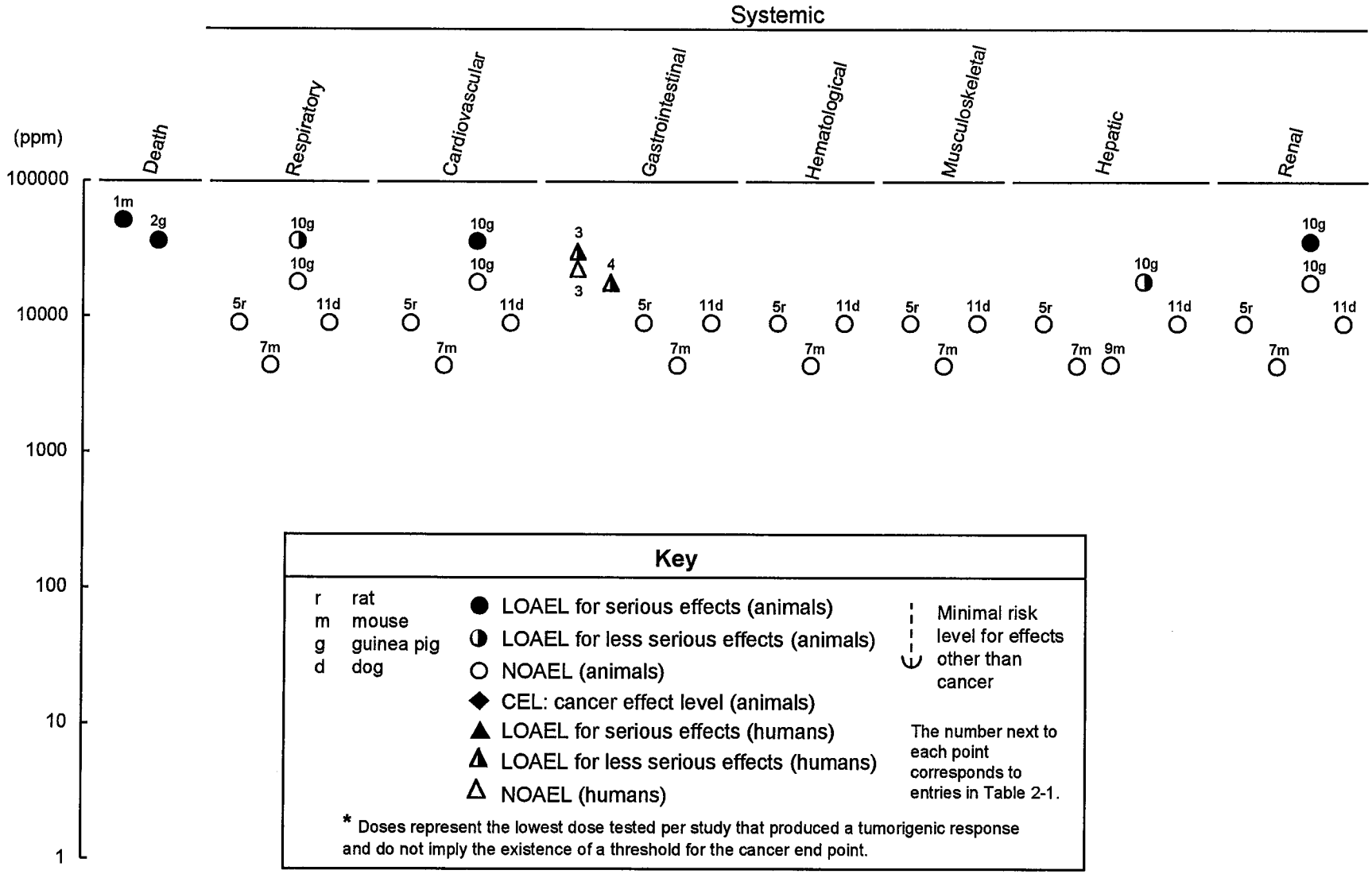


Figure 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (cont.)

Acute (≤14 days)

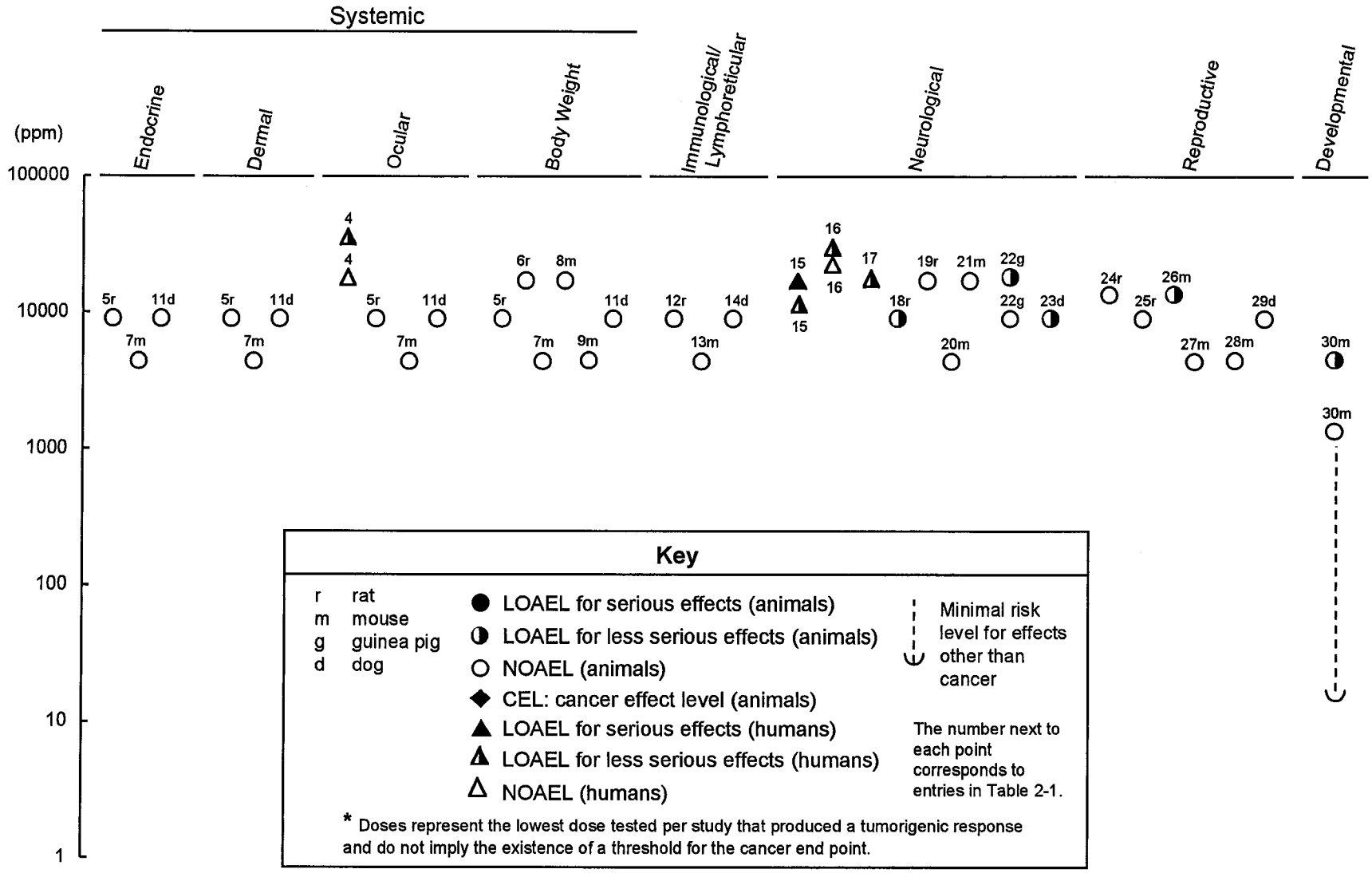


Figure 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (cont.)

Intermediate (15-364 days)

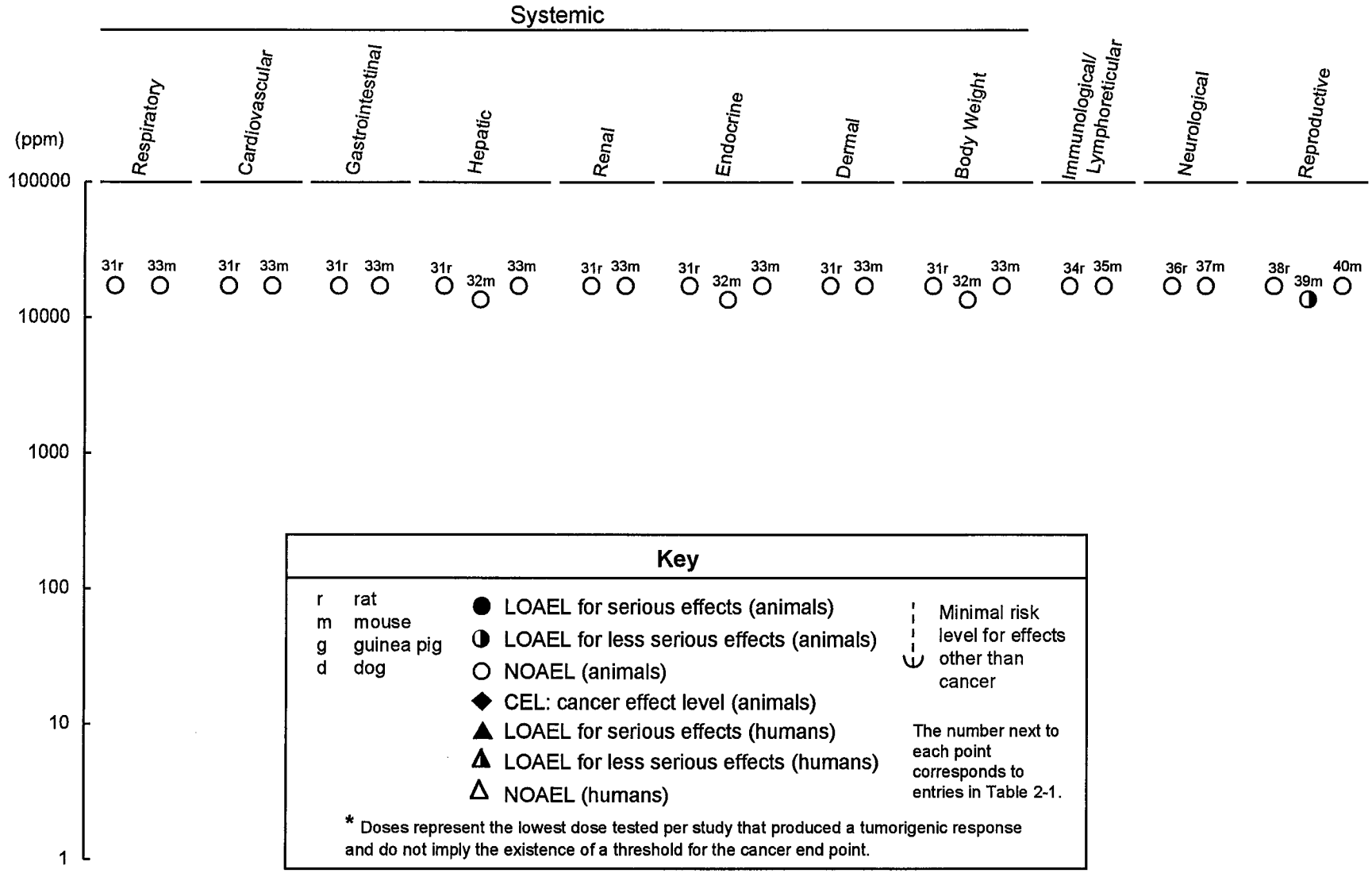
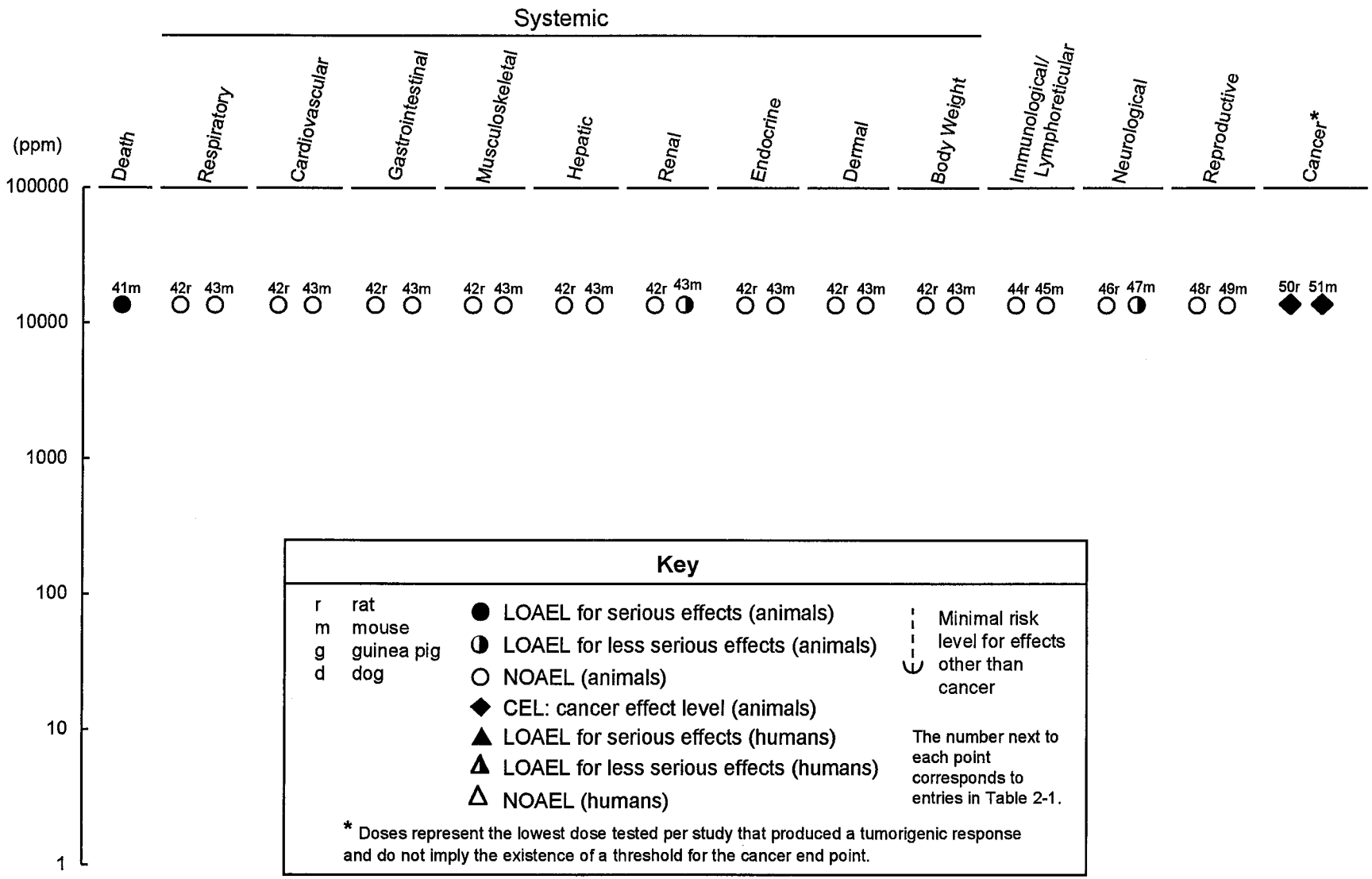


Figure 2-1. Levels of Significant Exposure to Chloroethane - Inhalation (cont.)

Chronic (≥365 days)



Studies in which animals were repeatedly exposed to chloroethane for 14 days or less did not report deaths resulting from inhalation of this compound. No mortality was reported in rats exposed to 436 ppm 4 hours/day for 8 exposures in 10 days (Gohlke and Schmidt 1972; Schmidt et al. 1972), in mice exposed to 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987, 1989), in rats and dogs exposed to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982) or in rats and mice exposed to 19,000 ppm 6 hours/day, 5 days/week for 2 weeks (NTP 1989).

Mortality was not increased significantly by chloroethane exposure in studies of intermediate duration (15-364 days). Mortality was not observed in rats or mice exposed to chloroethane at 19,000 ppm 6 hours/day, 5 days/week for 13 weeks (NTP 1989). At 10,000 ppm, 1 male mouse died. No discussion was provided on whether or not this death was exposure related. Therefore, this death is not included in Table 2-l or Figure 2- 1.

In a chronic inhalation study, rat survival was not reduced compared to controls following exposure to 15,000 ppm chloroethane 6 hours/day, 5 days/week for 1102 weeks (NTP 1989). The concurrent controls, however, had abnormally low survival rates after week 90 of the study. Survival was significantly reduced in mice following exposure to 15,000 ppm chloroethane for 100 weeks; the effect was found in males after 330 days and in females after 574 days (NTP 1989). An ascending urinary tract infection may have contributed to the reduced survival in male mice. The decreased survival in female mice was attributed to uterine cancer.

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

2.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l. The results of the study by Troshina (1966) were not used as levels of significant exposure because experimental methods and results were not described in sufficient detail.

Respiratory Effects. Chloroethane in combination with nitrous oxide and oxygen was used to maintain anesthesia in human patients previously made unconscious by administration of either thiopentone (thiopental), nitrous oxide, or a mixture of nitrous oxide, chloroethane, and oxygen (Cole 1956). A concentration of 20,000 ppm chloroethane was initially required to maintain anesthesia, but this could slowly be reduced to as low as 5,000 ppm in some cases. Respiration usually remained smooth and even, but some cases of tachypnea were seen. Respiratory rate was stimulated in 16 of 23 patients tested in a second similar study using 36,000 ppm chloroethane (Cole 1967). This study was not reported in Table 2-l or plotted in Figure 2- 1 as a NOAEL or LOAEL for the acute respiratory effects of chloroethane in humans because the compound was administered in conjunction with other anesthetic agents. Respiratory paralysis was reported to be the cause of death of a 14-year-old child who died during anesthesia with chloroethane (Kuschinsky 1970). A level of significant exposure was not based on this report because the concentration of chloroethane administered was not known.

Studies in animals also indicate that inhalation of chloroethane may affect respiration. Exposure to 10 ppm chloroethane for 10 minutes had no consistent effect on the respiratory rate of rabbits (Watanabe 1983). This study was not used as the basis for a NOAEL because changes in respiratory rate occurred, even though no trend was found. Inhalation of 20,000 ppm chloroethane for 9 hours resulted in only very mild tissue changes, but congestion, hemorrhage, and edema were found in the lungs of guinea pigs that died following exposure to 40,000 ppm or more (Sayers et al. 1929).

Hypertrophic bronchial tubes and interstitial pneumonia were found in rats given eight 4-hour exposures to 436 ppm chloroethane; however, these effects were also present to a lesser extent in controls (Gohlke and Schmidt 1972). Consequently, these results were not considered to be indicative of adverse respiratory effects produced by chloroethane. The only other respiratory effect reported by this study was a mild transitory increase in relative lung weight, which was also not considered adverse (Schmidt et al. 1972). Absolute and relative lung weights were not affected in rats or mice exposed to chloroethane at 15,000 ppm 6 hours/day for 5 days (Fedtke et al. 1994a). Histopathological changes were not observed in the respiratory tracts of mice exposed to chloroethane at 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987,1989). Histopathological examinations of respiratory organs and tissues were performed following inhalation of chloroethane for 6 hours/day, 5 days/week for 2 weeks at a concentration of 9,980 ppm in rats and dogs (Landry et al. 1982) and 19,000 ppm in rats and mice (NTP 1989). No effects were reported in either study

The NTP (1989) study is limited in that organs of only 3 of 10 exposed rats and 3 of 10 exposed mice were examined microscopically. Therefore, this study is not presented in Table 2-l or Figure 2-l for respiratory effects.

In an intermediate-duration study, inhalation of 19,000 ppm cbloroethane for 13 weeks (6 hours/day, 5 days/week) failed to produce lesions in the respiratory tissue of rats or mice as documented by complete histopathological examinations (NTP 1989). Inhalation of 216 ppm chloroethane for 6 months (4 hours/day, 6 days/week) caused thickening of the alveolar septa in the lungs of rats; the effect was produced by an increase in the number of macrophages (Troshina 1966). No respiratory effects were reported at 22.7 ppm.

Chronic exposure to 15,000 ppm chloroethane for approximately 2 years (6 hours/day, 5 days/week) had no non-neoplastic histopathological effects on the respiratory system in rats or mice (NTP 1989).

Cardiovascular Effects. There is some evidence that inhalation of chloroethane has cardiovascular effects in humans. Vagal stimulation followed by direct depression of cardiac tissues was reported in children exposed briefly to high concentrations of chloroethane (Bush et al. 1952). This study was not reported in Table 2-l or plotted in Figure 2-l because the effective concentration of chloroethane was not reported. A mixture of chloroethane, nitrous oxide, and oxygen was used to maintain anesthesia in patients previously made unconscious by administration of thiopentone (thiopental), or nitrous oxide, or the mixture described above (Cole 1956). A concentration of 20,000 ppm chloroethane was initially required to maintain anesthesia, but this could slowly be reduced to concentrations as low as 5,000 ppm in some cases. Pulse rate remained strong and no clinically detectable arrhythmias or changes in heart rate were observed. A similar study using 36,000 ppm chloroethane found increased systolic blood pressure and pulse rate in 16 of 25 patients tested, but again no cardiac arrhythmias were detected (Cole 1967). This study was not reported in Table 2-l or plotted in Figure 2- 1 as a NOAEL or LOAEL for the acute cardiovascular effects of chloroethane in humans because the compound was administered in conjunction with other anesthetic agents.

The cardiovascular effects of chloroethane have also been studied in animals. In dogs, acute exposure to anesthetic concentrations of chloroethane resulted in cardiac irregularities, including ventricular tachycardia and asystole (Haid et al. 1954; Morris et al. 1953). Chloroethane also sensitized the heart to the effects of epinephrine (Haid et al. 1954; Morris et al. 1953). Bush et al. (1952) found that cardiac depression occurred in dogs given anesthetic doses of chloroethane. This depression was initially due to stimulation of the vagus

nerve and occurred within 2 minutes of the onset of anesthesia. Direct depression of the cardiac tissue followed and was succeeded by ventricular fibrillation and asystole, which resulted in death. None of the above studies are presented in Table 2-1 or plotted in Figure 2-l because effective chloroethane concentrations were not reported.

Rabbits exposed to 10 ppm chloroethane for 10 minutes did not experience consistent changes in blood pressure or heart rate (Watanabe 1983). Although changes in these variables did occur, this study was not used as the basis for a NOAEL because no trend was found. The occurrence of undescribed "vascular disarrangements" was reported in rats and mice killed by exposure to over 54,948 ppm chloroethane for 2 hours (Troshina 1966). Degeneration of heart muscle was found in guinea pigs that died following exposure to 40,000 ppm chloroethane for 9 hours (Sayers et al. 1929). No effects were reported at lower concentrations.

Multiple-exposure studies of acute duration reported no significant cardiovascular effects. Rat heart weight was not affected by eight 4-hour exposures to 436 ppm chloroethane over a 10-day period (Schmidt et al.1972). When histopathological examination of rats and dogs exposed to 9,980 ppm chloroethane for 2 weeks (6 hours/day, 5 days/week) was done, no cardiovascular effects were found (Landry et al. 1982). Changes in heart weights and microscopic changes in the heart were not observed in mice exposed to chloroethane at 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987,1989). Microscopic examination of the heart in 3 of 10 rats and 3 of 10 mice exposed to chloroethane at 19,000 ppm 6 hours/day, 5 days/week for 2 weeks, did not reveal any effects (NTP 1989). Because histopathological examinations were completed on only a few animals, this study is not presented in Table 2-l and Figure 2-l for cardiovascular effects.

Inhalation of 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks, had no histopathological effect on the cardiovascular system of rats or mice (NTP 1989). Arterial blood pressure 24 mmHg below controls was reported in rats exposed 4 hours/day, 6 days/week for 6 months, to 2 16 ppm chloroethane (Troshina 1966). No effects on blood pressure were noted at 22.7 ppm.

In the only chronic inhalation study of chloroethane, histopathological examinations of the heart did not reveal any effects in rats or mice exposed to 15,000 ppm 6 hours/day, 5 days/week for approximately 2 years (NTP 1989).

Gastrointestinal Effects. Gastrointestinal effects have been reported in humans exposed to chloroethane by inhalation. Sayers et al. (1929) reported that mild abdominal cramps occurred in healthy human subjects who inhaled 2 breaths of 40,000 ppm chloroethane or 2-4 breaths of 20,000 ppm chloroethane. Exposure to 33,600 ppm chloroethane caused nausea and vomiting in human subjects after approximately 8 minutes; subjects exposed to 25,000 ppm did not become nauseated even after 21 minutes (Davidson 1925). Vomiting occurred in 10 of 23 patients who were anesthetized with 36,000 ppm chloroethane combined with nitrous oxide and oxygen (Cole 1967). A LOAEL was not reported in Table 2-l or plotted in Figure 2-l because chloroethane was administered in conjunction with other anesthetic agents.

Gastrointestinal effects in animals were studied by necropsy and histopathological examination. Congestion of the intestines was found in guinea pigs that died following exposure to 80,000 ppm for up to 4.5 hours (Sayers et al. 1929). Chloroethane concentrations below 40,000 ppm did not produce gastrointestinal effects in this study.

Exposure to 9,980 ppm chloroethane for 2 weeks had no histopathological effects on the gastrointestinal organs of rats or dogs (Landry et al. 1982). Histopathological changes were not observed in the gastrointestinal tracts of mice exposed to chloroethane at 4,843 ppm 23 hours/day for 11 days (Landry et al.1987, 1989), or in rats or mice exposed to 19,000 ppm 6 hours/day, 5 days/week for 2 weeks (NTP 1989). The NTP (1989) study is not presented in Table 2-l or Figure 2-l for gastrointestinal effects because histopathological examinations were completed on only 3 of 10 exposed rats and 3 of 10 exposed mice.

No gastrointestinal effects were found by histopathological examination in longer term studies. Chloroethane concentrations of 19,000 ppm for 13 weeks (6 hours/day, 5 days/week) in rats and mice and 15,000 ppm for approximately 2 years (6 hours/day, 5 days/week) in rats and mice (NTP 1989) were all without effect on this organ system.

Hematological Effects. There was a single report of a hematological effect following chloroethane inhalation in humans. A human subject exposed to 33,600 ppm chloroethane developed cyanosis within 8.5 minutes but only when the chloroethane was not mixed with oxygen (Davidson 1925). Therefore, this effect was probably due to lack of oxygen, and this result was not used as the basis for a LOAEL.

No effects on hematologic parameters (packed cell volume, hemoglobin, red blood cell counts, platelet counts, differential leukocyte counts, mean corpuscular volume, mean corpuscular hemoglobin) were noted in

mice exposed to chloroethane at 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987, 1989), or in rats or dogs exposed to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Hematologic effects were not examined in other inhalation studies of chloroethane.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following inhalation exposure to chloroethane.

Histopathological examination of muscle and bone following exposure of mice to chloroethane at 4,843 ppm 23 hours/day for 11 days did not reveal any effects (Landry et al. 1987, 1989). Histopathologic changes in muscle and bone were also not observed in rats or dogs exposed to chloroethane at 9,980 ppm 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Rats and mice exposed to 15,000 ppm chloroethane 6 hours/day, 5 days/week for approximately 2 years, were also examined; no increase in the occurrence of bone lesions was found (NTP 1989). The National Toxicology Program (NTP) studies of shorter duration did not include examination of bone or muscle tissue.

Hepatic Effects. In a case report of a woman who sniffed chloroethane (about 200-300 ml/day) for 4 months, an enlarged liver and mild transient disturbance of liver function which was not further described were noted (Hes et al. 1979). The woman had previously used other drugs but was reported to be free of addiction for 2 years before starting to use chloroethane. Moderately elevated serum alanine aminotransferase was observed in a man who abused chloroethane for 30 years (Nordin et al. 1988). During the 4 months before the man was examined he inhaled at least 100 ml/day chloroethane (Nordin et al. 1988). This subject also had a history of alcohol and sedative abuse, so it is not known for certain if the liver effects were a result of the chloroethane abuse.

Hepatic effects in animals have been studied by a number of researchers. A single 5minute exposure to an unspecified concentration of chloroethane produced an increase in the ratio of adenosine triphosphate/adenosine diphosphate (ATP/ADP) in the livers of mice (Oura et al. 1966). The effective concentration of chloroethane in this study was not reported, so no level of significant exposure was determined. Pale appearance, edema, congestion, and degeneration were seen in the livers of guinea pigs exposed to at least 20,000 ppm chloroethane for up to 9 hours (Sayers et al. 1929). Liver non-protein sulfhydryl (NPSH) concentration was reduced in both rats and mice following a single 6-hour exposure to chloroethane concentrations of 9,980 ppm for rats and 4,000 ppm for mice, but the study authors considered this effect to

be more adaptive than toxicologic since the change was small and no associated liver lesions were found (Landry et al. 1982).

Following 5 daily 6-hour exposures to chloroethane at 15,000 ppm, glutathione levels in the liver were reduced in male rats but not in female rats or in mice of either sex (Fedtke et al. 1994b). Liver weights were not affected in rats or mice following 5 daily 6-hour exposures to chloroethane at 15,000 ppm (Fedtke et al.1994a).

Serum amino transaminase activity (alanine and aspartate), liver enzyme activity, lipid content, histopathology, and liver weight were not significantly altered in rats given eight 4-hour exposures to 436 ppm chloroethane (Gohlke and Schmidt 1972; Schmidt et al. 1972). Histopathological effects were reported but apparently only in groups pre-treated with ethanol. It did not appear that significant tissue changes occurred in rats exposed to chloroethane alone. Mice exposed to 4,843 ppm chloroethane 23 hours/day for 11 days had increased relative liver weight and slightly increased hepatocellular vacuolation (Landry et al. 1987, 1989). The study authors considered these effects to be mild and not indicative of significant toxicity. No changes in liver weight were noted in mice exposed to chloroethane at 4,946 ppm 6 hours/day on gestation days 6-15 and sacrificed on gestation day 18 (Scortichini et al. 1986). There was a slight increase in relative liver weight in male rats exposed to 3,980 ppm or more for 6 hours/day, 5 days/week for 2 weeks, but since no other hepatic effects were reported, this effect was not thought to indicate significant liver toxicity (Landry et al. 1982). There were no hepatic effects in dogs exposed to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). No significant hepatotoxicity was observed in rats or mice examined histopathologically following exposure to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (NTP 1989). The NTP (1989) study is not presented in Table 2-l or Figure 2-l for hepatic effects because histopathological examinations were completed on only 3 of 10 exposed rats and 3 of 10 exposed mice.

Liver weight and histopathologic changes in the liver were not observed in mice exposed to 15,000 ppm chloroethane 6 hours/day for 21 days (Bucher et al. 1995). Relative liver weights were significantly ($p<0.05$) increased in male rats but not female rats or mice of either sex exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks (NTP 1989). Because histopathological changes were not observed, the increased relative liver weight is not considered adverse. Interference with hepatic function in rats, as indicated by reduced hippuric acid elimination following sodium benzoate loading, occurred following both a 60-day exposure to 5,305 ppm chloroethane and a 6-month exposure to 216 ppm (Troshina 1966). Fatty

degeneration of hepatocytes also occurred following a 6-month exposure to 216 ppm chloroethane (Troshina 1966).

Chronic exposure to 15,000 ppm chloroethane 6 hours/day, 5 days/week for approximately 2 years, produced no increase in the incidence of non-neoplastic hepatic lesions in rats or mice (NTP 1989).

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to chloroethane.

Inhalation of chloroethane has been shown to produce renal effects in animals. Pale appearance, congestion, and degeneration were seen in the kidneys of guinea pigs exposed to 40,000 ppm or more for up to 9 hours (Sayers et al. 1929). No effects were found following exposure to 20,000 ppm for 9 hours.

Exposure to 436 ppm chloroethane for 4 hours/day for 8 days had no effect on rat kidney histopathology, fat content, or weight (Gohlke and Schmidt 1972; Schmidt et al 1972). Inhalation of 4,843 ppm 23 hours/day for 11 days did not produce renal effects detectable by serum chemistry analysis or histopathological examination in mice (Landry et al. 1987, 1989). Absolute and relative kidney weights were not affected in rats or mice exposed to 15,000 ppm chloroethane for 5 daily 6-hour exposures (Fedtke et al. 1994a). Blood urea nitrogen (BUN) was decreased slightly in female rats following inhalation of at least 3,980 ppm for 2 weeks (Landry et al. 1982). However, the study authors did not consider this effect to be toxicologically significant since BUN is not a direct indicator of toxicity and no associated pathological lesions were found. No other renal effects were found in rats or dogs exposed to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Histopathological examination of 3 of 10 exposed rats and 3 of 10 exposed mice showed no evidence of nephrotoxicity after exposure to 19,000 ppm 6 hours/day, 5 days/week for 2 weeks (NTP 1989). Because of the small number of animals examined microscopically, this study is not presented in Table 2-l or Figure 2-l for renal effects.

Exposure to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks, had no effect on the occurrence of kidney lesions in rats or mice (NTP 1989). Inhalation of chloroethane for 6 months increased urinary amino acid levels in the rat (Troshina 1966). The concentration at which this effect occurred is not stated. Therefore, a concentration is not presented in Table 2-l or Figure 2-l.

Chloroethane vapor at a concentration of 15,000 ppm produced signs of mild nephrotoxicity in mice exposed 6 hours/day, 5 days/week for 100 weeks (NTP 1989). There was an increase in the incidence of scattered foci of tubular regeneration and minimal glomerulosclerosis in treated female mice, while treated male mice exhibited only slight enlargement of renal tubular cell nuclei. No renal effects were found in rats exposed to 15,000 ppm chloroethane 6 hours/day, 5 days/week for 102 weeks (NTP 1989).

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to chloroethane.

No effects on thyroid weight, thyroid histopathology, or adrenocorticotropic hormone activity were noted in rats exposed to 436 ppm chloroethane 4 hours/day for 8 exposures over 10 days (Gohlke and Schmidt 1972;Schmidt et al. 1972). Histopathologic changes were not observed in the adrenals, pancreas, parathyroid, pituitary, or thyroid glands of mice exposed to 4,843 ppm chloroethane 23 hours/day for 11 days (Landry et al. 1987, 1989), or rats or dogs exposed to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Microscopic examination of the adrenals, pancreas, parathyroid, pituitary, and thyroid glands from 3 of 10 rats and 3 of 10 mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks, did not reveal any effects (NTP 1989). Because histopathological examinations were completed on only a few animals, this study is not presented in Table 2-l and Figure 2-l for endocrine effects.

Histopathologic changes were not observed in the adrenals, pancreas, parathyroid glands, pituitary, or thyroid glands of rats or mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks, or those exposed to 15,000 ppm 6 hours/day, 5 days/week for approximately 2 years (NTP 1989).

Dermal Effects. No studies were located regarding dermal effects in humans following inhalation exposure to chloroethane.

Dermal effects following inhalation exposure to chloroethane were not reported in animal studies. No histopathological effects on the skin were found in mice exposed to 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987, 1989); in rats or dogs exposed to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982); or rats or mice exposed 6 hours/day, 5 days/week to 19,000 ppm for 2 weeks (NTP 1989), 19,000 ppm for 13 weeks (NTP 1989), or 15,000 ppm for approximately 2 years. The 2-week NTP (1989) study is not presented in Table 2-1 or Figure 2-B for dermal effects because histopathological examinations were completed on only 3 of 10 exposed rats and 3 of 10 exposed mice.

Ocular Effects. Mild eye irritation occurred in volunteers exposed briefly to 40,000 ppm chloroethane (Sayers et al. 1929). No eye irritation was reported followmg exposure to 20,000 ppm. Additional reports of eye irritation in humans during exposure to cbloroethane vapor were not identified.

Histopathological examinations of the eyes did not reveal any effects in mice exposed to 4,843 ppm chloroethane 23 hours/day for 11 days (Landry et al. 1987,1989), or in rats or dogs exposed to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Ophthalmoscopic examination of the eyes of the chloroethane-exposed dogs also did not reveal any effects.

Body Weight Effects. No studies were located regarding body weight effects in humans following inhalation exposure to chloroethane. Body weight gain was not significantly affected by exposures to 15,000 ppm chloroethane for 5 daily 6-hour exposures in rats or mice (Fedtke et al. 1994a); to 436 ppm 4 hours/day for 8 of 10 days in rats (Schmidt et al. 1972); to 4,843 ppm 23 hours/day for 11 days in mice (Landry et al. 1987, 1989); to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks, in rats or dogs (Landry et al.1982); or 19,000 ppm 6 hours/day, 5 days/week for 2 weeks, in rats or mice (NTP 1989). Exposure to 4,946 ppm chloroethane 6 hours/day on gestation days 6-l 5 did not affect body weight gain of pregnant mice (Scortichini et al. 1986).

Following longer duration exposures to chloroethane, body weight gain was not significantly affected in rats or mice by exposures to 19,000 ppm 6 hours/day, 5 days/week for 13 weeks, or 15,000 ppm 6 hours/day, 5 days/week for approximately 2 years (NTP 1989). Body weight gain of 62 g less than controls was reported in rats exposed to 216 ppm chloroethane for 6 months (Troshina 1966). Because experimental methods were not described in detail, the Troshina (1966) study is not presented in Table 2-l or Figure 2-l.

2.2.1.3 Immunological and Lymphoreticular Effects

One study of immunological effects in humans exposed to chloroethane was found. Troshina (1966) compared the leukocyte phagocytic activity of 25 workers who may have been exposed to chloroethane vapors for 1.5-3 years with that of 25 control workers and found a significant decrease in phagocytic activity in the exposed workers. Levels of chloroethane in the plant were not reported. This study was not used as the source of a LOAEL value because it did not contain an adequate description of either methods or results.

There were no reliable reports of immunological effects in animals after inhalation of chloroethane.

Rat spleen and thymus weight were not affected by exposure to 436 ppm chloroethane for 4 hours/day for 8 days (Schmidt et al. 1972). White blood cell counts were also unaffected in this study (Schmidt et al. 1972). Histological changes in the thymus, spleen, and lymph nodes were not observed in mice exposed to 4,843 ppm chloroethane 23 hours/day for 11 days (Landry et al. 1987,1989). There were no compoundrelated effects on organs or tissues of the immune system after exposure to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks, in rats or dogs (Landry et al. 1982), 19,000 ppm 6 hours/day, 5 days/week for 2 weeks, in rats or mice (NTP 1989), 19,000 ppm 6 hours/day, 5 days/week for 13 weeks, in rats or mice (NTP 1989), or 15,000 ppm 6 hours/day, 5 days/week for approximately 2 years, in rats or mice (NTP 1989).

Slightly congested or anemic spleens were observed in guinea pigs exposed to 40,000 ppm chloroethane for 90 minutes (Sayers et al. 1929). Reduced leukocyte phagocytic activity was reported in rats following both 60-day exposure to 5,305 ppm chloroethane and 6-month exposure to 2 16 ppm (Troshina 1966). These concentrations were not used as levels of significant exposure, however, because no experimental details were provided.

The highest NOAEL values for immunological effects from each reliable study in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.4 Neurological Effects

There are numerous reports of neurological effects in humans exposed to chloroethane by inhalation. Marked dizziness was reported in volunteers who were given 3 breaths of 20,000 ppm chloroethane (Sayers et al. (1929). A subjective feeling of intoxication and decreased reaction times were reported in persons during exposure to 13,000 ppm for 12 minutes (Davidson 1925). At 19,000 ppm, slight intoxication was recorded within 1 minute of exposure. This effect progressed to distinct intoxication and mild analgesia within 12 minutes. At higher concentrations, more pronounced effects appeared, such as slight incoordination within 15 minutes at 25,000 ppm and marked incoordination within 8 minutes at 33,600 ppm. Inhalation of 33,600 ppm chloroethane in oxygen produced unconsciousness in 13-17 minutes (Davidson 1925). The number of subjects exposed at each concentration was not clearly stated in this study, and there was no discussion regarding how long it took for the subjects to recover fully from the effects of chloroethane.

Chloroethane, combined with nitrous oxide and oxygen, was used to maintain anesthesia in patients previously made unconscious by administration of either thiopentone (thiopental), nitrous oxide, or a mixture of nitrous oxide, chloroethane, and oxygen (Cole 1956). A concentration of 20,000 ppm chloroethane was initially required to maintain anesthesia, but this could slowly be reduced to as low as 5,000 ppm in some cases. Anesthesia could be maintained up to an hour using chloroethane in this manner. In a similar study using 36,000 ppm chloroethane, the length of time required to recover from anesthesia varied from 3 to 15 minutes in 33 subjects (Cole 1967). This result was not used as a level of significant exposure because chloroethane was administered in combination with other anesthetic agents.

Unconsciousness is not the only neurological effect reported in humans following exposure to anesthetic concentrations of chloroethane. Anesthetic concentrations of chloroethane also produced vagus nerve stimulation leading to cardiac depression in subjects studied by Bush et al. (1952). A LOAEL was not taken from this study because the effective concentration of chloroethane was not reported. As indicated in Section 2.2.1.2, gastrointestinal effects (nausea, vomiting, mild abdominal cramps) have been reported in people recovering from chloroethane anesthesia (Cole 1967). Because these effects are thought to have a neurological basis, the NOAEL and LOAEL associated with the gastrointestinal effects in humans in the Davidson (1925) study are also presented in Table 2-l and plotted in Figure 2-l under neurological effects.

A woman who inhaled chloroethane daily as a narcotic for 4 months had several signs and symptoms indicating cerebellar dysfunction. A neurological examination revealed ataxia, nystagmus (rapid eye movement), scanning dysarthria (imperfect speech articulation), dysdiadochokinesia (inability to perform alternating movements) of the arm, and sluggish lower limb reflexes (Hes et al. 1979). After 1 month without chloroethane, her neurological condition returned to normal. The woman had previously used other drugs but was reported to be free of addiction for 2 years before starting to use chloroethane (Hes et al. 1979). In a second case of chloroethane abuse, neurological signs and symptoms observed during the withdrawal period included a grand mal seizure, ataxia, difficulties in walking, disorientation, short-term memory impairment, and visual hallucinations (Nordin et al. 1988). Electroneurography indicated neuropathy of motor and sensory neurons (Nordin et al. 1988). Because it provided a euphoric effect, this male subject had abused chloroethane for about 30 years, and during the 4 months before he was admitted to the hospital, inhaled at least 100 ml/day. This subject also had a history of alcohol and sedative abuse, although no ethanol was in his breath on hospital admission. After approximately 6 weeks, the neurological and mental changes regressed without any residual symptoms. The study authors indicated that it was not possible to determine if the nervous system effects were toxic effects of chloroethane or withdrawal

symptoms. Levels of significant exposure were not based on these reports because the effective concentration of chloroethane was not reported.

Only one study of chloroethane exposure in an industrial setting was found. Seventy-six workers in a butyl rubber plant possibly exposed to chloroethane vapors for 2 months to 3 years were examined; approximately half had autonomic nervous system dysfunction in the form of intensified parasympathetic tonus (Troshina 1966). The study author indicated that autonomous nervous system function was measured with a battery of tests, including Ashner's test, a synapse test, and a white spot test, but additional details were not provided. Concentrations of chloroethane in the plant were not reported.

Neurological effects of chloroethane inhalation have also been studied in animals. Guinea pigs exposed to 20,000 ppm chloroethane were unsteady, sluggish, and dizzy during a 9-hour exposure (Sayers et al. 1929). Those exposed to 40,000 ppm were unsteady and dizzy after 3 minutes of exposure. At higher concentrations (>51,000 ppm), these effects were seen after shorter exposure durations, and more severe effects were found such as inability to stand, lying on the side, convulsions, and unconsciousness. Two-hour inhalation of 54,948 ppm produced nervous excitation and convulsions followed by narcosis in mice and rats (Troshina 1966). Respiratory paralysis also occurred in some cases, leading to death. Histopathological examination revealed degeneration of nerve cells in the medulla oblongata and subcortical stratum of the brain (Troshina 1966). In dogs, concentrations of chloroethane that produced anesthesia also produced stimulation of the vagus nerve and, consequently, cardiac depression (Bush et al. 1952). Premeditation with anticholinergic drugs inhibited vagal stimulation (Bush et al. 1952). Muscle twitching and tremors have also been observed in dogs during chloroethane anesthesia (Morris et al. 1953). LOAELs were not taken from these studies because the effective concentrations of chloroethane were not reported.

There were few reports of neurological effects in studies of longer duration. Brain histopathology and weight in the rat were unaffected by eight 4-hour exposures to 436 ppm chloroethane (Gohlke and Schmidt 1972; Schmidt et al. 1972). Slight lethargy was observed in rats, and hyperactivity was observed in 1 of 2 dogs exposed to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Brain weight and brain or peripheral nerve histopathology were not affected. Evaluation of the dogs for gait, posture, cranial nerve reflexes, postural reactions, spinal cord reflexes, muscle tone, and pain perception also did not reveal any chloroethane-related effects (Landry et al. 1982). When mice received 11 days of near-continuous exposure to 4,843 ppm chloroethane, no neurological effects were found by function testing or histopathological examination (Landry et al. 1987, 1989). No compound-related neurological effects were

found in histopathological examinations of rats and mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 2 or 13 weeks (NTP 1989). No increase in the occurrence of non-neoplastic lesions was found in nervous system organs or tissues following exposure of rats and mice to 15,000 ppm chloroethane 6 hours/day, 5 days/week for approximately 2 years (NTP 1989). This study did, however, report hyperactivity of female mice during the daily exposure period. A temporary increase in the threshold of electrodermal excitability occurred in rats after 60 days of exposure to 5,305 ppm, but not after 6 months of exposure to 216 ppm (Troshina 1966).

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-l and plotted in Figure 2-l. The results of the study by Troshina (1966) were not used as levels of significant exposure because experimental methods and results were not described in sufficient detail.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to chloroethane.

Several studies investigated reproductive endpoints in animals. In dogs anesthetized with chloroethane, high concentrations resulted in decreased uterine motility and muscle tonus (Van Liere et al. 1966). This study was not used as the basis for a LOAEL because the effective concentration of chloroethane was not reported. In addition, the relevance of this endpoint to other reproductive effects is unclear. No effects on uterine weights were observed in rats exposed to 15,000 ppm chloroethane 6 hours/day for 5 days (Fedtke et al. 1994a). Compared to unexposed controls, absolute and relative uterine weights were decreased by approximately 35% in mice exposed to 15,000 ppm chloroethane 6 hours/day for 5 days (Fedtke et al. 1994a). Significant decreases in uterine glutathione levels were observed in both rats and mice (Fedtke et al. 1994b). The decreases in glutathione in the uterus were greater than the decreases in glutathione observed in the liver, lungs, and kidneys. A small increase in the average duration of the estrous cycle was observed in mice exposed to 15,000 ppm chloroethane 6 hours/day for 21 days (Bucher et al. 1995). Before the exposure, estrous cycle duration was 5.15±0.15 days, while during the exposure, estrous cycle duration was 5.52±0.19 days. Measurement of serum estradiol and progesterone did not reveal any consistent statistically significant changes attributable to chloroethane exposure.

Testes weights were not affected in rats exposed to 436 ppm chloroethane 4 hours/day for 8 days during a l0-day time period (Schmidt et al. 1972). Sperm motility in rats was reduced after exposure to chloroethane for 6 months (Troshina 1966). At 22.7 ppm, the effect subsided after the exposure period ended, but at 216 ppm no recovery occurred during the month after exposure. Methods and results were inadequately reported in this study, so it was not used for a LOAEL.

Histopathological changes in reproductive organs were not observed in mice exposed to 4,843 ppm chloroethane 23 hours/day for 11 days (Landry et al. 1987, 1989), or in rats and dogs exposed to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Microscopic examination of the reproductive organs of 3 of 10 rats and 3 of 10 mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks, did not reveal any effects (NTP 1989). Because histopathological examinations were completed on only a few animals, this study is not presented in Table 2-l or Figure 2-l for reproductive effects. No compound-related histopathological changes were found in the reproductive organs of rats or mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks, or to 15,000 ppm 6 hours/day, 5 days/week for approximately 2 years (NTP 1989).

No effects on the number of live and dead fetuses or on the number and position of resorption sites were observed in mice exposed to 4,946 ppm chloroethane 6 hours/day on gestation days 6-15 (Scortichini et al. 1986). Additional studies of reproductive outcome in animals following inhalation exposure to chloroethane were not identified.

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-l and plotted in Figure 2-l.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans following inhalation exposure to chloroethane.

Only one study of the developmental effects of chloroethane in animals was found. In mice, 6-hour inhalation exposure to 4,946 ppm chloroethane on gestation days 6-15 resulted in minimal evidence of fetotoxicity (Scortichini et al. 1986). A small, statistically significant ($p=0.05$) increase in the incidence of foramina of the skull bones (small centers of unossified bone) was observed. This effect was observed in 5,4,4, and

23% of the litters at 0, 491, 1,504, and 4,946 ppm, respectively. An increase in supernumerary ribs was also found, although this effect was not indicated as statistically significant. The incidences of litters with supernumerary ribs were 9,4, 19, and 18% at 0, 491, 1,504, and 4,946 ppm, respectively. No effects were observed on maternal body or liver weights, reproductive parameters, fetal body weight, or the incidence of external or visceral malformations in the fetuses The NOAEL and LOAEL for fetotoxic effects in mice are recorded in Table 2-l and plotted in Figure 2-l 0 Based on the NOAEL of 1,504 ppm for developmental effects in mice (Scortichini et al. 1986), an acute-duration inhalation MRL of 15 ppm was calculated, as described in the footnote to Table 2-1.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following inhalation exposure to chloroethane.

Chloroethane did not increase the number of micronuclei in bone marrow cells or affect DNA synthesis in mice exposed nose-only to 25,000 ppm chloroethane 6 hours/day for 3 days (Ebert et al. 1994). The investigators indicated that the exposure concentration used in this study was about 66% of the flammability limit and that it was the highest concentration that could be safely administered.

Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer in humans following inhalation exposure to chloroethane.

A study of the carcinogenicity of chloroethane vapor in animals has been completed. Inhalation exposure to 15,000 ppm chloroethane 6 hours/day, 5 days/week for 102 weeks, produced evidence of carcinogenicity in both male and female rats (NTP 1989). The combined incidence of skin trichoepitheliomas, sebaceous gland adenomas, and basal cell carcinomas was 10% (5/50) in treated male rats and 0% (0/50) in concurrent controls. This increase was statistically significant when compared to the mean historical inhalation control incidence of 0.7% (n=300) and the historical untreated control incidence of 2% (n=1,936). It is reasonable to combine incidence data of these neoplasms because they are morphologically similar (all are epithelial tumors arising from the epidermis or associated structures). Malignant brain astrocytomas were found in 6% (3/50) of the treated female rats and 0% (0/50) of the concurrent controls. This increase was statistically significant

compared to the historical inhalation control incidence of 0.3% (n=297) and the historical untreated glial cell tumor incidence of 1.2% (n=l,969). All three affected rats died before the end of the study and it was suggested that the brain tumors may have been the cause of death. The NTP (1989) concluded that this study provides equivocal evidence of the carcinogenicity of chloroethane in both male and female rats. A CEL of 15,000 ppm for rats is reported in Table 2-1 and plotted in Figure 2-l.

There was a highly significant increase in the incidence of uterine carcinomas of endometrial origin in female mice exposed to 15,000 ppm chloroethane 6 hours/day, 5 days/week for 100 weeks (NTP 1989). These tumors, which were highly malignant and metastasized to a wide variety of organs, were found in 86% (43/50) of treated females and 0% (0/49) of concurrent controls. In addition, there was a significant increase in hepatocellular carcinomas, which occurred in treated female mice at an incidence of 15% (7/48) and concurrent controls at 6% (3/49). A significant increase in the occurrence of lymphomas in treated female mice was discounted because concurrent control values were abnormally low compared to historical control values. In males, the combined incidence of alveolar and bronchiolar adenomas was 17% (8/48), a significant increase compared to the 6% (3/50) incidence in concurrent controls. The combined incidence of adenomas and carcinomas was 21% (10/48) in exposed mice and 10% (5/50) in concurrent controls. The study authors concluded that this study provides clear evidence of the carcinogenicity of chloroethane in female mice but that the study was inadequate for male mice because of low survival. A CEL of 15,000 ppm for mice is reported in Table 2- 1 and plotted in Figure 2- 1.

2.2.2 Oral Exposure

No studies were located regarding the following effects in humans or animals after oral exposure to chloroethane.

2.2.2.1 Death

2.2.2.2 Systemic Effects

2.2.2.3 Immunological and Lymphoreticular Effects

2.2.2.4 Neurological Effects

2.2.2.5 Reproductive Effects

2.2.2.6 Developmental Effects

2.2.2.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.2.6 Cancer

No studies were located regarding cancer in humans or animals after oral exposure to chloroethane.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals following dermal exposure to chloroethane.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, or ocular effects in humans or animals following dermal exposure to chloroethane.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following dermal exposure to chloroethane.

One study investigated the musculoskeletal effects of dermally applied chloroethane in animals. Chloroethane sprayed onto a l-2-cm^2 area on the thighs of rats until the skin was blanched produced local infiltration and disintegration of muscle fibers (Kenig 1956). This study, available only as an abstract, was not used as the basis for a LOAEL because the effective dose of chloroethane was not reported and few experimental details were provided.

Dermal Effects. Dermally applied chloroethane is used as a local anesthetic in humans (Nielsen 1980; Noble 1979; Ott 1969; Van Ketel 1976). When sprayed on the skin, chloroethane rapidly evaporates and causes the skin to freeze, which produces a numbing sensation. It is used for procedures such as skin biopsy and ear piercing that require short periods of surface anesthesia in a small area (Ott 1969). It is also used topically to relieve pain in facial muscles during physical therapy for those suffering from temperomandibular pain and dysfunction syndrome (also known as temperomandibular joint syndrome, or TMJ) (Marbach 1996). When used as a topical anesthetic, chloroethane is usually applied for 30 seconds or less. Symptoms of frostbite can result from prolonged exposures. Three children who had their earlobes sprayed with chloroethane for several minutes all developed chemical frostbite on their ears and necks (Noble 1979). This report was not used as the basis for a LOAEL because the effective dose of chloroethane was not reported. As discussed in Section 2.2.3.3, humans can develop dermal contact sensitivity reactions to chloroethane (Bircher et al. 1994; Kriechbaumer et al. 1998; Van Ketel 1976).

Dermal effects have also been reported in animals Chloroethane has the same topical anesthetic qualities in animals as it does in humans (Dobkin and Byles 1971). Chloroethane applied to a l-2-cm^2 area on the thighs of rats until the skin was blanched produced edema in the subcutaneous tissue of the application site (Kenig 1956). This study, available only as an abstract, was not used as the basis for a LOAEL because the effective dose of chloroethane was not reported and few experimental details were provided.

2.2.3.3 Immunological and Lymphoreticular Effects

Dermal exposure to chloroethane can result in contact sensitivity. Patch tests performed on two patients with eczema were strongly positive for chloroethane, while a third patient suffered an eczematous reaction after the use of chloroethane as a local anesthetic, indicating that allergy to chloroethane can occur. Patch tests on 15 control volunteers were negative (Van Ketel 1976). A punch biopsy taken from a woman with a positive patch test to chloroethane revealed observations consistent with a T-cell-mediated allergic reaction (Bircher et al. 1994). Microscopic examination showed marked spongiosis and a lymphohistocytic infiltrate. There was a marked dermal infiltrate of $CD3^+$ T cells (pan T cells), with a predominance of $CD4^+$ T cells (helper/suppressor cell subtypes). Most of the cells expressed lymphocyte function-associated antigen. A considerable number of CDI^+ Langerhans cells were also found in the epidermis.

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

2.2.3.4 Neurological Effects

Mild pain was reported when chloroethane was sprayed on a small area of 1 hand each of 40 women (Selby and Bowles 1995). The chloroethane was sprayed for 10 seconds, from a height of 20 cm. This procedure was used as analgesia for venous cannulation, a procedure that was reported to be more painful without pretreatment with chloroethane.

There is one study of the neurological effects of dermally applied chloroethane in animals. Rats were sprayed with chloroethane until their skin was blanched, and examination of the nerve fibers at the site of application (a 1-2-cm^2 area of the thigh) revealed thickening of the fibers and swelling of the Schwann cell nuclei (Kenig 1956). These effects subsided within 10 days of application. This study, available only as an abstract, was not used as the basis for a LOAEL because the effective dose of chloroethane was not reported and few experimental details were provided.

No studies were located regarding the following effects in humans or animals following dermal exposure to chloroethane.

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to chloroethane.

2 . 3 TOXICOKINETICS

Chloroethane is readily absorbed following inhalation exposure. Data regarding the absorption of chloroethane following oral exposure were not identified. Based on physical properties, a dermal flux rate of

0.99 mg/cm^2 hour has been estimated. Partition coefficients indicate that chloroethane, once absorbed, would have a greater affinity for fat than for muscle or the liver.

The metabolism of chloroethane has not been studied in humans. In rats and mice, the two major pathways of chloroethane metabolism are the production of acetaldehyde by cytochrome P450, and conjugation of chloroethane with glutathione to form *S*-ethyl-glutathione. Acetaldehyde is rapidly metabolized to acetic acid. The glutathione metabohtes are further metabolized to *S*-ethyl-L-cysteine in mice, and *S*-ethyl-*N*-acetyl-L-cysteine in both rats and mice. Glutathione conjugate metabolites of chloroethane are excreted in the urine, while unmetabolized chloroethane is exhaled.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Chloroethane is readily absorbed through the lungs in humans and animals (Konietzko 1984; Lehman and Flury 1943; Torkelson and Rowe 1981). The rapidity of anesthesia in humans and animals following inhalation exposure supports this contention (Dobkin and B yles 197 1; Finer 1966; Lawson 1965). Human subjects were exposed to about 5 mg ^{38}Cl-labeled chloroethane for 30 seconds by taking 1 breath through the mouth and then holding it for 30 seconds (Morgan et al. 1970). Approximately 18% of the radioactivity was exhaled in the first 2 breaths indicating that about 82% was retained.

No data are available to indicate that absorption of chloroethane would be different in children as compared to adults. Exposure to chloroethane is most likely via inhalation. Since infants and adolescents breathe more air per kilogram than adults, it is possible that children could inhale more chloroethane relative to their body weight than adults. However, infants have less developed alveoli than adults, which may result in a smaller surface area for absorption (NRC 1993).

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans or animals following oral exposure to chloroethane.

2.3.1.3 Dermal Exposure

A dermal flux rate of 0.99 mg/cm^2/hour was estimated based on the physical properties of chloroethane (Fiserova-Bergerova et al. 1990). Based on physical properties, the study authors considered chloroethane to have no significant dermal absorption potential. No quantitative studies were located regarding absorption in humans or animals following dermal exposure to chloroethane.

2.3.2 Distribution

Partition coefficients for human blood and serum measured *in vitro* at 40 °C were 1.9 for blood/air and 1.2 for serum/air (Morgan et al. 1970). A blood/air partition coefficient for humans of 2.69±0.2 has also been determined in vitro at 37°C (Gargas et al. 1989). Rat tissue/air partition coefficients of 38.6±0.7, 4.08±0.39, 3.61±0.32, and 3.22±0.68 for fat, blood, liver, and muscle, respectively, suggest that chloroethane has a higher affinity for fat than for blood, liver, or muscle (Gargas et al. 1989). These partition coefficients were determined *in vitro* at 37 °C using tissues from F344 rats.

No concrete data are available to indicate that distribution of chloroethane is different in children. Physical-chemical properties of chloroethane indicate that it would be readily soluble in fat. In the newborn and young infant, fat tissue is relatively scarce (15% of body weight; Morselli et al. 1980) as compared to an adult, indicating that distribution of lipophilic chloroethane will differ in infants and young children relative to adults. In addition, infants and younger children have much more total body and extracellular water relative to body weight than adults (Altman and Dittmer 1974), indicating that distribution of water-soluble compounds, such as chloroethane metabolites, will differ in children as compared with adults (Morselli et a1.1980).

The brain of a child is much larger, relative to body weight, than in the adult (Guzelian et al. 1992). Further, cerebral blood flow is greater, relative to brain weight, in the child than in the adult (Guzelian et al. 1992). Therefore, chloroethane present in the blood after exposures (such as inhalation) will more readily reach the brain of a child due to this increased blood flow. Since the central nervous system is the target organ for chloroethane's narcotic effects, the larger relative brain size of the child indicates that a child might experience a much larger exposure dose relative to body weight than an adult.

It is unknown if chloroethane can reach and cross the placenta or its precursors. However, based on physical-chemical characteristics of the compound, it is likely that it can. In addition, it is known that some chloroethane metabolites such as ethanol (Guzelian et al. 1992), can cross the placental barrier.

One study to date (Pellizari et al. 1982) determined that chloroethane does enter the milk of a lactating woman and can be detected. However, this study did not qluantify the chloroethane in milk, few women were tested, and the route of exposure to chloroethane was not determined. Therefore, it is impossible to estimate what percentage of exposed nursing mothers would be expected to excrete the compound in milk and what the significance of the compound in mother's milk would be for a nursing infant.

No data are available to indicate that females store chloroethane or its metabolites in their tissues. Data indicate that chloroethane is rapidly cleared within the body; therefore, it is unlikely that any of the compoundwould be stored in tissues, and it would not likely be available to be mobilized at a later time during pregnancy or lactation.

No data are available concerning the possibility of chloroethane entering into and adversely affecting parental germ cells.

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals following inhalation exposure to chloroethane. Reviews of the effects of chloroethane (Konietzko 1984; Lehman and Flury 1943) provide some general information about the distribution of chloroethane. The species in which the information was obtained was not stated. In the blood, approximately 75% of the chloroethane is bound to red blood cells, and 25% is in the plasma (Konietzko 1984). The highest concentration of chloroethane in the animal body was found in fatty tissue around the kidney, and the lowest was found in the cerebrospinal fluid (Konietzko 1984). The brain was said to accumulate a concentration two times that of the blood. Lehman and Flury (1943) reported that chloroethane content in the brain and medulla oblongata was especially high.

2.3.2.2 Oral Exposure

No studies were located regarding distribution of chloroethane in humans or animals following oral exposure.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of chloroethane in humans or animals following dermal exposure.

2.3.3 Metabolism

No studies were located regarding metabolism of chloroethane by humans. A review indicates that a small amount of chloroethane was metabolized to ethanol via dechlorination in animals following administration of high anesthetic doses (Konietzko 1984). The species was not identified.
Less than 0.5% of the dose was dechlorinated by rat liver microsomes in vitro (Van Dyke and Wineman 1971).

The metabolic rates for chloroethane were estimated for male F344 rats using a gas uptake method (Gargas et al. 1990). The rats were exposed to an initial concentration of 100, 535, 1,200, or 2,350 ppm, and the disappearance of the gas was studied for about 5 hours. A physiologically based pharmacokinetic (PBPK) model that assumed metabolism occurred exclusively in the liver was used to analyze the data. The metabolism of chloroethane was best described by a combination of a saturable pathway and a first-order pathway. The V_{maxc} which is the maximum velocity (V_{max}) scaled for a 1-kg animal, was determined to be 4 mg/hour (to calculate a V_{max} for an animal of any body weight [body weight in kg] use $V_{max} = V_{maxc}[BW]^{0.7}$). The rate constant for the saturable pathway (K_m was estimated to be 0.1 mgL. The first-order rate constant, k_{fc} which is the rate constant (K_f scaled for a l-kg animal, was 1 hr^{-1} (to calculate a k_f for any body weight use $k_f = k_{fc}[BW]^{-0.3}$).

The proposed metabolic pathways for chloroethane in rats and mice (Fedtke et al. 1994b) are shown in Figure 2-2. The two major pathways are the production of acetaldehyde by cytochrome P450, and conjugation of chloroethane with glutathione to form S-ethyl-glutathione. The metabolism of chloroethane to acetaldehyde was studied *in vitro* using livers from rats and mice exposed to chloroethane at 0 or 15,000 ppm 6 hours/day for 5 days (Fedtke et al. 1994a). The amounts of acetaldehyde detected ranged from 26.9 to 49.3% of the chloroethane metabolized, depending on pre-exposure to chloroethane, for the individual microsome preparations from rats and mice. The investigators found that exposure to chloroethane induced its own metabolism by approximately 100% in mice and female rats, with no effect in male rats. Based on

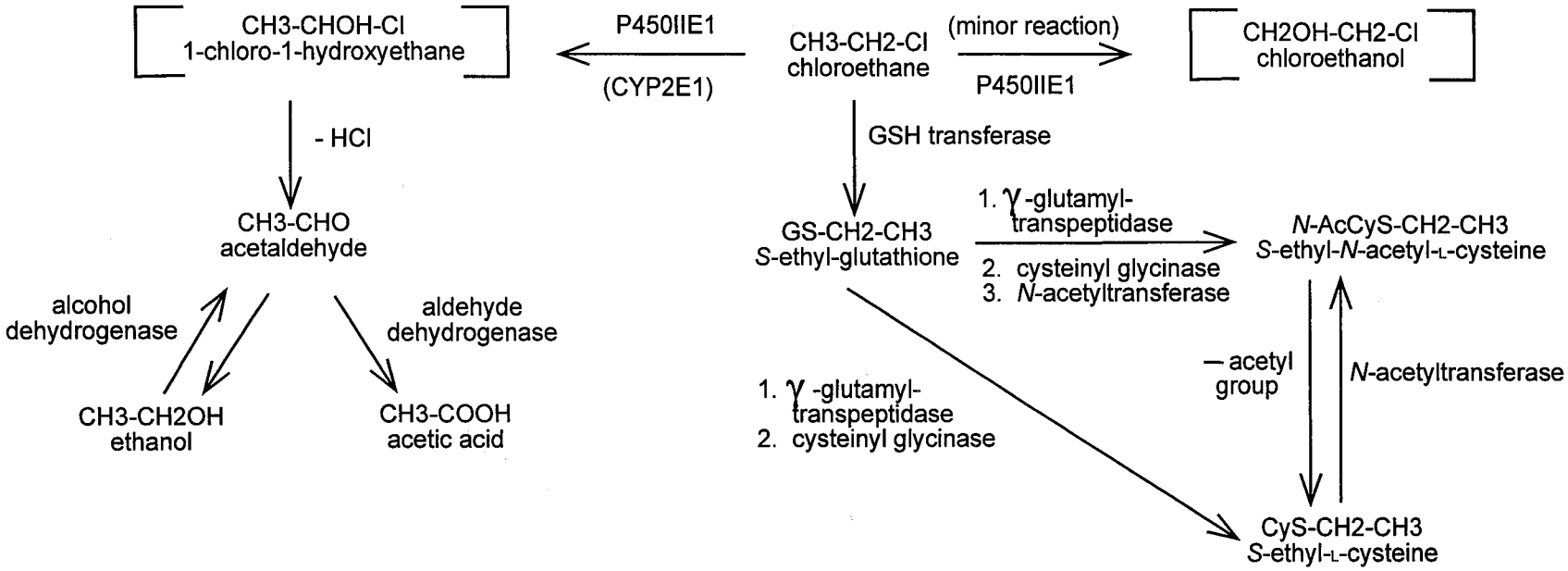
studies using specific P450 enzyme inducers and inhibitors, the investigators concluded that the P450 enzyme DE1 (CYP2El) was responsible for chloroethane metabolism. CYP2E1 also metabolizes alcohols, aldehydes, and ketones, and plays a role in gluconeogenesis within the body (Vieira et al. 1996).

Acetaldehyde is rapidly metabolized to acetic acid by aldehyde dehydrogenase. Therefore, increased acetaldehyde relative to normal levels was not detected in the serum of chloroethane-exposed rats or mice (15,000 ppm), or in the urine of exposed rats (Fedtke et al. 1994a). Small increases in acetaldehyde were detected in the urine of chloroethane-exposed mice. Acetaldehyde concentrations in the urine of male and female mice were 7.9-20.3 and 0-l 8.1 µmol/L, respectively, in unexposed mice, and 15.4-70.1 and 11.6-17 µmol/L, respectively, in chloroethane-exposed mice. Except for the approximately threefold greater metabolism of chloroethane in mice compared to rats, there was little difference between the species. The study authors concluded that the production of acetaldehyde from chloroethane was unlikely to have a role in the induction of uterine carcinomas in mice.

Glutathione levels were studied in rats and mice exposed to chloroethane at 0 or 15,000 ppm 6 hours/day for 5 days (Fedtke et al. 1994b). The animals were sacrificed immediately after the last exposure. Compared to controls, glutathione concentrations were significantly ($p<0.05$) decreased in the livers of male rats, in the kidneys of female rats, in the lungs of both sexes of rats and mice, and in the uteri of both rats and mice. The decreases in glutathione levels were most dramatic in the uterus, in which levels were approximately two-thirds lower than in controls. *In vitro* studies of chloroethane conjugation to glutathione, using liver cytosolic fractions from control and chloroethane-exposed rats and mice, indicated that the conjugation was catalyzed by glutathione-*S*-transferase enzymes (Fedtke et al. 1994b). Glutathione conjugation rates, in nmol chloroethane conjugated/minute mg protein, were greater in mice (0.71±0.19 in males; 1.01±0.19 in females) than in rats (0.17±0.19 in males; 0.16±0.03 in females). Chloroethane exposure had no effect on these rates in rats and slightly decreased the rates in mice. When urine was analyzed for glutathione metabolites, *S*-ethyl-*N*-acety-L-cysteine was detected in both rats and mice. *S*-Ethyl-L-cysteine was detected only in the urine of mice. The total amount of glutathione metabolites excreted during the 5-day exposure period was about fivefold higher in mice than in rats. The study authors concluded that rats completely metabolize *S*-ethyl-L-cysteine to more hydrophilic metabolites before urinary excretion, while these metabolic pathways were not available to the same extent in mice under the conditions of this study.

No data are currently available to indicate that the metabolism of chloroethane is different in children when compared to adults; however, some of the enzymes in the chloroethane metabolism scheme belong to enzyme

Figure 2-2. Metabolic Pathways of Chloroethane Biotransformation*



*Modified from Fedtke et al. 1994b
GSH = glutathione
[ ] = known metabolites that were not detected in the referenced study

families that are developmentally regulated to some extent either in humans or animals. Chloroethane is metabolized by both cytochrome P450 and by glutathione *S*-transferase. Studies have shown that liver glutathione *S*-transferase activities are low in prepubertal male and female rats, but as the rats reach sexual maturity (at around 30-50 days of age), glutathione-conjugating activity toward dichloronitrobenzene is two to threefold higher in males than females (Lamartiniere and Lucier 1983). The difference in glutathione *S*-transferase activity was dependent on pituitary secretions. Further research on hypophysectomized male and female rats revealed that growth hormones may contribute to the establishment of glutathione *S*-transferase activities (Lamartiniere 1981). No data are available to indicate that glutathione *S*-transferase activity is developmentally or sexually expressed in humans.

After glutathione conjugation of chloroethane, three other enzymes convert the conjugate to a more hydrophilic form to be excreted by the body. These enzymes are γ-glutamyltranspeptidase, cysteinyl glycinase, and *N*-acetyltransferase, NAT (Amdur et al. 1991). These three enzymes convert elatively hydrophobic glutathione conjugates to their respective mercapturic acids, which can be excreted more readily. There are two *N*-acetyltransferase enzyme families, NAT1 and NAT2. Of these enzymes, only NAT2 is developmentally regulated. It is unknown which NAT enzyme metabolizes chloroethane; therefore, it is unknown whether chloroethane is developmentally regulated by this metabolic pathway.

Studies have shown that the other enzyme metabolizing chloroethane, cytochrome P45OIIEl (CYP2El), is developmentally regulated in humans (Vieira et al. 1996). This enzyme is not detectable from livers of fetuses at 14-40 gestational weeks. However, the level of the protein rises sharply in the first day after birth (1 unit/mg protein) and continues to increase until it reaches adult values in children from 1 to 10 years of age, approximately 5 units/mg protein (Vieira et al. 1996).

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Excretion of chloroethane by the lungs is rapid in humans and animals (Adriani 1986; Konietzko 1984; Lehman and Flury 1943; Torkelson and Rowe 1981). In humans exposed briefly by inhalation to chloroethane, 30% of the retained dose was excreted in the breath within 1 hour (Morgan et al. 1970). Excretion over a longer period of time could not be measured because of the short half-life of the ^{38}Cl

radioisotope used in this study. Morgan et al. (1970) found that the rate of excretion of radioactivity in the urine of humans was very slow (i.e., <0.01% per minute) I hour after inhalation.

Small increases in acetaldehyde were detected in the urine of chloroethane-exposed mice but not rats (Fedtke et al. 1994a). Acetaldehyde concentrations in the urine of male and female mice were 7.9-20.3 and 0-l 8.1 µmol/L, respectively, in unexposed mice, and 15.4-70.1 and 11.6-17 µmol/L,respectively, in chloroethane-exposed mice. Acetaldehyde is rapidly metabolized to acetic acid; therefore it would be difficult to detect in whole animal studies. Glutathione conjugates have also been detected in the urine of rats and mice exposed to chloroethane (Fedtke et al. 1994b). Rats excreted the more hydrophilic *S*-ethyl-*N*-acetyl-L-cysteine, while mice excreted both *S*-ethyl-*N*-acetyl-L-cysteine and *S*-ethyl-L-cysteine. During the 5 days that rats and mice were exposed to chloroethane at 15,000 ppm for 6 hours/day, the total amount of glutathione metabolites excreted in the urine was about fivefold higher in mice than in rats.

2.3.4.2 Oral Exposure

No studies were located regarding excretion of chloroethane and metabolites in humans or animals following oral exposure.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of chloroethane and metabolites in humans or animals following dermal exposure.

No data are available to indicate that excretion of chloroethane is different in children,

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.

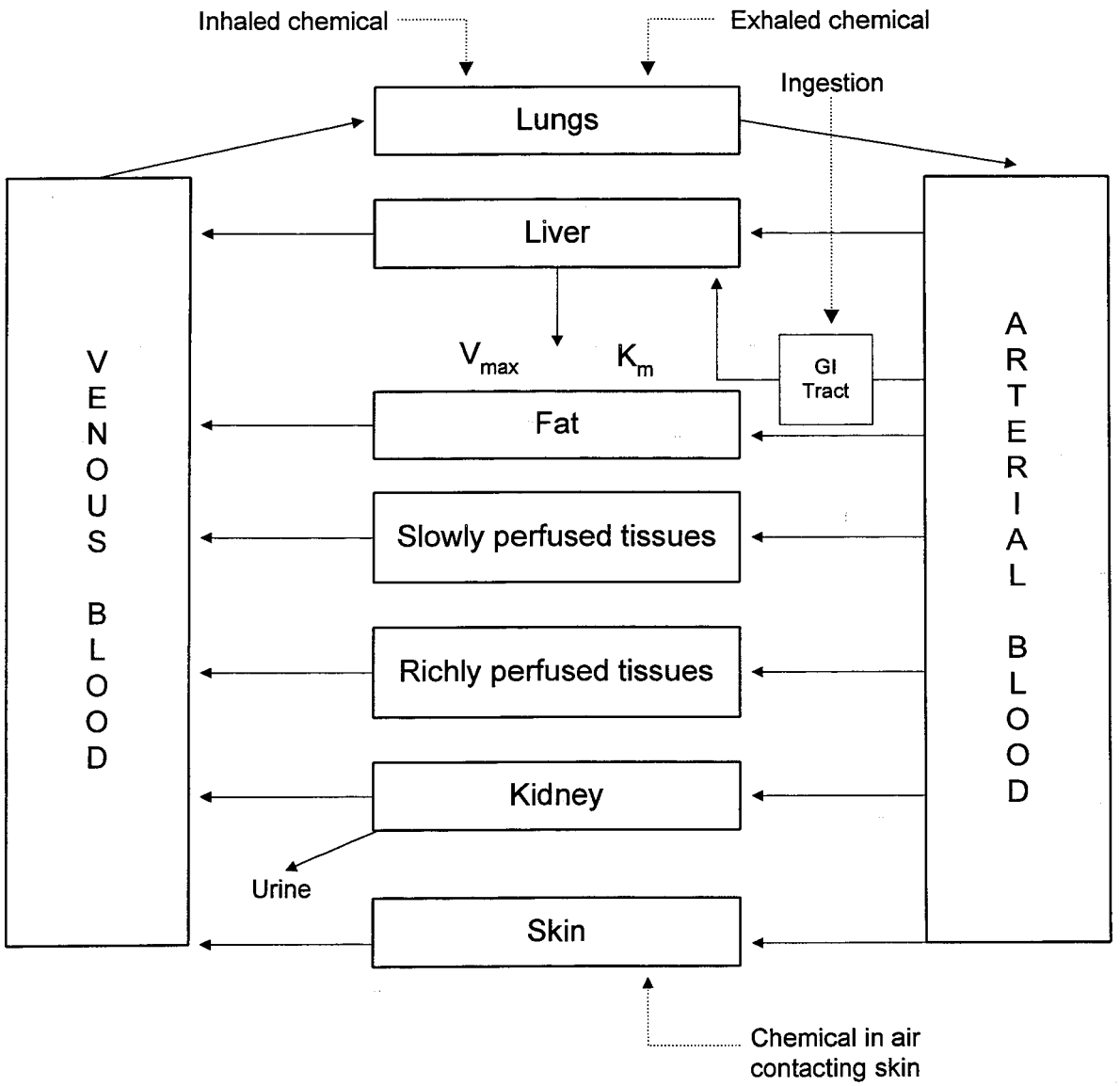
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al.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

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

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically-sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-3 shows a conceptualized representation of a PBPK model.

Figure 2-3. 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.

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

See Section 2.3.3 for discussion of a study that used a PBPK model to estimate the metabolic parameters for chloroethane in rats (Gargas et al. 1990). This study was not used for risk assessment, tissue dosimetry, or dose, route, or species extrapolation. Therefore, it is not discussed in this section.

There are no PBPK models for children, fetuses, pregnant women, infants or lactating women, or any other appropriate age group with which to make predictions concerning the pharmacokinetics of chloroethane in humans. In addition, these models are lacking in animals.

2.4 MECHANISMS OF ACTION

The exact mechanism of action for chloroethane toxicity has not been defined. It is generally accepted that chloroethane's ability to target the central nervous system and the heart is based on its physicalchemical characteristics and similarity to other volatile halogenated organics with anesthetic properties. These currently accepted beliefs do not suggest that differences exist between children and adults in regards to the mechanism of toxicity of chloroethane.

2.4.1 Pharmacokinetic Mechanisms

Because chloroethane is a small lipophilic compound, simple diffusion accounts for its absorption across membranes, and its higher affinity for lipids determines its distribution. A review regarding the kinetics of chloroethane indicates that 75% of the compound in blood is bound to red blood cells, and 25% is in plasma (Konietzko 1984). This is consistent with the lipophilic nature of chloroethane. The metabolism of chloroethane has been studied *in vitro* using liver microsomal preparations from rats and mice (Fedtke et al. 1994a). The observations that inhibitors of the P450 enzyme IlEI reduce chloroethane metabolism, and that inducers of P450 IIEI enhance metabolism of the compound to acetaldehyde, provide evidence that P450 IIEI is the principal P450 enzyme involved in the metabolism of chloroethane. In vitro studies using hepatic cytosolic fractions from the livers of rats and mice have shown that the conjugation of chloroethane with glutathione is catalyzed by glutathione -*S*-transferase enzymes (Fedtke et al. 1994b). In mice, both *S*-ethyl-*N*-acetyl-L-cysteine and *S*-ethyl-L-cysteine are formed and excreted in the urine, while in rats, only *S*-ethyl-*N*-acetyl-L-cysteine is formed and excreted in the urine.

2.4.2 Mechanisms of Toxicity

Chloroethane has a general anesthetic effect when inhaled at high concentrations by humans and animals. The anesthetic effect is thought to be produced by the compound itself. Although the specific mechanism of action is unknown, it is generally believed that chloroetbane's ability to induce anesthesia is related to the solubility of the compound in oils or fats. The lipophilicity of the nonpolar compound suggests that chloroethane is dissolved within and acts upon the lipid layer of cellular membrane or the hydrophobic areas of specific membrane-bound cellular proteins (Goodman and Gilman 1993). This hypothesis is supported by the findings of Balasubramanian and Wetlaufer (1966) who showed that chloroethane and other volatile anesthetics produced reversible structural changes in globular proteins *in vitro*. They proposed that the anesthetic activity of these compounds may be a result of their ability to produce structural changes in protein or lipoprotein structures.

Volatile anesthetics affect voltage-gated calcium channels (Langmoen et al. 1995). Using a guinea pig heartlung preparation, Doring (1975) found that volatile general anesthetics including chloroethane interfere with the calcium-mediated process of excitation-contraction coupling leading to a reduction in high energy phosphate (ATP) utilization. Extra calcium, cardiac glycosides, or β-adrenergic catecholamines did not reverse the effects. Doring (1975) indicated that, because of their lipophilic nature, volatile anesthetics may alter the lipid arrangement of the transverse tubule walls, resulting in permanent impairment of excitationcontraction coupling. In studies using chloroform, Doring (1975) was able to show ultrastructural changes in the transverse tubules, especially vacuolization and dilatation Electron microscopic examinations of hearts similarly exposed to chloroethane were not presented, but chloroethane would be expected to act in a manner similar to chloroform.

Chloroethane has been shown to have cardiotoxic effects in several studies (Bush et al. 1952; Cole 1967; Haid et al. 1954; Morris et al. 1953). At levels adequate to induce anesthesia, chloroethane sensitizes the heart to the effects of catecholamines (Haid et al. 1954; Morris et al. 1953). Catecholamine release can be induced by euphoria and excitement resulting from the effects of chloroethane on the central nervous system (Benowitz 1992). The myocardium can be sensitized to the effects of the catecholamines. This sensitization, along with asphyxia and hypoxia, which can also result from high concentrations of inhaled chloroethane, can cause arrhythmias, which can result in death (Benowitz 1992). It is possible that chloroethane and similar solvents may depress atrioventricular nodal conduction, causing atrioventricular block. Bradyarrhythmias

(abnormally slow hearth rhythms) may then occur to prevent ventricular arrhythmias, or asystole (lack of electrical or mechanical activity in the heart) may result.

Analysis of structure-activity relationships predicts that chloroethane is carcinogenic. The alerting substructure is the Cl-CH_2 group, which results in chloroethane being an alkylating agent and a mutagen to *Salmonella* (Tennant and Ashby 1991). It is not known why chloroethane does not cause respiratory cancers following inhalation exposure, or why it acts as a selective carcinogen resulting in uterine tumors in mice. Based on a lack of differences in P450 metabolism of chloroethane between rats and mice, decreased uterine glutathione levels in rats and mice following chloroethane exposure, and the urinary excretion of *S*-ethyl-Lcysteine in mice but not rats, Fedtke et al. (1994b) suggested that uterine tumor production is a result of the glutathione conjugation pathway, rather than a result of chloroethane metabolism by P450 enzymes. The study authors did not state which compound in the glutathione conjugation pathway was responsible for the carcinogenic effect of chloroethane.

2.4.3 Animal-to-Human Extrapolations

The metabolism of chloroethane has not been studied in humans. Therefore, it is not possible to determine which species of animal is the most appropriate model for humans exposed to chloroethane. Studies by Fedtke et al. (1994a, 1994b) indicate that compared to rats, mice have a greater capacity to metabolize chloroethane by both the P450 and glutathione conjugation pathways.

2.5 RELEVANCE TO PUBLIC HEALTH

Issues relevant to children are explicitly discussed in 2.6 Children's Susceptibility and 5.6 Exposures of Children.

Overview

Although chloroethane has been used as a general anesthetic in humans, very little is known about the effects of inhalation exposure to lower concentrations. The concentrations required to produce anesthesia, approximately 40,000 ppm, are near the explosion limit of this compound. Chloroethane is also used as a local anesthetic in humans. When chloroethane is sprayed on the skin, it rapidly evaporates and causes the skin to freeze, producing a numbing sensation. Oral exposure of humans to chloroethane has not been

studied. Because chloroethane is a gas, substantial oral exposure of humans to this compound is not expected.

Animal studies regarding the effects of chloroethane are predominantly focused on the inhalation route of exposure. At high concentrations for short periods of time, chloroethane clearly results in neurological effects producing unsteadiness followed by unconsciousness. A number of toxicity studies have not clearly identified a target organ of toxicity for chloroethane (Eandry et al. 1982, 1987,1989; NTP 1989).

One target of chloroethane toxicity in animals exposed to high concentrations is the uterus. Chloroethane has been shown to decrease uterine weight by 35% in mice exposed to 15,000 ppm chloroethane 6 hours/day for 5 days (Fedtke et al. 1994a). Significant decreases in uterine glutathione levels were also observed in both rats and r-nice (Fedtke et al. 1994b). Chloroethane has also been shown to produce uterine cancer in mice but not rats exposed to 15,000 ppm chloroethane for approximately 2 years (NTP 1989). The relevance of these uterine effects in animals to humans is not known.

In addition to uterine effects, limited studies of reproduction and development in mice have shown effects. A small increase in the average duration of the estrous cycle was observed in mice exposed to 15,000 ppm chloroethane 6 hours/day for 21 days (Bucher et al. 1995). Before the exposure, estrous cycle duration was 5.15±0.15 days, while during the exposure, estrous cycle duration was 5.52±0.19 days. Measurement of serum estradiol and progesterone did not reveal any consistent statistically significant changes attributable to chloroethane exposure. Evidence of fetotoxicity, a statistically significant increase in small centers of unossified bones of the skull, was observed in the offspring of mice exposed to 4,946 ppm chloroethane during gestation days 6-15 (Scortichini et al. 1986). Further studies are needed to confirm the reproductive and developmental toxicity of chloroethane and to determine that the effects are observed in another species in addition to mice.

Chloroethane is an alkylating agent and is mutagenic to *Samonella* (NTP 1989). Chloroethane has not been shown to cause genotoxic effects in *in vivo* assays in mice (Ebert et al. 1994). In a single high-concentration (15,000 ppm) study, chloroethane clearly caused uterine cancer in female mice, with equivocal evidence of carcinogenicity in rats (increased skin tumors in male rats and astrocytomas in the brains of female rats) (NTP 1989). Because only one concentration was tested, it cannot be determined whether or not the carcinogenic effect of chloroethane is a high-concentration phenomenon.

Minimal Risk Levels for Chloroethane

Inhalation MRLS

- An MRL of 15 ppm has been derived for acute-duration inhalation exposure (14 days or less) to chloroethane.

  This MRL is based on the developmental study by Scortichini et al. (1986) in which minimal fetotoxicity (a significant increase in the incidence of foramina of the skull bones) was observed in the offspring of mice exposed to 4,946 ppm chloroethane during gestation days 6-15. Fetotoxicity was not observed at 1,504 ppm, the NOAEL concentration that serves as the basis of the MRL. No additional developmental studies of chloroethane were identified.

Intermediate- and chronic-duration inhalation MRLs were not derived. The only concentration that resulted in adverse effects in longer duration studies was 15,000 ppm (NTP 1989). At this concentration in studies of about 2 years in duration, hyperactivity, renal effects, and decreased survival were observed in mice. In 13-week studies, no adverse effects were observed in rats or mice at 19,000 ppm (NTP 1989). Since the acuteduration inhalation MRL is based on a concentration much lower than those resulting in effects in longer duration studies, it should also be protective for intermediate- and chronic-duration inhalation exposure.

Oral MRLS

Oral data concerning the effects of chloroethane were not identified. Therefore, no oral MRLs were derived.

Death. Acute inhalation of high concentrations of chloroethane vapor is lethal to humans (Dawkins 1964; Konietzko 1984; Kuschinsky 1970; Lawson 1965; Lehman and Flury 1943; Yacoub et al. 1993) and animals (Lazarew 1929; Sayers et al. 1929; Troshina 1966). Death appears to be caused by asphyxiation, as well as effects on the heart and nervous system. The nervous system seems to be involved because neurological effects such as unsteadiness, loss of muscle coordination, and unconsciousness precede death in animals. Similar effects are seen in humans exposed to chloroethane. In addition, effects such as respiratory paralysis and cardiac depression, which have been reported during chloroethane exposure in both humans and animals, are at least partly neurological in origin. For example, cardiac depression can be caused by stimulation of the vagus nerve or by direct effect on the cardiac tissue. Bush et al. (1952) found that in dogs anesthetized with chloroethane, cardiac depression occurred first by vagal stimulation and then by direct effect on the heart. Upon overdose, the dogs died from cardiac arrest. Most human deaths caused by chloroethane were the result of overdose while under anesthesia. There is also one report of a death following abuse of chloroethane

(Yacoub et al. 1993). The specific level of exposure that causes death in humans is not known, but it probably exceeds 40,000 ppm, which is the concentration that was typically used to produce clinical anesthesia. Chloroethane is no longer used as a general anesthetic in the United States.

The long-term survival of mice was reduced by chronic exposure to 15,000 ppm chloroethane vapor (NTP 1989). An ascending urinary tract infection may have contributed to the reduced survival in male mice. The decreased survival in female mice was attributed to uterine cancer. Decreased survival was not observed in rats, but control survival was abnormally low for this species which obscured the results (NTP 1989). There is no evidence that humans would respond to chronic chloroethane exposure in a manner similar to the mouse, but these data suggest the possibility that sub-anesthetic concentrations of chloroethane may be potentially hazardous to humans if inhaled for an extended period of time.

Reliable information regarding death of humans or animals following oral consumption of chloroethane was not found. Because chloroethane is a gas, accidental oral exposure to doses of chloroethane large enough to result in deaths is highly unlikely. Although no studies of the acute lethality of dermally-applied chloroethane were located, it is unlikely that brief dermal exposure is lethal to humans since chloroethane is in widespread use as a topical anesthetic, and reports of accidental death from this use were not found. Further, as previously discussed, chloroethane is expected to evaporate quickly from the skin since its standard state is a gas. Therefore, it is unlikely to remain on the skin long enough to be absorbed at a dose that would result in death.

Systemic Effects. The systemic effects of chloroethane, which is a gas, have not been studied by the oral route of exposure. Few studies regarding dermal exposure to chloroethane were identified. Therefore, in the following discussion, unless stated otherwise, exposure is via inhalation.

Respiratory Effects. When used as a general anesthetic, chloroethane sometimes increases the respiratory rate of humans (Cole 1956, 1967). Respiratory paralysis was reported to be the cause of death of a 14-year old who died during anesthesia (Kuschinsky 1970). Mild lung effects have also been reported in animals exposed to very high concentrations of chloroethane for short periods of time (Gohlke and Schmidt 1972; Sayers et al. 1929). Histopathological changes in the lungs of animals were not observed in studies of longer duration (Landry et al. 1982, 1987,1989; NTP 1989).

The exposure concentrations (up to 19,000 ppm) used in the inhalation studies are much higher than one is likely to encounter in occupational settings or in the vicinity of hazardous waste sites. Therefore, respiratory effects resulting from chloroethane exposure are highly unlikely.

Cardiovascular Effects. Chloroethane has been shown to interfere with cardiac function in animals when inhaled at anesthetic concentrations. Cardiac depression, ventricular tachycardia, ventricular fibrillation, asystole, and sensitization to endogenous and exogenous epinephrine have all been observed in dogsanesthetized with chloroethane (Bush et al. 1952; Haid et al. 1954; Morris et al. 1953). Severe, irreversible, contractile failure of the heart occurred in a guinea pig heart-lung preparation after exposure to chloroethane vapor, and elevated ratios of ATP/ADP and creatine-P/inorganic-P were found in the heart, indicating that a reduction in high-energy phosphate utilization had taken place (Doring 1975). These results, together with the previously reported finding of cardiac depression in humans exposed briefly to high concentrations of chloroethane (Bush et al. 1952), suggest that high levels of chloroethane vapor in the air may be potentially hazardous to humans because of effects on the heart. Longer studies at lower concentrations have not reported any histopathological changes in the heart (Landry et al. 1982, 1987,1989; NTP 1989). Cardiovascular effects are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Gastrointestinal Effects. Abdominal cramps and nausea have been reported by persons exposed to chloroethane at very high concentrations for short periods of time (Davidson 1925; Sayers et al. 1929). Vomiting has also been reported in patients as they recovered from chloroethane anesthesia (Cole 1967). It is not clear if gastrointestinal effects are a direct irritant effect of chloroethane or if they are secondary to nervous system effects. Histopathological changes in the gastrointestinal tract of animals were not observed in longer studies (Landry et al. 1982, 1987, 1989; NTP 1989). Gastrointestinal tract effects are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Hematological Effects. Cyanosis has been reported in humans following inhalation exposure to chloroethane at very high concentrations (Davidson 1925). Since this effect was observed when chloroethane was not mixed with oxygen, it is very likely that it was the result of a lack of oxygen rather than a direct effect of chloroethane. Hematological effects were not observed in mice exposed to chloroethane for 11 days (Landry et al. 1987, 1989) or in rats or dogs exposed to chloroethane for 2 weeks (Landry et al. 1982).

Based on the available animal data, hematological effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following exposure to chloroethane. Histopathological changes in the muscle and bone have not been observed in animals following inhalation exposure (Landry et al. 1982, 1987, 1989; NTP 1989). Disintegration of muscle fibers has been observed in rats after chloroethane was applied dermally until the skin was blanched (Kenig 1956). This study suggests that improper use of chloroethane as a topical anesthetic could result in adverse effects on the underlying muscle. Musculoskeletal effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Hepatic Effects. An enlarged liver and mild transient disturbance of liver function were reported in a woman who sniffed chloroethane for 4 months (Hes et al. 1979). Moderately elevated serum alanine aminotransferase was observed in a man who abused chloroethane for 30 years (Nordin et al. 1988). Liver effects reported in animals exposed to high concentrations of chloroethane include an increase in the liver ATP/ADP ratio (Oura et al. 1966), decreased liver glutathione (Fedtke et al. 1994b), and decreased liver non-protein sulfhydryl concentrations (Landry et al. 1982). Increased liver weights have also been reported (Landry et al. 1982,1987, 1989). These mild liver effects may be considered an adaptive response to chloroethane exposure rather than a toxicologic effect. Other studies have not reported liver weight changes or histopathological changes in the liver (Bucher et al. 1995; NTP 1989). Based on the available data, hepatic effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Renal Effects. No studies were located regarding renal effects in humans following exposure to chloroethane. Mild signs of nephrotoxicity were observed in mice exposed to relatively high concentrations for 100 weeks (NTP 1989), while no renal effects were observed in rats exposed at the same concentrations for 102 weeks (NTP 1989). Additional acute- and intermediate-duration studies have not reported significant renal effects in animals (Fedtke et al. 1994a; Landry et al. 1982, 1987, 1989; NTP 1989; Schmidt et al. 1972). Based on the available animal data, renal effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Endocrine Effects. No studies were located regarding endocrine effects in humans following exposure to chloroethane. Endocrine gland effects have not been observed in animals exposed to chloroethane (Gohlke and Schmidt 1972; Landry et al. 1982, 1987, 1989; NTP 1989; Schmidt et al. 1972). Based on the available animal data, endocrine effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings or in the environment, including hazardous waste sites.

Dermal Effects. No studies were located regarding dermal effects in humans following inhalation exposure to chloroethane. Following inhalation exposure of animals to chloroethane, dermal effects have not been reported (Landry et al. 1982, 1987, 1989; NTP 1989). Chloroethane has a local anesthetic effect in humans and animals following dermal application. It rapidly evaporates and draws heat from the skin, causing the skin to freeze. Application for too long a time can result in frostbite. Noble (1979) reported frostbite in three children sprayed with chloroethane for several minutes. Contact dermal sensitivity has also been reported in persons exposed to chloroethane (Bircher et al. 1994; Kriechbaumer et al. 1998; Van Ketel 1976). Chloroethane applied to rats until the skin was blanched caused edema in the subcutaneous tissue at the site of application (Kenig 1956). Because chloroethane is used as a topical anesthetic, many people may be at risk of developing sensitivity to chloroethane or of the hazard of freezing of the skin if chloroethane is used incorrectly. Sensitized individuals may react to chloroethane in the environment or at hazardous waste sites.

Ocular Effects. Mild eye irritation has been reported in volunteers exposed briefly to very high concentrations of chloroethane (Sayers et al. 1929). Effects on the eyes have not been reported in animals exposed to chloroethane (Landry et al. 1982, 1987,1989). Based on the available data, ocular effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings and in the environment, including hazardous waste sites.

Body Weight Effects. Body weight effects have not been reported in animals exposed to chloroethane (Fedtke et al. 1994a; Landry et al. 1982,1987,1989; NTP 1989; Schmidt et al. 1972; Scortichini et al. 1986). Based on the available animal data, body weight effects in humans are unlikely to occur at concentrations of chloroethane normally found at occupational settings and in the environment, including hazardous waste sites.

Immunological and Lymphoreticular Effects. No immunological effects were reported in humans (Troshina 1966) or animals (Landry et al. 1982, 1987, 1989; NTP 1989; Schmidt et al. 1972) after inhalation exposure to chloroethane, but contact dermatitis has been found in humans treated dermally with chloroethane (Bircher et al. 1994; Van Ketel 1976). This effect is notable because of the widespread use of chloroethane as a topical anesthetic. Sensitized individuals may react to chloroethane in the environment or at hazardous waste sites.

Neurological Effects. Chloroethane has a general anesthetic effect when inhaled at high concentrations by humans and animals. The severity of the effect increases with the concentration of chloroethane and the duration of exposure. In humans, unconsciousness was produced by inhalation of 33,600 ppm chloroethane for approximately 15 minutes (Davidson 1925). Cbloroethaue is no longer used as a general anesthetic in the United States, but in the past, concentrations of approximately 40,000 ppm were used clinically to produce anesthesia (Lawson 1965). The gastrointestinal effects reported in patients as they recovered from chloroethane anesthesia (Cole 1967; Davidson 1925; Sayers et al. 1929) may be secondary to the neurological effects. In animals, clinically effective anesthetic concentrations range from 30,000 to 45,000 ppm (Dobkin and Byles 1971). Induction of anesthesia using chloroethane is rapid, and so is recovery. The anesthetic effect is thought to be produced by the compound itself; however, its mechanism of action is unknown. Balasubramanian and Wetlaufer (1966) showed that the vapors produced from pure liquid chloroethane and other volatile anesthetics produced reversible structural changes in globular proteins *in vitro*. They proposed that the anesthetic activity of these compounds might be due to their ability to produce structural changes in protein or lipoprotein structures in cell membranes. Following abuse of chloroethane, ataxia, nystagmus, scanning dysarthria, dysdiadochokinesia of the arm, and sluggish lower limb reflexes were reported (Hes et al. 1979). These effects were reversible after 1 month without chloroethane exposure. In a second case of chloroethane abuse, neurological and mental changes (grand ma1 seizure, ataxia, difficulties in walking, disorientation, short-term memory impairment, visual hallucinations) were observed following recovery after 30 years of chloroethane abuse (Nordin et al. 1988). The study authors indicate that it was not possible to determine whether the nervous system effects were toxic effects of chloroethane or withdrawal symptoms.

Animal studies examining the histology of nervous system tissue have not revealed any adverse effects following inhalation exposure (Gohlke and Schmidt 1972; Landry et al. 1982, 1987, 1989; NTP 1989; Schmidt et al. 1972). Except for observations during exposure, neurological function has not been studied in animals following intermediate or chronic inhalation exposure.

Chloroethane is still used as a local anesthetic It is applied to the skin, and its rapid evaporation results in cooling. Mild pain has been reported during the dermal application of chloroethane to the skin of humans (Selby and Bowles 1995). Application of chloroethane to the skin of rats has been reported to result in thickening of nerve fibers and swelling of Schwann cell nuclei (Kenig 1956).

The nervous system is a target of chloroethane exposure, and functional effects of chloroethane exposure have not been well studied. Therefore, it is not known if neurological effects may occur in humans at concentrations of chloroethane normally found at occupational settings and in the environment, including hazardous waste sites.

Reproductive Effects. Studies of reproductive effects in humans exposed to chloroethane were not identified. Several studies investigated reproductive endpoints in animals. In dogs anesthetized with chloroethane, high concentrations resulted in decreased uterine motility and muscle tone (Van Liere et al. 1966). Uterine weight was decreased by approximately 35% in mice exposed to high concentrations of chloroethane (Fedtke et al. 1994a). Significant decreases in uterine glutathione levels have also been reported in rats and mice exposed to chloroethane (Fedtke et al. 1994b). The decreases in glutathione in the uterus were greater than the decreases in glutathione observed in the liver, lungs, and kidneys. A small increase in the average duration of the estrous cycle was observed in mice exposed to high concentrations of chloroethane 6 hours/day for 2 1 days (Bucher et al. 1995). Measurement of serum estradiol and progesterone did not reveal any consistent statistically significant changes attributable to chloroethane exposure. Sperm motility in rats was reduced after exposure to chloroethane for 6 months (Troshina 1966). Histopathological effects have not been observed in reproductive organs of animals exposed to chloroethane (Landry et al. 1982, 1987, 1989; NTP 1989). No effects on the number of live and dead fetuses or the number and position of resorption sites were observed in mice exposed to chloroethane during gestation days 6-15 (Scortichini et al. 1986). Additional studies of reproductive outcome in animals following inhalation exposure to chloroethane were not identified.

Based on decreases in uterine glutathione in rats and mice, decreases in uterine weight in mice, and the development of uterine cancer in mice exposed to chloroethane (NTP 1989) (see Cancer discussion in Section 2.5), the uterus appears to be a target of chloroethane exposure in mice; rats are apparently less sensitive to these effects. Further studies are required to determine the mechanism of uterine toxicity in mice and to determine the relevance of these effects to humans exposed to chloroethane at concentrations normally found at occupational settings and in the environment, including hazardous waste sites.

Developmental Effects. No studies were located regarding developmental effects in humans following exposure to chloroethane. Only one study of the developmental effects of chloroethane in animals was found. In this mouse study, minimal evidence of fetotoxicity (increase in small centers of unossified bones of the skull) was observed at the highest concentration tested (Scortichini et al. 1986). This study serves as the basis for the acute-duration inhalation MRL. Further study is required to determine the relevance of developmental effects in animals to humans exposed to chloroethane at concentrations normally found at occupational settings and in the environment, including hazardous waste sites.

Genotoxic Effects. Results of mutagenicity tests performed *in* vivo and *in vitro* are shown in Tables 2-2 and 2-3, respectively. Chloroethane did not increase the number of micronuclei in bone marrow cells or affect DNA synthesis in mice exposed nose-only to 25,000 ppm chloroethane 6 hours/day for 3 days (Ebert et al. 1994). The investigators indicated that the exposure concentration used in this study was about 66% of the flammability limit and that it was the highest concentration that could be safely administered. Using a desiccator for exposure to the gas, positive rest&s in reverse mutation assays using *Salmonella typhimurium* strain TA1535 with and without activation were reported by NTP (1989). In strain TAl00, the results were positive only with metabolic activation, while the results were negative in strain TA98 both with and without metabolic activation. NTP (1989) indicated that the mutagenic activity of chloroethane in *S. typhimurium* was consistent with an alkylating agent. Chloroethane was positive for gene mutation in Chinese hamster ovary cells exposed *in vitro* (Ebert et al. 1994). Negative results were reported for chloroethane in a cell transformation assay using mouse BALB/c-3T3 cells (Tu et al. 1985). Although chloroethane is mutagenic in *in vitro* assays, negative results were observed in *in vivo* studies, and the data are insufficient to predict that chloroethane poses a genotoxic threat to humans.

Existing data are inconclusive concerning the genotoxicity of chloroethane. Despite this lack of data, the volatility of chloroethane, its rapid clearance from the body, and its quick metabolism within the body indicate it is unlikely that it would reach germ cells to result in any potential genotoxic effect.

Cancer. No studies were located regarding the carcinogenicity of chloroethane in humans, but chloroethane has been shown to be carcinogenic in animals. In a study by the NTP (1989), 86% of female mice chronically exposed to chloroethane vapor developed highly malignant uterine carcinomas. Uterine tumors were not observed in any of the control mice. The incidence of hepatocellular carcinomas also increased significantly in female mice. Male mice had an increased incidence of alveolar and bronchiolar adenomas, but because male survival was substantially reduced toward the end of the study these results are not conclusive. Male

TABLE 2-2. Genotoxicity of Chloroethane *In Vivo*

Species (test system)	End point	Results	Reference
Mouse	Micronuclei	–	Ebert et al. 1994
Mouse	Unscheduled DNA synthesis	–	Ebert et al. 1994

– = negative result; DNA = deoxyribonucleic acid

TABLE 2-3. Genotoxicity of Chloroethane *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium[a]				
Strain TA1535	Gene mutation	+	+	NTP 1989
Strain TA100	Gene mutation	+	–	NTP 1989
Strain TA98 (desiccator test for exposure to gases)	Gene mutation	–	–	NTP 1989
Strains TA1535, TA100	Gene mutation	+	+	Milman et al. 1988
Eukaryotic organisms:				
Mammalian cells				
Mouse BALB/c-3T3 cells	Cell transformation	No data	–	Milman et al. 1988; Tu et al. 1985
Chinese hamster ovary cells	Gene mutation	+	+	Ebert et al. 1994
Mouse B6C3F$_1$ hepatocyte primary culture	DNA repair	No data	–	Milman et al. 1988

[a]Mutagenic activity consistent with an alkylating agent - positive in base substitution strains

+ = positive result; – = negative result; DNA = deoxyribonucleic acid

rats had marginally increased incidences of skin tumors, and female rats had marginally increased incidences of brain astrocytomas, providing equivocal evidence that chloroethane is carcinogenic in rats (NTP 1989). The fact that chloroethane is carcinogenic in mice and may be carcinogenic in rats as well suggests the possibility that this compound may also be carcinogenic in humans. Based on limited evidence of carcinogenicity in animals and no human data, IARC (1991) considers chloroethane to be in Group 3, not classifiable as to its carcinogenicity to humans. The carcinogenicity of chloroethane has not been classified by EPA (IRIS 1997) or NTP (DHHS 1994). The data are not sufficient to predict whether chloroethane is carcinogenic at concentrations that occur in the environment or at hazardous waste sites. OSHA has recommended that ethyl chloride be treated in the workplace with caution because of the structural similarity to the four confirmed halogenated animal carcinogens: ethylene dichloride; hexachloroethane; 1,1,2,2-tetrachloroethane; and 1,1,2-trichloroethane (NIOSH 1997).

2.6 CHILDREN'S SUSCEPTIBILITY

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

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in section 5.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both pre-natal and post-natal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980;

NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Widdowson and Dickerson 1964; Foman et al. 1982; Owen and Brozek 1966; Altman and Dittmer 1974; Foman 1966). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults and sometimes unique enzymes may exist at particular developmental stages (Leeder and Kearns 1997; Komori 1990; Vieira et al. 1996; NRC 1993). Whether differences in xenobiotic metabolism make the child more or less susceptible also depend on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in the newborn who has a low glomerular filtration rate and has not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; West et al. 1948; NRC 1993). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer lifetime in which to express damage from chemicals; this potential is particularly
relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

Children have infrequently been observed for health effects following exposure to chloroethane. Effects observed in humans exposed to chloroethane have resulted primarily from inhalation exposure. Respiratory paralysis was reported to be the cause of death of a 14-year-old child who died during anesthesia with chloroethane (Kuschinsky 1970); however, the concentration of chloroethane administered was not known. Another study reported vagal stimulation, followed by depression of cardiac tissues in children exposed briefly to reportedly high concentrations of chloroethane; the specific levels were not indicated (Bush et al. 1952).

Chloroethane has also been used and sometimes misused as a topical anesthetic in both children and adults (Nielsen 1980; Noble 1979; Ott 1969; Van Ketel 1976). Misuse occurs when excessive amounts of chloroethane are sprayed on the skin for long periods of time. Three children suffered frostbite on the

exposed skin of their ears and necks after having their earlobes sprayed with chloroethane for several minutes (Noble 1979).

Effects seen in adults exposed to chloroethane are also expected in children. In particular, the nervous system is likely to be a sensitive target of chloroethane, as it is in adults. Since infants and young children have a larger proportion of their bodies as brain mass, and since blood flow is greater to this organ in children, one might predict on pharmacokinetic grounds that these ages of children would be more susceptible to the anesthetic effects of chloroethane than adults In addition, chloroethane distribution may be very different in children relative to adults due to the difference in fat and water content and lean body mass in children.

No studies were identified that reported effects caused by chloroethane in adults exposed as children and there is no information on the health effects of exposures in immature animals. There are no data concerning the effects of chloroethane exposure on human development and there is only one developmental study in animals. This study (Scortichini et al. 1986) reported that at the highest concentration administered to mice, delayed ossification of skull bones occurred. However, no other developmental parameters were affected, and no maternal toxicity was reported.

There are no data available concerning the pharmacokinetics of chloroethane in children. There are no human or animal studies available concerning the ability of chloroethane or its metabolites to reach and cross the placenta. One study determined that chloroethane can be detected in the breast milk of nursing mothers (Pelizzari et al. 1982), but the study was not quantitative and did not offer data concerning the percentage of nursing mothers that might excrete the compound in milk after exposure, nor did it provide a range of concentrations of the compound in this medium. No studies were identified that determined if chloroethane was stored in maternal tissues. However, the rapid clearance of chloroethane, as well as its volatility, suggest that it would not be stored within the body for an extended period of time, so pre-conception maternal exposure is not likely to result in exposure to children during gestation or lactation. See Section 2.3 for further information.

No data are currently available to indicate that the metabolism of chloroethane is different in children when compared to adults; however, some of the enzymes in the chloroethane metabolism scheme belong to enzyme families that are developmentally regulated to some extent either in humans or animals. Chloroethane is metabolized by both cytochrome P450 and by glutathione *S*-transferase. Studies have shown that liver glutathione S-transferase activities are low in prepubertal male and female rats, but as the rats reach sexual

maturity (at around 30-50 days of age), glutathione-conjugating activity toward dichloronitrobenzene is two to threefold higher in males than females (Lamartiniere and Lucier 1983). The difference in glutathione *S*-transferase activity was dependent on pituitary secretions. Further research on hypophysectomized male and female rats revealed that growth hormones may contribute to the establishment of glutathione S-transferase activities (Lamartiniere 198 1). No data are available to indicate that glutathione *S*-transferase activity is also developmentally or sexually expressed in humans.

After glutathione conjugation of chloroethane, three other enzymes convert the conjugate to a more hydrophilic form to be excreted by the body. These enzymes are γ-glutamyltranspeptidase, cysteinyl glycinase, and *N*-acetyltransferase, NAT (Amdur et al. 1991). These three enzymes convert relatively hydrophobic glutathione conjugates to their respective mercapturic acids, which can be excreted more readily. There are two *N*-acetyltransferase enzyme families, NAT 1 and NAT2. Of these enzymes, only NAT2 is developmentally regulated. It is unknown which NAT enzyme metabolizes chloroethane; therefore, it is unknown whether chloroethane is developmentally regulated by this pathway.

Studies have shown that cytochrome P450 IIEl is developmentally expressed in humans (Vieira et al. 1996). This enzyme is not detectable from livers of fetuses at 14-40 gestational weeks. However, the level of the protein rises sharply in the first day after birth (1 unit/mg protein), and continues to increase until it reaches adult values of approximately 5 units/mg protein, in children from 1 to 10 years of age (Vieira et al 1996).

It is unknown whether children differ from adults in their susceptibility to chloroethane, despite the theoretical reasons for which they might potentially differ, as discussed above.

There are no data concerning parental exposure affecting children, including pre-conception exposure. There are no data concerning pre-conception exposure of either parent to germ line mutations, developmental defects, childhood cancer, or other health effects. Chloroethane is positive in *in vitro* mutagenicity studies in bacterial and mammalian cells, but is negative in *in vivo* mammalian cell tests. These inconclusive results do not allow the prediction of chloroethane genotoxicity in humans.

2.7 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 or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium).

Biomarkers of exposure to chloroethane are discussed in Section 2.7.1. 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 chloroethane are discussed in Section 2.7.2.

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 2.9, Populations That Are Unusually Susceptible.

There are no known biomarkers of exposure or effect that have been validated in children or adults exposed as children. There are no known biomarkers of exposure and effect that are unique to children. Further, there are no known biomarkers of exposure and effect in adults that could identify childhood exposure. Since

chloroethane is rapidly metabolized in the body, biomarkers for adults or children would be limited to current exposures.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Chloroethane

Studies of the association of environmental concentrations of chloroethane with levels of chloroethane in the breath, fluids, and body tissues were not identified. Because a portion of the chloroethane inhaled is exhaled, measurement of chloroethane in breath may serve as a useful biomarker of exposure. In rats and mice, chloroethane is metabolized to acetaldehyde and the glutathione conjugates, *S*-ethyl-*N*-acetyl-L-cysteine and *S*-ethyl-L-cysteine (Fedtke et al. 1994a, 1994b). Further research is required to determine if urinary excretion of glutathione conjugates would serve as a useful biomarker following exposure of humans to chloroethane. The glutathione conjugates *S*-ethyl-*N*-acetyl-E-cysteine and *S*-ethyl-L-cysteine would not be biomarkers unique to chloroethane exposure. Acetaldehyde forms adducts with plasma proteins. Because ethanol is also metabolized to acetaldehyde, it has been suggested that the measurement of these adducts, or of antibodies produced in response to these adducts, may serve as a biomarker of ethanol exposure (Won-all et al. 1994). The measurement of acetaldehyde protein adducts, or the associated antibodies, may also serve as a biomarker of chloroethane exposure. It should be noted that formation of antibodies to these compounds can result from exposure to chemicals other than chloroethane.

2.7.2 Biomarkers Used to Characterize Effects Caused by Chloroethane

Anesthesia is rapidly produced in humans by inhalation of chloroethane at a concentration of approximately 40,000 ppm. Other effects reported at anesthetic concentrations include cardiac irregularities, respiratory paralysis, and nausea. A blood concentration of 20-30 mg percent was reported for this exposure level (Adriani 194 1). No other studies were located regarding levels of chloroethane in human tissues and fluids associated with effects. Because these effects occur following exposure to many chemicals, they would not serve as useful biomarkers for chloroethane exposure.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990), and for information on biomarkers for neurological effects see OTA (1990).

2.8 INTERACTIONS WITH OTHER CHEMICALS

The interaction between chloroethane and ethanol was studied by Schmidt et al. (1972) and Gohlke and Schmidt (1972), who found that chloroethane enhanced the effects of ethanol in rats. Inhalation of chloroethane 4 hours/day for 8 of 10 days in conjunction with ethanol treatment led to greater changes in liver enzyme levels (decreased succinate dehydrogenase and nonspecific esterase and increased acid phosphatase) than were produced by ethanol alone. In addition, inflammation of the liver and fatty degeneration of hepatocytes were most prominent in rats given chloroethane in addition to ethanol. These results, although limited, are interesting because both ethanol and chloroethane are metabolized by CYP2El to acetaldehyde. Therefore, one compound could compete for active sites in CYP2E1, resulting in delayed metabolism of the other compound. However, ethanol, as well as chloroethane, induces CYP2El to expression, so more enzyme should be produced to handle a metabolic challenge (Leeder and Kearns 1997).

A study in cats demonstrated that the extent of methemoglobinemia induced by intravenous administration of aniline was significantly reduced in cats anesthetized with chloroethane compared to unanesthetized cats (McLean et al. 1967). The rate at which the methemoglobin disappeared, however, was also significantly reduced in the anesthetized cats compared with unanesthetized cats. The results suggest that concurrent exposure to aniline and chloroethane may induce less methemoglobin than exposure to aniline alone, but the methemoglobin induced by the combined exposure would persist longer than that induced by exposure to aniline alone. A similar effect was not observed when cats were anesthetized with chloralose and treated with phenylhydroxylamine, the aniline metabolite that results in methemoglobin formation. Therefore, the study authors concluded that chloralose acts by inhibiting the metabolism of aniline. It is not known if chloroethane acts in the same manner.

No studies were available investigating the interactions of chloroethane with other chemicals in children or in adults.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to chloroethane than will most persons exposed to the same level of chloroethane 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 chloroethane, or compromised function of

target organs affected by chloroethane. Populations who are at greater risk due to their unusually high exposure to chloroethane are discussed in Section 5.7, Populations with Potentially High Exposure.

Persons with prior exposure to ethanol may be at higher risk from chloroethane exposure because chloroethane has been shown to enhance the effects of ethanol in rats (Gohlke and Schmidt 1972; Schmidt et al. 1972). Because chloroethane is metabolized by the liver (Fedtke et al. 1994a, 1994b), and minimal liver effects have been observed in animals following inhalation exposure (Landry et al. 1987, 1989; Oura et al. 1966; Sayers et al. 1929; Troshina 1966), persons with compromised liver function may be at greater risk following exposure to chloroethane.

It is unknown whether children differ in their susceptibility to chloroethane from adults. This is discussed in detail in 2.6 Children's Susceptibility.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to chloroethane. 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 chloroethane. 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 chloroethane: Bronstein AC, Currance PL. 1988. Emergency Care for Hazardous Materials Exposure; Haddad LM, Winchester H. 1990. Clinical Management of Poisoning and Drug Overdose; Stutz DR, Ulin S. 1992. Hazardous Materials Injuries.

There are no known pediatric-specific methods for reducing peak absorption following exposure or reducing body burden. None of the methods for reducing peak absorption or body burden are contraindicated in children. No data were available to indicate that the methods used in adults have been validated in children.

2.10.1 Reducing Peak Absorption Following Exposure

Because chloroethane is a gas, human exposure is most likely to occur by inhalation. Moving the subject to fresh air is the best way to reduce absorption of chloroethane following inhalation exposure (Haddad and Winchester 1990).

2.10.2 Reducing Body Burden

Animal studies suggest that the body does not retain significant amounts of chloroethane (Fedtke et al. 1994a, l994b). Because some of the absorbed chloroethane is exhaled, increasing the ventilation rate once the subject is removed from exposure may help to enhance elimination.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

No methods for interfering with the mechanism of action of chloroethane were identified.

2.11 ADEQUACY OF THE DATABASE

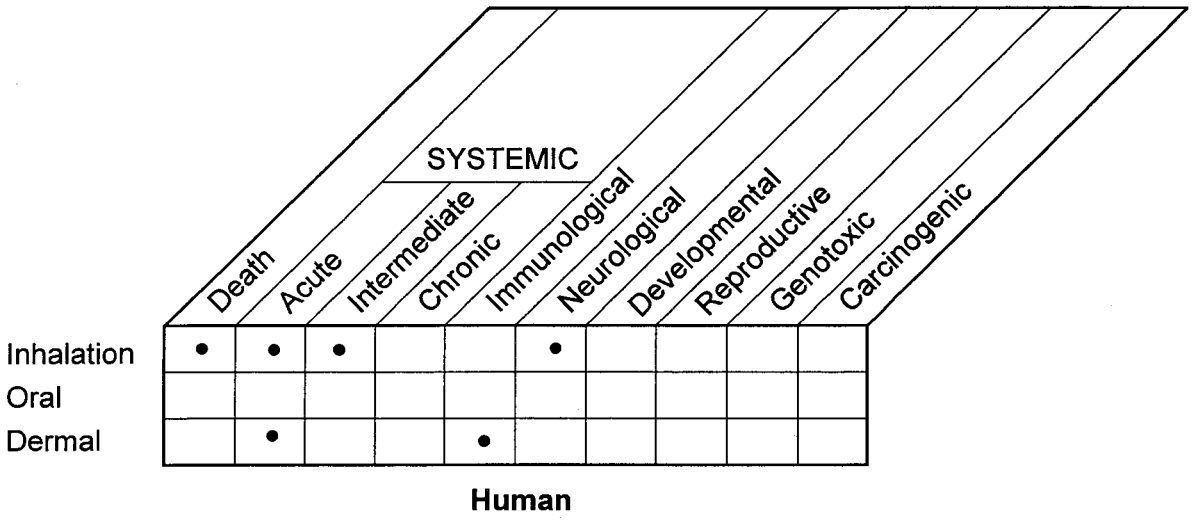
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chloroethane is available. Where adequate information is not 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 chloroethane.

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.

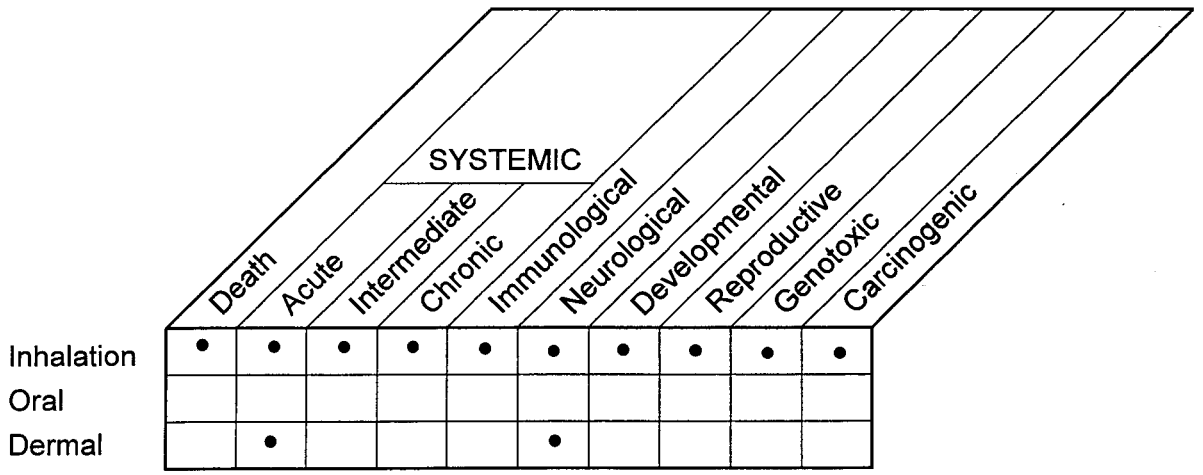
2.11.1 Existing Information on Health Effects of Chloroethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to chloroethane are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of chloroethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs*

FIGURE 2-4. Existing Information on Health Effects of Chloroethane



Human



Animal

• Existing Studies

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. As can be seen from the figure, chloroethane exposure by the inhalation route in animals has been well studied; however, there are few studies of the health effects of chloroethane exposure by other routes. The lack of studies of oral and dermal exposure is consistent with the fact that chloroethane is a gas at room temperature.

2.11.2 Identification of Data Needs

Acute-Duration Exposure. Tests of the acute toxicity of chloroethane by inhalation exposure have provided information on the levels of chloroethane that produce neurological effects in humans (Davidson 1925; Sayers et al. 1929) and animals (Landry et al. 1982; Sayers et al. 1929) and the levels that produce death in animals (Sayers et al. 1929). Other toxic effects, such as those on the heart, have been reported (Bush et al. 1952; Haid et al. 1954), but the precise levels at which they occur have not been identified. Studies that carefully examine tissues histologically and look for other subtle effects are needed. They might provide information on the mechanisms of chloroethane lethality and neurotoxicity and provide further information on other toxic effects. The acute-duration inhalation MRL is based on an acute-duration developmental study in which minimal fetotoxicity was observed in the offspring of mice exposed to chloroethane on gestation days 6-15 (Scortichini et al. 1986).

No reliable studies of the oral or dermal toxicity of chloroethane were located. Reliable oral exposure studies are needed. Many people are exposed to chloroethane through its use as a topical anesthetic. Frostbite has occurred following prolonged skin application (Noble 1979). Studies of the acute dermal toxicity of chloroethane are needed to estimate safe application times. There is one report of eye irritation in humans caused by exposure to high concentrations of chloroethane vapor (Sayers et al. 1929), but skin irritation has not been studied for any exposure route.

Intermediate-Duration Exposure. Repeated-dose studies of the toxicity of chloroethane by inhalation exposure have been performed in rats (Landry et al. 1982; NTP 1989), mice (Landry et al. 1987, 1989; NTP 1989), and dogs (Landry et al. 1982) at several dosage levels and for several durations of exposure. Reports indicate that inhalation abuse of chloroethane by adults and children may be increasing (Hersh 199 1; Walker 1993). Human studies involving chloroethane abusers or animal studies using doses comparable to those sniffed from household products are needed to help elucidate the systemic effects caused by the compound.

Reliable studies of repeated-dose exposure to chloroethane are not available for other routes of exposure. Reliable oral exposure studies are needed. Chloroethane is also repeatedly used as a local anesthetic to treat sports injuries and in the treatment of musculoskeletal facial pain (Marbach 1996). Repeated-dose dermal studies are needed to provide information on whether repeated dermal exposure of humans is hazardous.

Chronic-Duration Exposure and Cancer. A 2-year bioassay on inhaled chloroethane was performed in rats and mice by the National Toxicology Program (NTP 1989). Survival of mice was reduced compared to controls as a result of ascending urinary tract infections in males and uterine cancer in females. The only systemic effects noted were in the kidney (scattered foci of tubular regeneration, minimal glomerulosclerosis) in female mice. Female mice were also hyperactive during the exposures.

Chloroethane was carcinogenic in female mice resulting in uterine cancer (NTP 1989). Because of reduced survival of male mice, the study was considered inadequate, although there was an increased incidence of alveolar/bronchiolar neoplasms of the lungs. In exposed rats, there was equivocal evidence of carcinogenicity based on skin trichoepitheliomas, sebaceous gland adenomas, or basal cell carcinomas in males, and malignant astrocytomas in the brain of females. A chronic study in which several exposure levels are tested is needed to provide more information on the danger to humans at lower exposure levels. Studies of chronic toxicity and carcinogenicity do not exist for other routes of exposure. Therefore, studies on chronic oral exposure to chloroethane are needed.

Genotoxicity. The available genotoxicity studies indicate that chloroethane is mutagenic in bacteria (NTP 1989) and in mammalian cells *in vitro* (Ebert et al. 1994) but not clastogenic in mammalian cells *in vivo* (Ebert et al. 1994). Additional genotoxicity tests are needed to determine whether it is possible that chloroethane is genotoxic in humans.

Reproductive Toxicity. Several studies investigated reproductive endpoints in animals. Uterine weight was decreased by approximately 35% in mice exposed to high concentrations of chloroethane (Fedtke et al. 1994a). Significant decreases in uterine glutathione levels have also been reported in rats and mice exposed to chloroethane (Fedtke et al. 1994b). A small increase in the average duration of the estrous cycle was observed in mice exposed to high concentrations of chloroethane (Bucher et al. 1995). Measurement of serum estradiol and progesterone did not reveal any consistent statistically significant changes attributable to chloroethane exposure. Sperm motility in rats was reduced after exposure to chloroethane for 6 months (Troshina 1966). Histopathological effects have not been observed in reproductive organs of animals

exposed to chloroethane (Landry et al. 1982, 1987, 1989; NTP 1989). No effects on the number of live and dead fetuses or on the number and position of resorption sites were observed in mice exposed to chloroethane on gestation days 6-15 (Scortichini et al. 1986).

Based on decreases in uterine glutathione in rats and mice (Fedtke et al. 1994b), decreases in uterine weight in mice (Fedtke et al. 1994a), and the development of uterine cancer in mice exposed to chloroethane (NTP 1989) (see Cancer discussion in this Section 2.11.2), the uterus appears to be a target of chloroethane exposure in mice; rats are apparently less sensitive to these effects. The relevance of uterine effects in animals to human chloroethane exposure is not known, and further studies to examine the mechanisms of uterine effects observed in chloroethane-exposed mice are needed. A multigeneration study to determine if uterine effects, estrous cycle effects, and effects on sperm motility impact reproductive performance is also needed.

Developmental Toxicity. Only one study of the developmental effects of chloroethane in mice was
found. In this study, minimal evidence of fetotoxicity (increase in small centers of unossified bones of the skull) was observed at the highest concentration tested (Scortichini et al. 1986). This study serves as the basis for the acute-duration inhalation MRL. Additional developmental studies in other species are needed Because chloroethane is a neurotoxin, studies of the developmental neurotoxicity of chloroethane are also needed to assess the potential risk to humans.

Immunotoxicity. Several studies included histopathological examinations of immunological organs and tissues following inhalation exposure to chloroethane (Landry et al. 1982, 1987, 1989; NTP 1989) but found no effects. Studies in which tests of immune function were performed are needed to provide more useful information on the immunotoxicity of chloroethane. Three reports on sensitization produced by dermally applied chloroethane in humans (Bircher et al. 1994; Kriechbaumer et al. 1998; Van Ketel 1976) were found. Because many people are dermally exposed to chloroethane as a topical anesthetic, studies of this phenomenon are needed.

Neurotoxicity. Studies of chloroethane inhalation in humans and animals have provided information on the neurological effects produced by acute exposure to chloroethane and the levels at which they occur. Most repeated-exposure studies involved only behavioral observations and histopathological examinations of neurological organs and tissues; one case report involved a neurological examination of an adult male, which revealed marked nystagmus, ataxia and vertigo, but nothing abnormal upon evaluation of the brain, brain

stem, or spine upon MRI (Walker 1993). In addition, two studies in mice (Landry et al. 1987, 1989) and one in dogs (Landry et al. 1982) were identified, neither of which reported signs of neurotoxicity. Reliable studies of neurotoxicity following exposure by other routes do not exist. Controlled studies regarding the neurological effects of chloroethane are needed.

Epidemiological and Human Dosimetry Studies. No epidemiological or human dosimetry studies of chloroethane have been performed. High inhalation concentrations of chloroethane are anesthetic in humans and overdose can be lethal because of cardiovascular or respiratory effects. Chronic inhalation exposure has produced cancer in animals (NTP 1989). The general population might be exposed to chloroethane by inhalation of contaminated ambient air or intentional use as a topical anesthetic. Occupational exposure may occur by inhalation or dermal contact. Epidemiological studies of people who live near industries releasing chloroethane or near hazardous waste sites, of people who use chloroethane as a topical anesthetic, and of people who are occupationally exposed to chloroethane are needed to provide information on whether chloroethane is carcinogenic or has other toxic effects in humans at environmentally relevant concentrations. If such effects are identified, human dosimetry studies may be able to correlate levels of chloroethane in human tissues or fluids with health effects.

Biomarkers of Exposure and Effect

Exposure. Studies of the association of environmental concentrations of chloroethane with levels of chloroethane in the breath, fluids, and body tissues were not identified. Studies examining the association between air and breath levels of chloroethane are needed. Further research is required to determine if urinary excretion of glutathione conjugate metabolites or acetaldehyde-protein adducts (Worrall et al. 1994) would serve as a useful biomarker following exposure of humans to chloroethane.

Effect. Unique biomarkers of effect have not been identified for exposure to chloroethane. Further research regarding the biochemical effects of chloroethane is needed to identify biomarkers of effect for chloroethane.

Absorption, Distribution, Metabolism, and Excretion. A single breath absorption study (Morgan et al. 1970) is the only quantitative study regarding the absorption, distribution, metabolism, and excretion of chloroethane in humans. Studies in rats and mice indicate that chloroethane is readily absorbed following inhalation exposure and metabolized to acetaldehyde and glutathione conjugates (Fedtke et al. 1994a, 1994b). Additional quantitative studies of the pharmacokinetics of chloroethane are needed.

Comparative Toxicokinetics. A study that compares the metabolism of chloroethane in rats and miceindicates that mice have a greater capacity to metabolize chloroethane than rats (Fedtke et al. 1994a, 1994b). An *in vitro* study using human liver preparations to study the metabolism of chloroethane is needed to determine which species is the most appropriate model for the metabolism of chloroethane.

Methods for Reducing Toxic Effects. Other than removing the subject from exposure (Haddad and Winchester 1990) and increasing ventilation rate to enhance elimination after the subject is removed from exposure, methods for reducing toxic effects were not identified. As more information is learned regarding the mechanism of chloroethane toxicity, methods for reducing the toxic effects of chloroethane can be developed.

Children's Susceptibility. No studies involving exposure of children or immature animals to chloroethane have provided quantitative doses. There are two very qualitative studies in children associated with the use of chloroethane as an anesthetic (Nielsen 1980; Noble 1979). There currently exists a need for studies with children or immature animals exposed to the compound to investigate any differences in dose absorption, metabolism, excretion, and presence and severity of effects, Current knowledge of differences in physiology and biochemistry between children and adults indicate that distribution and metabolism mightdiffer between children and adults. However, experiments evaluating qualitative and quantitative differences in these processes would greatly facilitate the understanding of adverse effects of chloroethane in the developing human.

Definitive studies do not exist evaluating whether pharmacokinetics of chloroethane are different in children as compared with adults. Furthermore, no PBPK models exist on any age of children or adults that might inform the public as to the pharmacokinetics of the compound.

Studies are needed to determine whether chloroethane or its metabolites cross the placenta and no studies have evaluated placental or cord blood concentrations of chloroethane or its metabolites in humans or animals. It is unknown whether the delayed bone development seen in the Scortichini et al. (1986) study was due to chloroethane or its metabolites crossing the placenta or to some indirect effect on the fetus. Experiments evaluating these parameters are needed, as well as experiments to determine whether chloroethane significantly accumulates in breast milk. One study detected the compound in breast milk (Pellizari et al, 1982), but neither route of exposure of the mother nor concentration of chloroethane in the milk was identified. In addition, studies determining whether chloroethane would be stored in maternal

tissues would be informative, although the volatility of the compound, as well as data indicating its rapid clearance from the body following inhalation exposure (Morgan et al. 1970), indicate that tissue storage is not expected.

Adequate data do not exist on the effect, if any, chloroethane exposure has on fetal development. The one available prenatal developmental study and data needs on this topic are discussed above in the Developmental Effects subsection. Reliable studies of this type are needed in determining the fetotoxicity of chloroethane, as well as the potential of the compound for disrupting normal child development. Studies on postnatal exposures and their influence on development in immature animals would also be useful.

Child health data needs relating to exposure are discussed in 5.8.1 Data Needs: Exposures of Children.

Data Needs for Modeling

Studies which provide information on the physiological biochemical parameters specific to chloroethane in human and animal tissues are needed. For instance, there are no data on organ volumes, alveolar ventilation,cardiac output, or organ perfusion rates, among other parameters, in humans and animals. A PBPK model in rats exposed to chloroethane via inhalation was developed with the assumption that metabolism of the compound occurred exclusively in the liver (Gargas et al. 1990). The authors determined a V_{maxc} which is the maximum velocity (V_{max}) scaled for a 1 -kg animal, the K_m (rate constant for the saturable pathway), and the first-order rate constant, K_{fc}, which is the rate constant (K_f) scaled for a l-kg animal.

Other biochemical parameters that affect metabolism and clearance have not been investigated. Waller et al. (1996) modeled the cytochrome P450-mediated metabolism of chloroethane using three-dimensional quantitative structure-activity relationships (3D-QSAR). Their models have predicted a metabolic clearance rate for chloroethane. Other studies, involving the experimental or modeled estimation of other biochemical parameters, such as excretory clearance, binding and reactivity, absorption constants, inhibition rate constants, first pass effects, and other parameters that may influence the rate of elimination and bioavailability were not available. Studies investigating these parameters using human or animal tissues would provide much-needed information concerning the metabolism of chloroethane.

2.11.3 Ongoing Studies

Ongoing studies regarding chloroethane were not identified in the CRISP (1996), FEDRIP (1998), or CRIS/USDA (1998) databases.