3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,2-dichloroethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of 1,2-dichloroethane are indicated in Tables 3-1 and 3-2 and Figures 3-1 and 3-2. Because cancer effects could occur at lower exposure levels, Figure 3-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for 1,2-dichloroethane. 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.

3.2.1 Inhalation Exposure

Adverse health effects in humans associated with acute and occupational inhalation exposure to 1,2-dichloroethane vapor were described in a number of studies. A case study reported by Nouchi et al. (1984) detailed the clinical effects, blood chemistry, and autopsy findings of a 51-year-old man who died after being exposed to 1,2-dichloroethane vapor for 30 minutes while removing 1,2-dichloroethane residue from the hold of an oil tanker. Exposure is likely to have occurred both by the inhalation and dermal routes. No estimate of the exposure concentration was available, although exposure conditions were described as a "thick vapor of dichloroethane." This study, considered a reliable description of the manifestations of 1,2-dichloroethane-induced toxic effects in humans, is the source for much of the discussion of human data in this section. The available information suggests that massive, acute inhalation exposure to 1,2-dichloroethane can induce neurotoxic, nephrotoxic, and hepatotoxic effects in humans, as well as respiratory distress, cardiac arrhythmia, nausea, and vomiting. The possibility that existing medical conditions contributed to the observed symptoms and autopsy findings could not be evaluated because the individual's medical and behavioral histories were not reported. No information was located regarding immunological, reproductive, or developmental effects in humans following inhalation exposure to 1,2-dichloroethane.

Although considerable information is available on the effects of 1,2-dichloroethane following inhalation exposure in laboratory animals, many of the short-term studies used only a limited number of animals and are, therefore, of only limited utility. Targets of 1,2-dichloroethane inhalation toxicity in animals include the immune system, central nervous system, liver, and kidney. Limited evidence suggests that the heart may also be a target organ. 1,2-Dichloroethane has also produced genotoxic effects in animals exposed by inhalation (see Section 3.3).

Table 3-1 and Figure 3-1 describe the health effects observed in experimental animals associated with exposure level and exposure duration. Effects of 1,2-dichloroethane in humans are not included in the LSE table and figure because exposure levels were not reported and the effects investigated were not subtle.

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Wistar)	5 d 7hr/d				1500 (29/29 died)	Heppel et al. 1945
2	Rat (Wistar)	1d 7hr				1500 (4/20 died)	Heppel et al. 1945
3	Rat (NS)	14 d 5 d/wk 7 hr/d				1000 (20/26 died)	Heppel et al. 1946
4	Rat (Sprague-Dawley)	9 d Gd 6-15 7 hr/d				300 (10/16 died)	Rao et al. 1980; Schlacter et al. 1979
5	Rat	9 d Gd6-15 7hr/d				300 (2/3 died)	Schlacter et al. 1979
6	Rat (Wistar)	1 d 0.1 to 8 hr				1000 (LC_{50})	Spencer et al. 1951
7	Rat (Wistar)	2-3 d 7 hr/d				400 (24/40 died)	Spencer et al. 1951
8	Mouse (NS)	1 d 7hr				1500 (20/20 died)	Heppel et al. 1945
9	Gn Pig (NS)	1 d 7 hr				1500 (6/12 died)	Heppel et al. 1945
10	Gn Pig (NS)	4 d 7hr/d				1500 (9/9 died)	Heppel et al. 1945

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
11	Gn Pig (NS)	4 d 5d/wk 7 hr/d				1000 (16/16 died)	Heppel et al. 1946
12	Gn Pig (NS)	14-32 d 5d/wk 7hr/d				400 (8/8 died)	Spencer et al. 1951
13	Dog (NS)	6 d 7hr/d				1500 (2/3 died)	Heppel et al. 1945
14	Rabbit (NS)	5 d 7 hr/d				1500 (4/5 died)	Heppel et al. 1945
15	Rabbit (NS)	1 d 7hr				3000 (12/16 died)	Heppel et al. 1945
16	Rabbit (New Zealand)	12 d Gd 6-18 7 hr/day				100 (4/21 died)	Rao et al. 1980; Schlacter et al. 1979
	Systemic						
17	Monkey (Rhesus)	8-12 d 5d/wk 7hr/d	Hemato	100	400 (increased clotting time)		Spencer et al. 1951
			Hepatic	100	400 (fatty degeneration)		
			Renal	100	400 (tubular degeneration)		
18	Rat (Sprague-Dawley)	14 d Gd 6-20 6 hr/d	Bd Wt	254 F	329 F (24% reduced maternal body weight gain)		Payan et al. 1995
19	Rat	10 d Gd6-15 7hr/d	Bd Wt	100		300 (12% maternal body weight loss)	Schlacter et al. 1979

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
20	Gn Pig (NS)	1-14 d 5d/wk 7hr/d	Hepatic		400 M (slight parenchymal degradation)		Spencer et al. 1951
			Renal		400 M (increased kidney weight, swelling of tubular epithelium)		
	Immunological/Lymphoreticular						
21	Rat (Sprague-Dawley)	12 d 5d/wk 5hr/d		100			Sherwood et al. 1987
22	Rat (Sprague-Dawley)	1 d 5hr		200			Sherwood et al. 1987
23	Mouse (CD-1)	5 d 3hr/d		2.3			Sherwood et al. 1987
	Developmental						
24	Rat (Sprague-Dawley)	14 d Gd 6-20 6 hr/d		329 F			Payan et al. 1995
25	Rat (Sprague-Dawley)	9 d Gd6-15 7hr/d		100		300 (embryolethality at maternally toxic exposure level)	Rao et al. 1980; Schlacter et al. 1979
26	Rabbit (New Zealand)	12 d Gd 6-18 7 hr/d		300			Rao et al. 1980; Schlacter et al. 1979

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form
	INTERMEDIATE EXPOSURE							
	Death							
27	Monkey (NS)	9 wk 7 hr/d 5d/w				1000	(2/2 died)	Heppel et al. 1946
28	Rat (NS)	14 wk 5d/wk 7hr/d				400	(9/16 died)	Heppel et al. 1946
29	Gn Pig (NS)	25 wk 5 d/wk 7 hr/d				200	(5/14 died)	Heppel et al. 1946
30	Gn Pig (NS)	14 wk 5 d/wk 7 hr/d				400	(7/12 died)	Heppel et al. 1946
31	Dog (NS)	9 wk 5 d/wk 7hr/d				1000	(2/6 died)	Heppel et al. 1946
32	Rabbit (NS)	20 wk 5 d/wk 7hr/d				400	(5/5 died)	Heppel et al. 1946
33	Rabbit (NS)	13 wk 5 d/wk 7 hr/d				1000	(5/6 died)	Heppel et al. 1946
34	Cat (NS)	11wk 5 d/wk 7 hr/d				1000	(2/6 died)	Heppel et al. 1946

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Systemic						
35	Monkey (NS)	25 wk 5 d/wk 7 hr/d	Resp	200			Heppel et al. 1946
			Cardio		200 (fatty degeneration)		
			Hepatic		200 (fatty degeneration)		
			Renal	200			
			Endocr		200 (calcification of the adrenal medulla)		
36	Rat (NS)	15 wk 5 d/wk 7 hr/d	Resp	100			Heppel et al. 1946
			Cardio	100			
			Hepatic	100			
			Renal	100			
			Endocr	100			
37	Rat (Wistar)	198-212d 5 d/wk 7 hr/d	Resp	200			Spencer et al. 1951
			Cardio	200			
			Hemato	200			
			Hepatic	200			
			Renal	200			
			Endocr	200			
			Bd Wt	200			
38	Mouse (NS)	4 wk 5 d/wk 7 hr/d	Resp	100			Heppel et al. 1946
			Cardio	100			
			Hepatic	100			
			Renal	100			
			Endocr	100			

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
39	Gn Pig (NS)	246 d 5 d/wk 7 hr/d	Resp	200			Spencer et al. 1951
			Cardio	200			
			Hemato	200			
			Hepatic		100 (increased liver weight, fatty degeneration)		
			Renal	200			
			Endocr	200			
			Bd Wt	200			
40	Dog (NS)	8 mo 5 d/wk 7 hr/d	Resp	400			Heppel et al. 1946
			Cardio	400			
			Hemato	400			
			Hepatic		400 (fatty degeneration)		
			Renal		400 (fatty changes)		
			Endocr	400			
41	Rabbit (NS)	25 wk 5 d/wk 7 hr/d	Resp	200			Heppel et al. 1946
			Cardio	200			
			Hemato	200			
			Hepatic	200			
			Renal	200			
			Endocr	200			

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
42	Rabbit (albino)	232-248 d 5 d/wk 7 hr/d	Resp	400			Spencer et al. 1951
			Cardio	400			
			Hemato	400			
			Hepatic	400			
			Renal	400			
			Endocr	400			
			Bd Wt	400			
	Immunological/Lymphoreticular						
43	Rat (Wistar)	198-212d 5 d/wk 7 hr/d		200			Spencer et al. 1951
44	Gn Pig (NS)	246 d 5 d/wk 7 hr/d		200			Spencer et al. 1951
45	Rabbit (albino)	232-248 d 5 d/wk 7 hr/d		400			Spencer et al. 1951
	Neurological						
46	Dog (NS)	8 mo 5 d/wk 7 hr/d		400			Heppel et al. 1946
	Reproductive						
47	Rat (Sprague-Dawley)	1 gen 7 d/wk 6 hr/d		150			Rao et al. 1980

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Systemic						
48	Rat (Sprague-Dawley)	2 yr 5d/wk 7hr/d	Resp	50			Cheever et al. 1990
			Cardio	50			
			Gastro	50			
			Hemato	50			
			Musc/skel	50			
			Hepatic	50[b]			
			Renal	50			
			Dermal	50			
			Ocular	50			
			Endocr	50			
			Bd Wt	50			
	Immunological/Lymphoreticular						
49	Rat (Sprague-Dawley)	2 yr 5d/wk 7hr/d		50			Cheever et al. 1990
	Neurological						
50	Rat (Sprague-Dawley)	2 yr 5d/wk 7hr/d		50			Cheever et al. 1990

Table 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form
					Less serious (ppm)	Serious (ppm)	
51	Rat (Sprague-Dawley)	2 yr 5d/wk 7hr/d		50			Cheever et al. 1990

[a]The number corresponds to entries in Figure 3-1.
[b]Used to derive a chronic inhalation minimal risk level (MRL) of 0.6 ppm; exposure level divided by an uncertainty factor of 90 (3 for interspecies extrapolation, 10 for human variability, and 3 as a modifying factor for database deficiencies).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day; gen = generation; Hemato = hematological; hr = hour; LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; ppm = parts per million; Resp = respiratory; wk=week(s); yr = year(s)

Figure 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation

Acute (≤14 days)

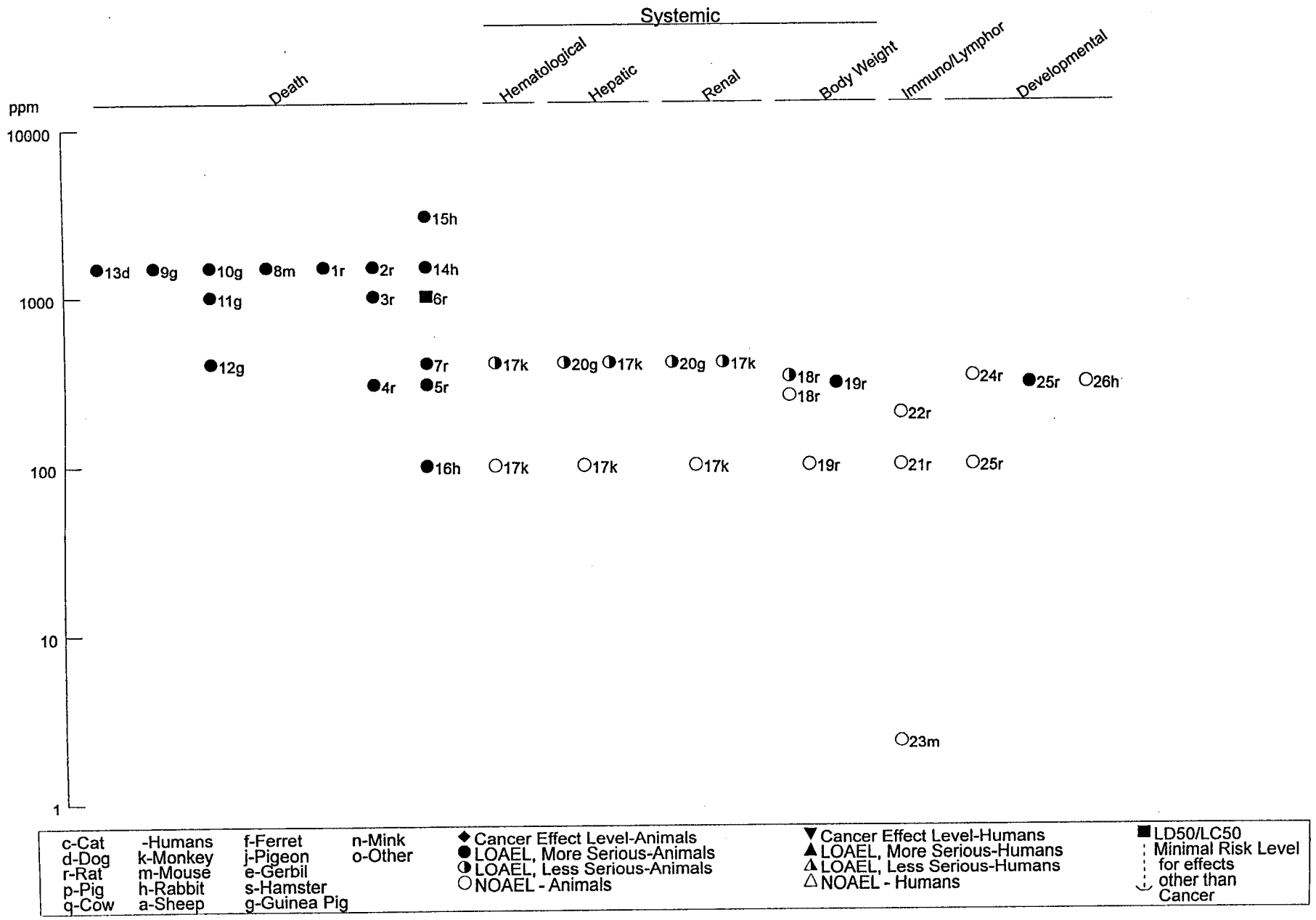


Figure 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (*continued*)

Intermediate (15-364 days)

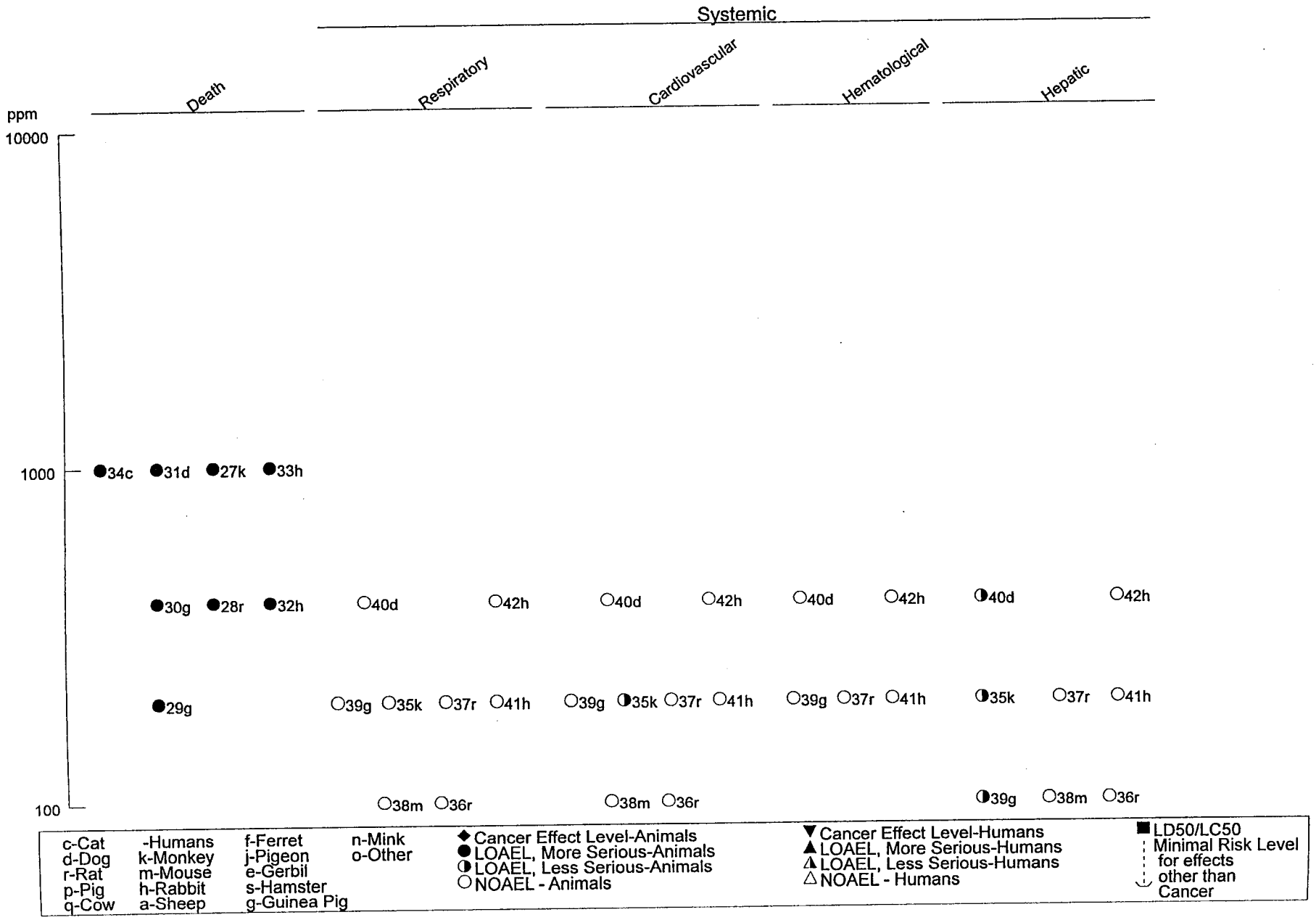


Figure 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (*continued*)

Intermediate (15-364 days)

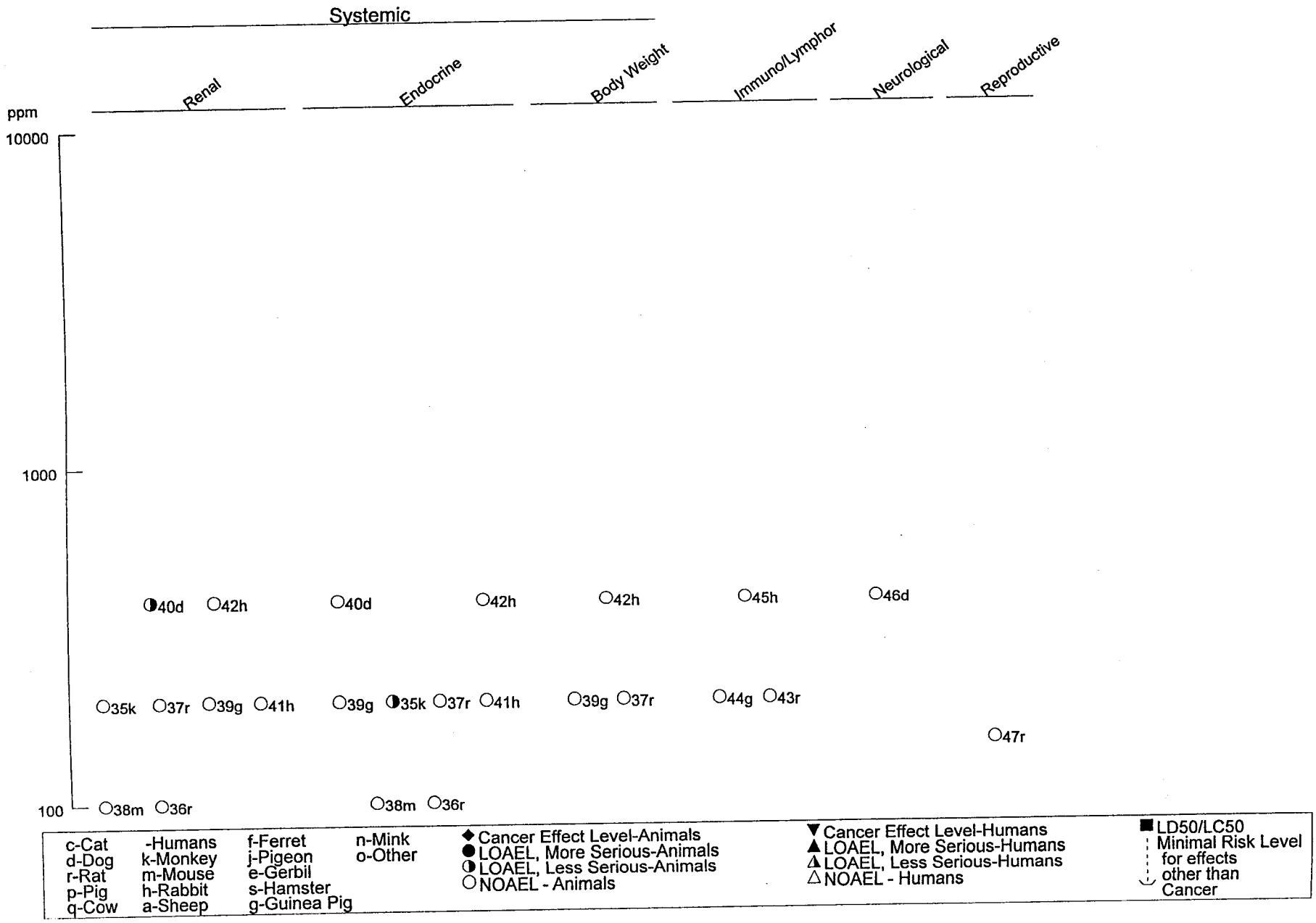
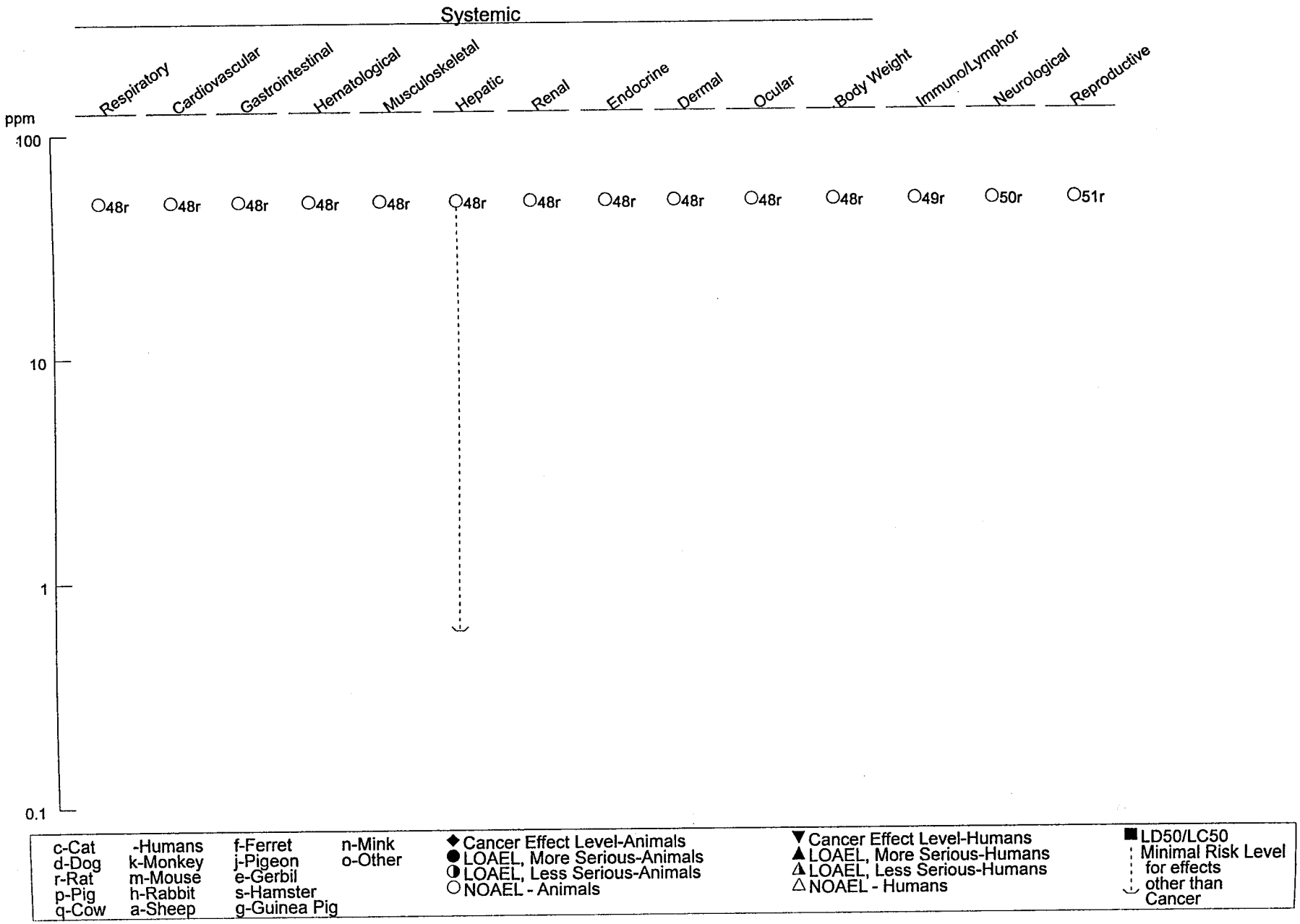


Figure 3-1. Levels of Significant Exposure to 1,2-Dichloroethane - Inhalation (*continued*)

Chronic (≥365 days)



3.2.1.1 Death

Exposure to concentrated 1,2-dichloroethane vapor can be lethal to humans. A 51-year-old man who inhaled concentrated vapor for only 30 minutes died 5 days later from cardiac arrhythmia (Nouchi et al. 1984). No attempt was made to estimate the actual exposure concentration, although it was described as a "thick vapor of dichloroethane." An autopsy revealed congestion of the lungs, degenerative changes in the myocardium, liver necrosis, renal tubular necrosis, and shrunken nerve cells in the brain.

In animals, acute inhalation exposure to 1,2-dichloroethane in sufficient concentrations also causes death. Heppel et al. (1945, 1946) and Spencer et al. (1951) examined the toxic effects of inhaled 1,2-dichloroethane in a number of species. Acute intermittent exposure (#14 days) resulted in death in rabbits at 100 ppm, in rats and guinea pigs at 400 ppm, and in mice, and dogs at 1,500 ppm. These were the lowest exposure concentrations that produced death in animals. Gross observations at necropsy revealed liver and kidney effects ranging from increased organ weight to necrosis, pulmonary congestion, and fatty infiltration and degeneration of the myocardium (Heppel et al. 1945, 1946; Spencer et al. 1951). An LC_{50} of 1,000 ppm was determined for an 8-hour exposure in rats; shorter exposure durations resulted in higher LC_{50} values (Spencer et al. 1951). Necropsy of these rats revealed histopathological changes in the liver and kidney. High mortality (10/16 died) was seen in rat dams exposed to 300 ppm for 7 hours/day on 9 consecutive days during gestation (Rao et al. 1980; Schlacter et al. 1979).

Intermediate-duration intermittent exposures (6–25 weeks) caused deaths in guinea pigs, rats, and mice exposed to 200 ppm, rats and rabbits exposed to 400 ppm, and dogs, cats, and monkeys exposed to 1,000 ppm (Heppel et al. 1946). Necropsy of these animals showed liver, kidney, heart, and lung effects similar to those observed following acute exposure. In a chronic inhalation study, there was no exposure-related effect on survival in rats that were intermittently exposed to 50 ppm of 1,2-dichloroethane for 2 years (Cheever et al. 1990).

The LC_{50} value and LOAEL values from each reliable study for death in each species and duration category are presented in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The systemic effects of 1,2-dichloroethane in humans and animals after inhalation exposure are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for all systemic end points in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Short-term exposure to concentrated 1,2-dichloroethane in air may produce adverse respiratory effects in humans. In the case study reported by Nouchi et al. (1984), respiratory distress was reported 20 hours after the initial exposure; autopsy revealed that the lungs were severely congested and edematous. Chronic bronchitis and a dry pharynx were reported in a packing plant employee following 5 months of repeated exposures to unreported air concentrations of 1,2-dichloroethane (McNally and Fostvedt 1941), but the authors regarded the symptoms as transitory.

In animals, acute exposure to high concentrations of 1,2-dichloroethane was also associated with pulmonary congestion. A single 7-hour exposure to 3,000 ppm of 1,2-dichloroethane produced death with accompanying pulmonary congestion in mice, rats, rabbits, and guinea pigs (Heppel et al. 1945). Lower concentrations of 1,2-dichloroethane did not produce lung lesions.

No pulmonary lesions were found by histological examination in rats and mice exposed to 100 ppm intermittently for 4–15 weeks, rabbits and monkeys exposed to 200 ppm intermittently for 25 weeks, or dogs exposed to 400 ppm intermittently for 8 months (Heppel et al. 1946). A limited number of rabbits, monkeys, and dogs were exposed, and not all of these animals were histologically examined. Similarly, there were no histopathological changes in the lung following intermittent exposures to 200 ppm for 28–35 weeks in rats and guinea pigs, or 400 ppm for 33–35 weeks in rabbits (Spencer et al. 1951). Chronic intermittent exposure to 50 ppm of 1,2-dichloroethane for 2 years caused no histological alterations in respiratory tract of rats (Cheever et al. 1990).

Cardiovascular Effects. Autopsy findings in a 51-year-old man included diffuse degenerative changes of the myocardium such as fragmentation, loss of nuclei of myocardial fibers, and interstitial edema (Nouchi et al. 1984); death was attributed to cardiac arrhythmia. However, since Nouchi et al. (1984) did not report on the medical and behavioral history of the individual, data were insufficient to conclude that these cardiac effects were due exclusively to 1,2-dichloroethane. Blood pressure was within the normal range in two packing plant employees subsequent to repeated occupational exposures

to unreported air concentrations of 1,2-dichloroethane over 2- or 5-month periods (McNally and Fostvedt 1941).

Cardiac lesions have also been reported in animals exposed to 1,2-dichloroethane. Acute lethal concentrations produced myocarditis in rats, dogs, and monkeys (Heppel et al. 1946). Guinea pigs that died following intermittent exposure to $200 ppm for 25 weeks had fatty infiltration and degeneration of the heart (Heppel et al. 1946). Among animals that survived intermediate-duration exposure to 1,2-dichloroethane, cardiac changes were observed only in monkeys. Fat droplets were found in the myocardium of 2 monkeys intermittently exposed to 200 ppm for 25 weeks; no control animals were used (Heppel et al. 1946). No cardiovascular lesions were seen upon gross or microscopic examination in rats and mice intermittently exposed to 100 ppm for 4–15 weeks, in rabbits intermittently exposed to 200 ppm for 25 weeks, or in dogs intermittently exposed to 400 ppm for 8 months (Heppel et al. 1946). However, only two to six rabbits and three dogs per exposure level were tested, and histopathology was conducted on only a few animals. Similarly, there were no histopathological changes in the heart following intermittent exposures to 200 ppm for 28–35 weeks in rats and guinea pigs, or 400 ppm for 33–35 weeks in rabbits (Spencer et al. 1951). In a chronic study, intermittent exposure to 50 ppm of 1,2-dichloroethane for 2 years failed to produce cardiovascular lesions in rats (Cheever et al. 1990).

Gastrointestinal Effects. A 51-year-old man who inhaled a thick vapor of 1,2-dichloroethane for 30 minutes vomited periodically immediately following exposure (Nouchi et al. 1984). He died 5 days later. Nausea and vomiting were reported shortly following a single 4-hour occupational exposure in three knitting factory workers who wrung out yarn that had soaked in an open vat of 1,2-dichloroethane (Wirtschafter and Schwartz 1939). Two packing plant employees who were repeatedly exposed to unreported air concentrations of 1,2-dichloroethane on the job for 2 to 5 months experienced periods of epigastric pain, nausea, and vomiting (McNally and Fostvedt 1941).

In animal studies, gastrointestinal effects, including emesis and passing of red watery stools, preceded death in dogs intermittently exposed to 1,500 ppm of 1,2-dichloroethane for 6 days (Heppel et al. 1945). Congestion of the gastrointestinal tract was noted in these animals at necropsy. Gastrointestinal lesions were not found in rats exposed to 50 ppm of 1,2-dichloroethane for 2 years (Cheever et al. 1990).

Hematological Effects. Transient leukocytosis was reported during 5 days subsequent to a single 4-hour occupational exposure in three knitting factory workers who wrung out yarn that had soaked in an open vat of 1,2-dichloroethane (Wirtschafter and Schwartz 1939). McNally and Fostvedt (1941)

indicated that hematological parameters (hemoglobin concentration, erythrocyte count, leukocyte count, and differential counts) in packing plant workers were not adversely affected subsequent to repeated occupational exposures to unreported (but potentially occasionally high) air concentrations of 1,2-dichloroethane over 2- or 5-month periods.

Only one study provided any indication of hematological effects in animals. Increased plasma prothrombin clotting time was reported in 2 monkeys exposed to 400 ppm of 1,2-dichloroethane intermittently for 8–12 days (Spencer et al. 1951). This study was limited because only two monkeys were examined and one moribund monkey was killed after eight exposures. Intermediate-duration studies of 1,2-dichloroethane found no hematological changes in rats, guinea pigs, rabbits, or dogs following intermittent exposures to 200–400 ppm for . 32–35 weeks (Heppel et al. 1946; Spencer et al. 1951). Chronic exposure to 50 ppm for 2 years did not produce indications of blood cell changes in rats as detectable by histological examination of the spleen and bone marrow (Cheever et al. 1990); blood parameters were not monitored, limiting the usefulness of the study for assessing hematological effects.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following inhalation exposure to 1,2-dichloroethane.

Histological examination of skeletal muscle and skin showed no effects in rats that were intermittently exposed to 50 ppm of 1,2-dichloroethane for 2 years (Cheever et al. 1990).

Hepatic Effects. The liver may be a target of 1,2-dichloroethane toxicity following inhalation exposure in humans. Nouchi et al. (1984) found an enlarged liver, high serum levels of lactate and ammonia, and increased serum levels of aspartate amino transferase (AST; also known as glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT; also known as glutamic pyruvic transaminase [SGPT]), 2 enzymes routinely used as indicators of liver damage, in a man exposed to concentrated 1,2-dichloroethane vapors for 30 minutes. The man died 5 days after exposure, and postmortem histopathological examination of the liver revealed extensive centrilobular necrosis and the presence of very few vacuolated cells, although it is not known to what degree this condition was pre-existing. Mixed workplace exposure to 1,2-dichloroethane and vinyl chloride (exposure levels ranging up to 5.3 and 23.5 ppm, respectively, by area sampling, and up to 334 and 6.2 ppm, respectively, by personal sampling) was associated with a combined exposure-related increase in the prevalence of abnormal levels of ALT in a group of 251 male workers in a vinyl chloride manufacturing facility (Cheng et al. 1999); the contribution of 1,2-dichloroethane to the observed effect is uncertain.

There are also reports of hepatic effects in animals following acute-duration inhalation exposure to 1,2-dichloroethane. Serum levels of enzymes used as indicators of hepatic damage (e.g., AST, ALT, sorbitol dehydrogenase [SDH]) were significantly elevated in rats exposed to $850 ppm for 4 hours (Brondeau et al. 1983). No effect was seen at 618 ppm. No histopathology was performed in this study to verify the occurrence of damage to the liver, but other studies have reported liver lesions in animals acutely exposed to lower concentrations. Monkeys intermittently exposed to 400 ppm for 8–12 days had marked fatty degeneration of the liver (Spencer et al. 1951). Monkeys exposed to 100 ppm did not show this effect. Slight parenchymatous degradation of the liver was found in guinea pigs exposed to 400 ppm for #14 days (Spencer et al. 1951). This study was limited by the use of a small number of animals.

Longer-term exposure to 1,2-dichloroethane vapor produced hepatic effects in guinea pigs, dogs, and monkeys. Guinea pigs intermittently exposed to 100 ppm of 1,2-dichloroethane for 246 days exhibited increased liver weight and hepatic fatty infiltration (Spencer et al. 1951). Monkeys exposed to 200 ppm for 25 weeks and dogs exposed to 400 ppm for 8 months also exhibited fatty degeneration of the liver (Heppel et al. 1946). However, no hepatic effects were observed upon gross and microscopic examination in mice, rats, or rabbits intermittently exposed to concentrations of 100–400 ppm for 4–30 weeks (Heppel et al. 1946; Spencer et al. 1951). There were a number of deficiencies in the studies of Heppel et al. (1946) and Spencer et al. (1951); many of the tests used a limited number of animals, and no control monkeys were examined by Heppel et al. (1946).

In the only chronic inhalation study of 1,2-dichloroethane, groups of 50 male and 50 female rats were intermittently exposed to 50 ppm for 2 years (Cheever et al. 1990). No histological changes were found in the liver, bile duct, or any other tissues, indicating that the exposure concentration is a NOAEL. Based on the NOAEL of 50 ppm for liver effects, and considering the other evidence for hepatotoxicity of 1,2-dichloroethane following longer-term vapor exposures, a chronic inhalation MRL of 0.6 ppm was calculated as described in the footnote to Table 3-1 and in Appendix A.

Renal Effects. 1,2-Dichloroethane is acutely nephrotoxic in humans following inhalation exposure. In the case study reported by Nouchi et al. (1984), a man who inhaled 1,2-dichloroethane fumes for 30 minutes had hepatic dysfunction and eventually exhibited kidney failure, as part of general organ failure, followed by cardiac arrest and death. Microscopic examination revealed acute tubular necrosis.

Acute-duration inhalation exposure to 1,2-dichloroethane also produced renal effects in animals. Cloudy swelling of the renal tubular epithelium and increased kidney weight were reported in guinea pigs, and

degeneration of the tubular epithelium was reported in monkeys following intermittent exposure to 400 ppm for 8–12 days (Spencer et al. 1951). No renal effects were noted in monkeys exposed to 100 ppm for 8–12 days. These were the only species examined for renal effects following acute exposure, and only a small number of animals was examined in each case.

Kidney lesions have also been reported following longer-term exposure of animals to 1,2-dichloroethane. Dogs intermittently exposed to 400 ppm for 8 months exhibited fatty changes in the kidney (Heppel et al. 1946). In guinea pigs, degeneration of the kidney was observed, but only at lethal concentrations (Heppel et al. 1946). Renal effects were not detected in rats, mice, guinea pigs, or rabbits intermittently exposed to 100–400 ppm of 1,2-dichloroethane for 4–30 weeks (Heppel et al. 1946; Spencer et al. 1951). In all of these studies, a limited number of animals were exposed, and only a few of those were examined for histopathology. In a chronic study, no histopathological changes developed in the kidneys of rats exposed to 50 ppm of 1,2-dichloroethane intermittently for 2 years (Cheever et al. 1990).

Endocrine Effects. No studies were located regarding endocrine effects in humans after inhalation exposure to 1,2-dichloroethane.

Endocrine function has not been evaluated in inhalation toxicity studies in animals. Histological examinations of endocrine system tissues were performed in several studies with essentially negative results, but lack of histopathology does not necessarily indicate that there were no functional endocrinologic changes. Acute intermittent exposure to 1,2-dichloroethane caused congestion of the adrenal cortex in guinea pigs exposed to 1,500 ppm for 4 days (Heppel et al. 1945, 1946), but this exposure was lethal in most animals. An intermediate-duration study noted calcification of the adrenal medulla in 1 of 2 monkeys intermittently exposed to 200 ppm for 25 weeks (Heppel et al. 1946), but the evidence for this effect is inconclusive because only 2 monkeys were studied, no control animals were examined, and adrenal effects have not been reported in other long-term inhalation studies by Heppel et al. (1946) or other investigators. Histopathological examinations failed to detect changes in endocrine tissues following intermittent exposures to 100 ppm for 4 or 15 weeks in rats and mice (Heppel et al. 1946), 200 ppm for .25–35 weeks in rats, guinea pigs, and rabbits (Heppel et al. 1946; Spencer et al. 1951), 200 or 400 ppm for .32–35 weeks in rabbits (Heppel et al. 1946; Spencer et al. 1951), or 400 ppm for 8 months in dogs (Heppel et al. 1946). The histological examinations in these studies were limited to the adrenal gland and/or pancreas.

The only chronic inhalation study of 1,2-dichloroethane found that intermittent exposure to 50 ppm for 2 years induced a slight increase in the incidence of unspecified basophilic focal changes in the pancreas in female rats, but no histological alterations in the adrenal, thyroid, parathyroid, or pituitary glands (Cheever et al. 1990). The toxicological significance of the pancreatic changes is unclear because the incidence was not reported, the effect was induced in only one sex (females), additional exposure levels were not tested, and the study was designed to evaluate carcinogenicity.

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

Dermal Effects. No studies were located regarding dermal effects in humans after inhalation exposure to 1,2-dichloroethane.

Histological examinations showed no changes in the skin of rats exposed to 50 ppm of 1,2-dichloroethane intermittently for 2 years (Cheever et al. 1990).

Ocular Effects. No studies were located regarding ocular effects in humans after inhalation exposure to 1,2-dichloroethane.

Ocular effects reported in animals acutely exposed to 1,2-dichloroethane by inhalation were corneal clouding and lacrimation (Heppel et al. 1945, 1946). These effects probably resulted from direct ocular contact with 1,2-dichloroethane vapor and are discussed in more detail in Section 3.2.3. In a chronic study, rats that were exposed to 50 ppm of 1,2-dichloroethane intermittently for 2 years had no histological changes in the eyes (Cheever et al. 1990).

Body Weight Effects. No studies were located regarding effects on body weight in humans after acute inhalation exposure to 1,2-dichloroethane. A weight loss of 10 pounds was reported in a packing plant employee who was repeatedly exposed to unreported, but potentially high, air concentrations of 1,2-dichloroethane for 9 weeks, although the period over which the weight was lost relative to the exposure period was not reported (McNally and Fostvedt 1941).

Adverse changes in body weight (decreased gain or weight loss) occurred in maternal rats that were intermittently exposed to 300 or 329 ppm of 1,2-dichloroethane during gestation, although these effects were not observed at 100 or 254 ppm (Payan et al. 1995; Rao et al. 1987; Schlacter et al. 1979). No

changes in body weight gain were caused by intermittent exposures to 200 ppm for 28–35 weeks in rats and guinea pigs (Spencer et al. 1951), 400 ppm for 33–35 weeks in rabbits (Spencer et al. 1951), or 50 ppm for 2 years in rats (Cheever et al. 1990).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after inhalation exposure to 1,2-dichloroethane.

Acute intermittent exposure to 1,2-dichloroethane caused chronic splenitis in rats exposed to 1,000 ppm for 14 days (Heppel et al. 1946), but this exposure was lethal in most of the animals tested.

There is evidence that acute exposure to 1,2-dichloroethane affects the ability to fight infection arising from inhaled microbial pathogens in animals. Female mice (4–5 weeks old) exposed to 5.4–10.8 ppm of 1,2-dichloroethane for 3 hours exhibited increased susceptibility to *Streptococcus zooepidemicus* (i.e., increased mortality following infection), suggesting reduced pulmonary defenses in the exposed mice (Sherwood et al. 1987); male mice were not evaluated. No effect was observed at 2.3 ppm. Additionally, female mice that were similarly exposed to 10.8 ppm had reduced bactericidal activity in the lungs 3 hours after exposure to *Klebsiella pneumoniae*. Male rats exposed to #100 ppm for 5 hours/day for 12 days, or to a single 5-hour exposure to #200 ppm, did not exhibit reduced bactericidal activity after *K. pneumoniae* challenge (female rats were not evaluated); mortality following *S. zooepidemicus* challenge was not evaluated in rats. In addition, no effects on lymphocyte function (as indicated by blastogenesis to T- and B-cell mitogens) were seen in rats exposed to #100 ppm 5 hours/day for 12 days. Results reported in Sherwood et al. (1987) suggest that rats may be less susceptible to the detrimental immunological effects of 1,2-dichloroethane than mice and/or that male rodents are less susceptible than females. The relevance of the immunological effects in mice to human immunotoxicity is uncertain, since the massive bacterial challenges given to mice in the study are unlikely to be representative of normal immunological challenges in humans. In addition, Sherwood et al. (1987) concluded that the interspecies differences in immunotoxicity observed in the study suggest against extrapolating from animals to humans.

Immune function has not been evaluated in intermediate- or chronic-duration inhalation studies of 1,2-dichloroethane, although histopathological examinations failed to detect lesions in immune system tissues following intermittent exposure to 200 ppm for 212–246 days in rats and guinea pigs (Spencer et

al. 1951), to 400 ppm for 232–248 days in rabbits (Spencer et al. 1951), or to 50 ppm for 2 years in rats (Cheever et al. 1990).

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

3.2.1.4 Neurological Effects

Inhalation of high concentrations of 1,2-dichloroethane can affect the nervous system of humans. It has been reported that 1,2-dichloroethane is an anesthetic narcotic in humans, and that it is as potent an anesthetic as gasoline, benzene, carbon tetrachloride, and chloroform when inhaled for periods of an hour or more (Garrison and Leadingham 1954). A 51-year-old sailor exposed to a concentrated vapor of 1,2-dichloroethane for 30 minutes suffered central nervous system effects, such as irritability and periodic vomiting, immediately following exposure (Nouchi et al. 1984). Twenty hours later, he was drowsy and became delirious and tremulous; he lapsed into a coma 4 hours later, with a generalized continuous clonic jerk. His electroencephalogram showed slow wave abnormality. He died 5 days after exposure. Upon autopsy, the Purkinje cell layer of his cerebellum showed a shrunken appearance with pyknotic nuclei. Weakness, dizziness, and trembling were reported shortly following a single 4-hour occupational exposure in three knitting factory workers who wrung out yarn that had soaked in an open vat of 1,2-dichloroethane (Wirtschafter and Schwartz 1939). Two packing plant employees who were repeatedly exposed to unreported air concentrations of 1,2-dichloroethane on the job for 2–5 months reported drowsiness during work hours or sleeplessness, and upon physical examination, they exhibited nervousness, “marked” nystagmus, tremor of the tongue, or sluggish patellar reflex (McNally and Fostvedt 1941).

Acute-duration exposure to concentrated 1,2-dichloroethane also produces neurological effects in animals. Rats experienced central nervous system depression after exposure to $12,000 ppm for 30 minutes (Spencer et al. 1951); the authors did not conclusively attribute apparent neurological effects of inactivity, stupor, and “slowness of response to handling” observed at #3,000 ppm to central nervous system depression. Exposure to 20,000 ppm for 15 minutes resulted in central nervous system depression sufficient to cause death; no histopathology was conducted on the brain or peripheral nerves. Uncertain gait, narcosis, prostration, or unconsciousness were seen in rats, guinea pigs, and rabbits exposed once to 3,000 ppm for 7 hours, but were not reported at 1,500 ppm; 7-hour exposures to 1,500 ppm on 5 consecutive days induced transitory tremors, convulsions, or coma in rats and dogs (Heppel et al. 1945).

Longer-term exposure to lower concentrations of 1,2-dichloroethane did not appear to produce neurological effects, although sensitive indicators of subtle neurological effects were not examined. Negative results were obtained by physical examination (without histopathology) of dogs intermittently exposed to 400 ppm for 8 months (Heppel et al. 1946) and by histopathological examination of the brain from rats intermittently exposed to 50 ppm for 2 years (Cheever et al. 1990). The highest NOAEL values for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

Studies regarding reproductive effects in humans after inhalation exposure to 1,2-dichloroethane are limited to a single account of increased rates of premature births in female workers and in wives of male workers who were exposed in a Chinese synthetic fiber factory (Zhao et al. 1989). Concentrations of 1,2-dichloroethane ranged from 0.4 to 384 ppm at two locations. Female subjects were exposed throughout pregnancy, and male workers were exposed for at least 1 year before their wives became pregnant. These results should be treated with caution because the study evaluated a small number of subjects (44 male and 54 female exposed workers), the authors indicated that co-exposure to other chemicals occurred in most cases, and the study was generally deficient in reporting the study design including accounting for possible confounding environmental and behavioral factors.

Some studies in rodents (Vozovaya 1974, 1977; Zhao et al. 1989) found that inhalation exposure to 1,2-dichloroethane either prior to mating and continuing into gestation or throughout gestation caused pre-implantation loss and embryolethality, although the reliability of these studies is unclear because of deficiencies in reporting study design and results. Pre-implantation loss was reportedly increased (31.0% compared to 10.2% in controls, $p<0.05$) in unspecified rodents that were exposed to 51.9 ppm “during the entire pregnancy period”; one account of the study indicated that a 2-week pre-mating exposure also occurred (Zhao et al. 1997), although this could not be corroborated from the original study (Zhao et al. 1989). Intermittent exposure of rats to 4.7±7 ppm for 4 months prior to the mating period, followed by inhalation exposure during pregnancy, produced a statistically significant ($p<0.01$) increase in embryo mortality (Vozovaya 1977). Fertility was decreased, and stillbirths and perinatal mortality were increased in the first generation of a two-generation reproduction study in rats that were intermittently exposed to 14 ppm of 1,2-dichloroethane over a period of 6 months (Vozovaya 1974). In contrast to the studies summarized above, a well-designed study by Rao et al. (1980) showed no adverse effects on the fertility, gestation, or survival in pups of male and female rats intermittently exposed to #150 ppm for 60 days pre-

mating, then throughout mating, gestation, and lactation (excluding gestation day 21 through postpartum day 4). No gross or histopathological lesions were observed in reproductive organs of rats exposed to 50 ppm intermittently for 2 years (Cheever et al. 1990).

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

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to 1,2-dichloroethane.

The overall evidence from inhalation studies in rats and rabbits indicates that 1,2-dichloroethane is not a developmental toxicant. 1,2-Dichloroethane was not fetotoxic or teratogenic in the offspring of rats that were intermittently exposed to 100 ppm on days 6–15 of gestation (Rao et al. 1980; Schlacter et al. 1979). Exposure to 300 ppm produced high maternal mortality with fetolethality, and one rat had a total resorption of the litter. Another study similarly found that exposure to 1,2-dichloroethane during gestation days 6–20 was not fetotoxic or teratogenic to rats at concentrations as high as those producing maternal toxicity (329 ppm) (Payan et al. 1995). There were no exposure-related changes in numbers of implantations, resorptions, and live fetuses, fetal sex ratio or body weights, or external, visceral, or skeletal development, although maternal body weight gain was 24% reduced at 329 ppm; no maternal effects occurred at lower concentrations (150–254 ppm). Developmental toxicity was reported in one study in rats, but the reliability of the data is unclear (Vozovaya 1977). Exposure to 4.7±7 ppm of 1,2-dichloroethane for 4 months before mating followed by exposure during pregnancy was embryotoxic and caused hematomas in the head and neck region and anterior extremities of the fetuses. The reliability of the Vozovaya (1977) data cannot be assessed due to lack of statistical analysis and uncertainties in the reported results. Zhao (1984) reported no developmental changes in F1 and F2 generations of mice after the parental dams were exposed by inhalation for 4 hours per day to up to 62.5 ppm on gestation days 6–15, or to 250 ppm on gestation days 9 and 10. The F1 generation was not postnatally exposed to 1,2-dichloroethane. No changes were observed in the following parameters: fetal survival, length, or weight; external, skeletal, or visceral appearance; pup survival; onset of pup physical changes and reflex acquisition; or pup weight gain. In spite of reporting deficiencies leading to critical uncertainties in the adequacy of the study design, the results are suggestive that 1,2-dichloroethane is not developmentally toxic in mice under reported study conditions.

Rabbits that were intermittently exposed to 100 or 300 ppm of 1,2-dichloroethane on days 6–18 of gestation experienced some maternal deaths, but there were no chemical-related fetotoxic or teratogenic effects as indicated by pregnancy and resorption incidences, litter size, fetal body measurements, and soft-tissue and skeletal examinations (Rao et al. 1980).

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

3.2.1.7 Cancer

Specific evidence associating inhalation exposure to 1,2-dichloroethane with the occurrence of cancer in humans was not found in the literature reviewed. Several epidemiological studies have been conducted on workers in the chemical industry to investigate the high incidence of brain tumors observed among workers employed in petrochemical plants (Austin and Schnatter 1983a, 1983b; Reeve et al. 1983; Teta et al. 1989; Waxweiler et al. 1983), the incidence of stomach cancer and leukemia at a plant that used 1,2-dichloroethane in the production of ethylene oxide (Hogstedt et al. 1979), and the increased deaths due to pancreatic cancer and lymphatic and hematopoietic cancers in a cohort of workers in chlorohydrin production plants where 1,2-dichloroethane was a production byproduct (Benson and Teta 1993). Increased risk of primary breast cancer (odds ratio [OR]=2.2; 95% confidence interval [CI]=1.4–3.6; no latency) was observed in Danish men who were occupationally exposed to unreported levels of gasoline and combustion products containing 1,2-dichloroethane, compared to workers who were not exposed (according to job type and trade code) (Hansen 2000). The OR increased to 2.5 (95% CI=1.3–4.5) among workers with a latency of >10 years (Hansen 2000). Male residents in areas near a municipal solid waste site in Montreal, Quebec, which emitted airborne 1,2-dichloroethane (among a number of other volatile substances) showed increased risk of stomach cancers (relative risk [RR]=1.3; 95% CI=1.0–1.5), liver and intrahepatic bile duct cancers (RR=1.3; 95% CI=0.9–1.8), and cancers of the trachea, bronchus, and lung (RR=1.1; 95% CI=1.0–1.2) (Goldberg et al. 1995). Female residents showed increased risk of stomach cancer (RR=1.2; 95% CI=0.9–1.5) and cervix uteri cancer (RR=1.2; 95% CI=1.0–1.5). None of these epidemiology studies dealt with 1,2-dichloroethane exposure exclusively, and the concurrent exposure to other chemicals or solvents confounded the results. None of these studies could specifically link chemical exposure with the excess cancer incidence.

The carcinogenicity of inhaled 1,2-dichloroethane has been evaluated in chronic experiments in both rats and mice. Maltoni et al. (1980) exposed Sprague-Dawley rats and Swiss mice to 1,2-dichloroethane at

concentrations of #250 ppm 7 hours/day, 5 days/week, for 78 weeks; no treatment-related increase in the incidence of tumors was observed in treated rats or mice. However, this study is limited for a number of reasons. Chemical administration and study duration were less than lifetime. Furthermore, the maximum tolerated dose was exceeded at the highest dose tested (250 ppm), and survival in mice was poor. Therefore, only a small number of surviving animals were at risk for late-developing tumors. The plausible explanations for the negative results obtained in this study may include the differences in the metabolic pathways and the amount of toxic metabolites reaching the target tissues (see Section 3.5.1). A chronic study in which rats were exposed to 50 ppm of 1,2-dichloroethane intermittently for 2 years also failed to find carcinogenic effects (Cheever et al. 1990). However, this study was limited by the use of a single dose level that may have been considerably lower than the maximum tolerated dose (MTD) (the relatively low exposure concentration of 50 ppm was chosen because it was the U.S. occupational standard at the time the experiment was initiated). An abstract reported that inhalation exposure to 1,2-dichloroethane at unreported levels for 6 hours/day, 5 days/week, for 2 years induced mammary gland fibroadenomas and subcutis fibromas in both sexes of F344 rats, mammary gland adenocarcinomas/ adenomas in female rats, peritoneal mesotheliomas in male rats, hepatic hemangiosarcomas in male BDF1 mice, and bronchio-alveolar carcinomas/adenomas, mammary gland adenocarcinomas, and uterine endometrial stromal polyps in female mice (Matsushima et al. 1998). The full study report was not located and, thus, adequacy of the study design and conduct could not be evaluated.

3.2.2 Oral Exposure

Information concerning the toxic effects of ingested 1,2-dichloroethane in humans was derived primarily from case reports of individuals who accidentally or intentionally ingested 1,2-dichloroethane. Only crude estimates of ingested dose were available, limiting the value of the data. The available information indicates that 1,2-dichloroethane can cause death from cardiac arrhythmia after a sufficient single oral dose (Garrison and Leadingham 1954; Hueper and Smith 1935; Martin et al. 1969; Schönborn et al. 1970). Other symptoms reported include bronchitis, hemorrhagic gastritis and colitis, hepatocellular damage, renal tubular necrosis and calcification, central nervous system depression, and histological changes in brain tissue (Hueper and Smith 1935; Lochhead and Close 1951; Przezdziak and Bakula 1975; Yodaiken and Babcock 1973). No studies were located regarding immunological, reproductive, or developmental effects in humans following oral exposure to 1,2-dichloroethane.

The toxicity of ingested 1,2-dichloroethane has been well studied in animals. Targets of 1,2-dichloro-ethane toxicity in orally exposed animals included the immune system, central nervous system, liver, and

kidney. 1,2-Dichloroethane also produced genotoxic effects (see Section 3.3) and carcinogenic effects in animals exposed by this route.

Table 3-2 and Figure 3-2 describe the health effects observed in laboratory animals associated with oral exposure levels at varying time and exposure durations.

3.2.2.1 Death

Ingestion of large amounts of 1,2-dichloroethane may be lethal to humans. Hueper and Smith (1935) reported a case in which a 63-year-old man accidentally swallowed approximately 2 ounces (60 mL) of 1,2-dichloroethane and died 22 hours later of circulatory failure. A 50-year-old man mistakenly ingested approximately 30 mL of 1,2-dichloroethane and died after 10 hours (Lochhead and Close 1951). A 14-year-old boy died 5 days after ingesting 15 mL of 1,2-dichloroethane (Yodaiken and Babcock 1973). A 30-year-old man ingested approximately 40 mL of 1,2-dichloroethane and died 28 hours later (Garrison and Leadingham 1954). Another man who drank 50 mL of 1,2-dichloroethane died 22 hours later of circulatory failure (Hueper and Smith 1935). Schönborn et al. (1970) reported a case of an 18-year-old man who became drowsy and cyanotic, and exhibited bradycardia after drinking approximately 50 mL of Marament (a pharmaceutical formulation), which was equivalent to 50 g of 1,2-dichloroethane (714 mg/kg, assuming 70 kg body weight); he died 17 hours later in a state of circulatory shock. A hospital patient accidentally ingested a "small" quantity of 1,2-dichloroethane and died 18 hours later after intensive supportive measures were taken; the immediate cause of death was not reported (Hubbs and Prusmack 1955). In two other cases of 1,2-dichloroethane poisoning, the patients drank 15–20 mL Marament; they suffered gastrointestinal disorders and were discharged from the hospital in a few days (Schönborn et al. 1970). These patients received prophylactic heparinization 3–4 days before the appearance of blood coagulation disorders. Only crude estimates of ingested dose were available, limiting the value of the data.

Death has also occurred in animals following oral exposure to 1,2-dichloroethane. An acute oral LD_{50} value of 680 mg/kg has been reported for rats (McCollister et al. 1956); treatment was by gavage, but the dosage levels tested and the time of death after administration were not reported. Daily gavage doses of 300 mg/kg for 10–14 days caused 80–100% mortality in rats (Daniel et al. 1994; van Esch et al. 1977). Munson et al. (1982) used log probability analysis to determine LD_{50} values of 489 and 413 mg/kg for male and female mice, respectively; the mice died over a 48-hour period following gavage.

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Human	once				714 (death)	Schonborn et al. 1970
2	Rat (Sprague-Dawley)	10 d 1x/d (GO)				300 M (death in 8/10 F and 10/10 M)	Daniel et al. 1994
3	Rat (albino)	1 d (G)				680 (LD_{50})	McCollister et al. 1956
4	Rat (F344/N)	3 d 1x/d (GO)				480 M (10/10 died)	NTP 1991a
5	Rat (Wistar)	14 d 5d/wk 1x/d (GO)				300 (6/6 died)	van Esch et al. 1977
6	Mouse (CD-1)	1 d (G)				413[b] F (LD_{50})	Munson et al. 1982
						489 M (LD_{50})	
	Systemic						
7	Human	once	Resp			570 (congestion and edema)	Martin et al. 1969
			Cardio			570 (cardiac arrest)	
			Gastro			570 (gastrointestinal hemorrhage)	
			Hemato			570 (incoagulable blood)	
			Hepatic			570 (severe atrophy of liver)	

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
8	Human	once	Cardio			714 (decreased coagulation factors, circulatory shock, bradycardia)	Schonborn et al. 1970
			Gastro			714 (necrosis and hemorrhagic enteritis)	
			Hemato			714 (decreased coagulation factors)	
			Hepatic			714 (necrosis)	
			Renal			714 (bleeding; hyperemia)	
9	Rat (Sprague-Dawley)	10 d 1x/d (GO)	Resp	100		300 (gross pathologic changes in lungs of rats that died)	Daniel et al. 1994
			Cardio	100			
			Gastro	30	100 (minimal inflammatory changes in forestomach)		
			Hemato	100			
			Musc/skel	100			
			Hepatic	100			
			Renal	100			
			Endocr	100			
			Dermal	100			
			Bd Wt	100			
10	Rat (Sprague-Dawley)	14 d Gd 6-20 1x/d (GO)	Bd Wt	158 F	198 F (30% decreased maternal body weight gain)		Payan et al. 1995

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
11	Rat (Wistar)	14 d 5d/wk 1x/d (GO)	Resp	100			van Esch et al. 1977
			Hemato	100			
			Hepatic	100			
			Renal	100			
			Endocr	100			
			Bd Wt	100			
12	Mouse (CD-1)	14 d 1x/d (G)	Resp	49			Munson et al. 1982
			Hemato	4.9	49	(decreased leukocytes)	
			Hepatic	49			
			Renal	49			
	Immunological/Lymphoreticular						
13	Rat (Sprague-Dawley)	10 d 1x/d (GO)		100			Daniel et al. 1994
	Neurological						
14	Rat (Sprague-Dawley)	10 d 1x/d (GO)		100			Daniel et al. 1994
15	Rat (Sprague-Dawley)	once (G)		170			Kanada et al. 1994
	Reproductive						
16	Rat (Sprague-Dawley)	10 d 1x/d (GO)		100			Daniel et al. 1994

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
17	Rat (Sprague-Dawley)	14 d Gd 6-20 1x/d (GO)		158		198 F (increased resorptions and nonsurviving implants, decreased maternal body weight gain)	Payan et al. 1995
	Developmental						
18	Rat (Sprague-Dawley)	14 d Gd 6-20 1x/d (GO)		158		198 F (increased resorptions and nonsurviving implants, decreased maternal body weight gain)	Payan et al. 1995
19	Mouse (CD-1)	7 d Gd 7-14 ad lib (W)		510			Kavlock et al. 1979

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Death						
20	Rat (F344/N)	13 wk 5d/wk 1x/d (GO)				240 (10/10 died)	NTP 1991a
21	Mouse (B6C3F1)	6 wk 5d/wk 1x/d (GO)				398[b] M (5/5 died) 631 F (5/5 died)	NCI 1978
22	Mouse (B6C3F1)	13 wk (W)				4926 (9/10 died)	NTP 1991a
	Systemic						
23	Rat (NS)	5-7 wk 2x/d (F)	Hepatic	66	176 (increased liver total fat and triglycerides)		Alumot et al. 1976

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
24	Rat (Sprague-Dawley)	90 d 1x/d (GO)	Resp	150			Daniel et al. 1994
			Cardio	150			
			Gastro	150			
			Hemato	150			
			Musc/skel	150			
			Hepatic	150			
			Renal	150			
			Endocr	150			
			Dermal	150			
			Ocular	150			
			Bd Wt	75	150 (17% reduced body weight gain)		

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
25	Rat (F344/N, Sprague-Dawley, Osborne-Mendel)	13 wk (W)	Resp	492			NTP 1991a
			Cardio	492			
			Gastro	492			
			Hemato	492			
			Musc/skel	492			
			Hepatic	492			
			Renal		58[c] (increased absolute and relative kidney weights with renal tubular regeneration at higher doses)		
			Endocr	492			
			Dermal	492			
			Ocular	492			
			Bd Wt	147	259 (10% decreased body weight gain)		

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
26	Rat (F344/N)	13 wk 5d/wk 1x/d (GO)	Resp	480			NTP 1991a
			Cardio	480			
			Gastro	120	240 (forestomach hyperplasia and inflammation)		
			Hemato	240			
			Musc/skel	480			
			Hepatic	480			
			Renal	480			
			Endocr	480			
			Dermal	480			
			Ocular	480			
			Bd Wt	480			
27	Rat (Wistar)	90 d 5d/wk 1x/d (GO)	Resp	90			van Esch et al. 1977
			Cardio	90			
			Gastro	90			
			Hemato	90			
			Musc/skel	90			
			Hepatic	90			
			Renal	90			
			Endocr	90			
			Bd Wt	30	90 M (22% decreased body weight gain)		

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
28	Mouse (CD-1)	90 d ad lib (W)	Resp	189					Munson et al. 1982
			Hemato	189					
			Hepatic	189					
			Renal	189					
29	Mouse (B6C3F1)	13 wk (W)	Resp	4207					NTP 1991a
			Cardio	4207					
			Gastro	4207					
			Hemato	4207					
			Musc/skel	4207					
			Hepatic	4207					
			Renal		249	(tubular regeneration)	4207	(karyomegaly, mineralization, tubular dilation, protein casts)	
			Endocr	4207					
			Dermal	4207					
			Ocular	4207					
			Bd Wt	2710	4207	(10% decreased body weight gain)			
	Immunological/Lymphoreticular								
30	Rat (Sprague-Dawley)	90 d 1x/d (GO)		150					Daniel et al. 1994
31	Rat (F344/N)	13 wk 5d/wk 1x/d (GO)		120	240	(thymic necrosis in rats that were moribund or died)			NTP 1991a

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form
32	Rat	13 wk (W)		492				NTP 1991a
33	Mouse (CD-1)	90 d ad lib (W)		189				Munson et al. 1982
34	Mouse (B6C3F1)	13 wk (W)		4207				NTP 1991a
	Neurological							
35	Rat (Sprague-Dawley)	90 d 1x/d (GO)		150				Daniel et al. 1994
36	Rat (F344/N)	13 wk 5d/wk 1x/d (GO)		120		240	(tremors and necrosis in cerebellum in rats that died)	NTP 1991a
37	Rat (F344/N, Sprague-Dawley, Osborne-Mendel)	13 wk (W)		492				NTP 1991a
38	Rat (Wistar)	90 d 5d/wk 1x/d (GO)		90				van Esch et al. 1977

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
39	Mouse (B6C3F1)	13 wk (W)		4207			NTP 1991a
	Reproductive						
40	Rat (Sprague-Dawley)	90 d 1x/d (GO)		150			Daniel et al. 1994
41	Rat (F344/N)	13 wk 5d/wk 1x/d (GO)		480			NTP 1991a
42	Rat (F344/N, Sprague-Dawley, Osborne-Mendel)	13 wk (W)		492			NTP 1991a
43	Rat (Wistar)	90 d 5d/wk 1x/d (GO)		90			van Esch et al. 1977
44	Mouse (ICR Swiss)	49 wk 2 gen ad lib (W)		50			Lane et al. 1982
45	Mouse (ICR Swiss)	24 wk F/1B gen ad lib (W)		50			Lane et al. 1982

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
46	Mouse (B6C3F1)	13 wk (W)		4207			NTP 1991a
	Developmental						
47	Mouse (ICR Swiss)	18 d ad lib (W)		50			Lane et al. 1982
	Cancer						
48	Mouse Eu-pim-1 transgenic	40 wk 7d/wk 1x/d (GO)				141 F (CEL-malignant lymphoma in 33% of predisposed strain of mice)	Storer et al. 1995

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Death						
49	Rat (Osborne-Mendel)	78 wk 5d/wk 1x/d (GO)				95 (42/50 (84%) died)	NCI 1978
50	Mouse (B6C3F1)	78 wk 5d/wk 1x/d (GO)				299 (36/50 (72%) died)	NCI 1978
	Systemic						
51	Rat (NS)	2 yr 2x/d (F)	Hepatic	42.5			Alumot et al. 1976
			Renal	42.5			
52	Rat (Osborne-Mendel)	78 wk 5d/wk 1x/d (GO)	Resp	95			NCI 1978
			Cardio	95			
			Gastro		47 F (forestomach acanthosis and hyperkeratosis)		
			Hepatic	95			
			Renal	95			
			Endocr	95			
			Bd Wt	95			

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
53	Mouse (B6C3F1)	78 wk 5d/wk 1x/d (GO)	Resp	299 F			NCI 1978
			Cardio	299 F			
			Gastro	299 F			
			Hepatic	299 F			
			Renal	299 F			
			Endocr	299 F			
			Bd Wt	149 F	299 F (30% reduced body weight gain in mice that had tumors and high mortality)		
	Immunological/Lymphoreticular						
54	Rat (Osborne-Mendel)	78 wk 5d/wk 1x/d (GO)		95			NCI 1978
55	Mouse (CD-1)	78 wk 5d/wk 1x/d (GO)		299 F			NCI 1978
	Neurological						
56	Rat (Osborne-Mendel)	78 wk 5d/wk 1x/d (GO)		95			NCI 1978

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less serious (mg/kg/day)		Serious (mg/kg/day)	
57	Mouse (CD-1)	78 wk 5d/wk 1x/d (GO)		299 F				NCI 1978
	Reproductive							
58	Rat (NS)	2 yr 2x/d (F)		42.5				Alumot et al. 1976
59	Rat (Osborne-Mendel)	78 wk 5d/wk 1x/d (GO)		95				NCI 1978
60	Mouse (CD-1)	78 wk 5d/wk 1x/d (GO)		195 M 299 F				NCI 1978
	Cancer							
61	Rat (Osborne-Mendel)	78 wk 5d/wk 1x/d (GO)					47 (CEL-hemangiosarcoma of the spleen, liver, adrenal gland, pancreas, and other organs)	NCI 1978

Table 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)		
62	Mouse (B6C3F1)	78 wk 5d/wk 1x/d (GO)				149 F	(CEL-pulmonary adenoma, mammary gland adenocarcinomas, and combined endometrial polyps and sarcomas)	NCI 1978

[a]The number corresponds to entries in Figure 3-2.
[b]Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[c]Used to derive an intermediate oral minimal risk level (MRL) of 0.2 mg/kg-day; dose divided by an uncertainty factor of 300 (10 for interspecies extrapolation, 3 for use of minimal LOAEL, and 10 for human variability).

ad lib = ab libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); (F) = feed; Endocr = endocrine; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; gen = generation; (GO) = gavage in oil; Hemato = hematological; kg = kilogram; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mg = milligram; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = water; wk = week(s); x = times; yr = year(s)

Figure 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral

Acute (≤14 days)

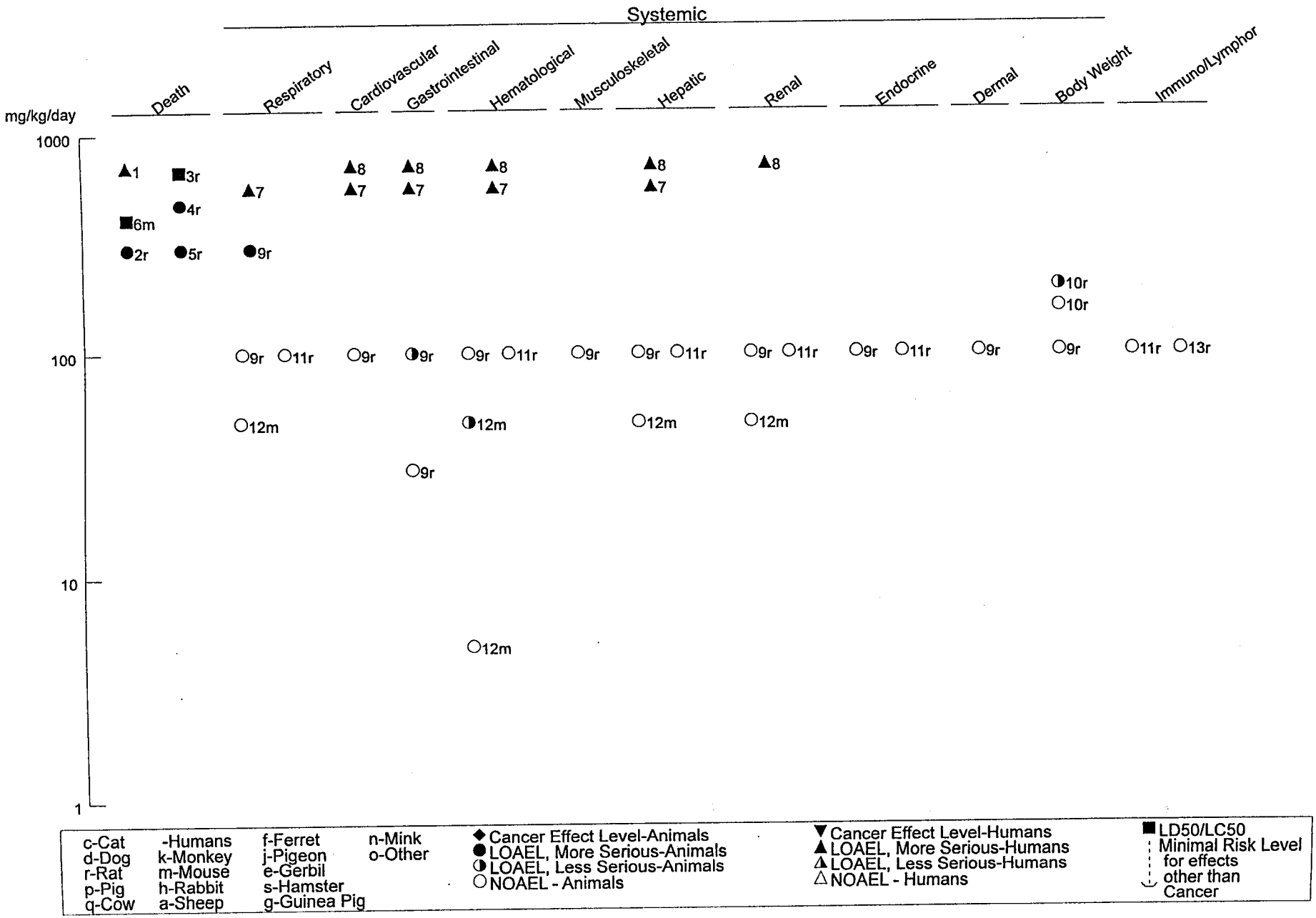


Figure 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (*continued*)

Acute (≤14 days)

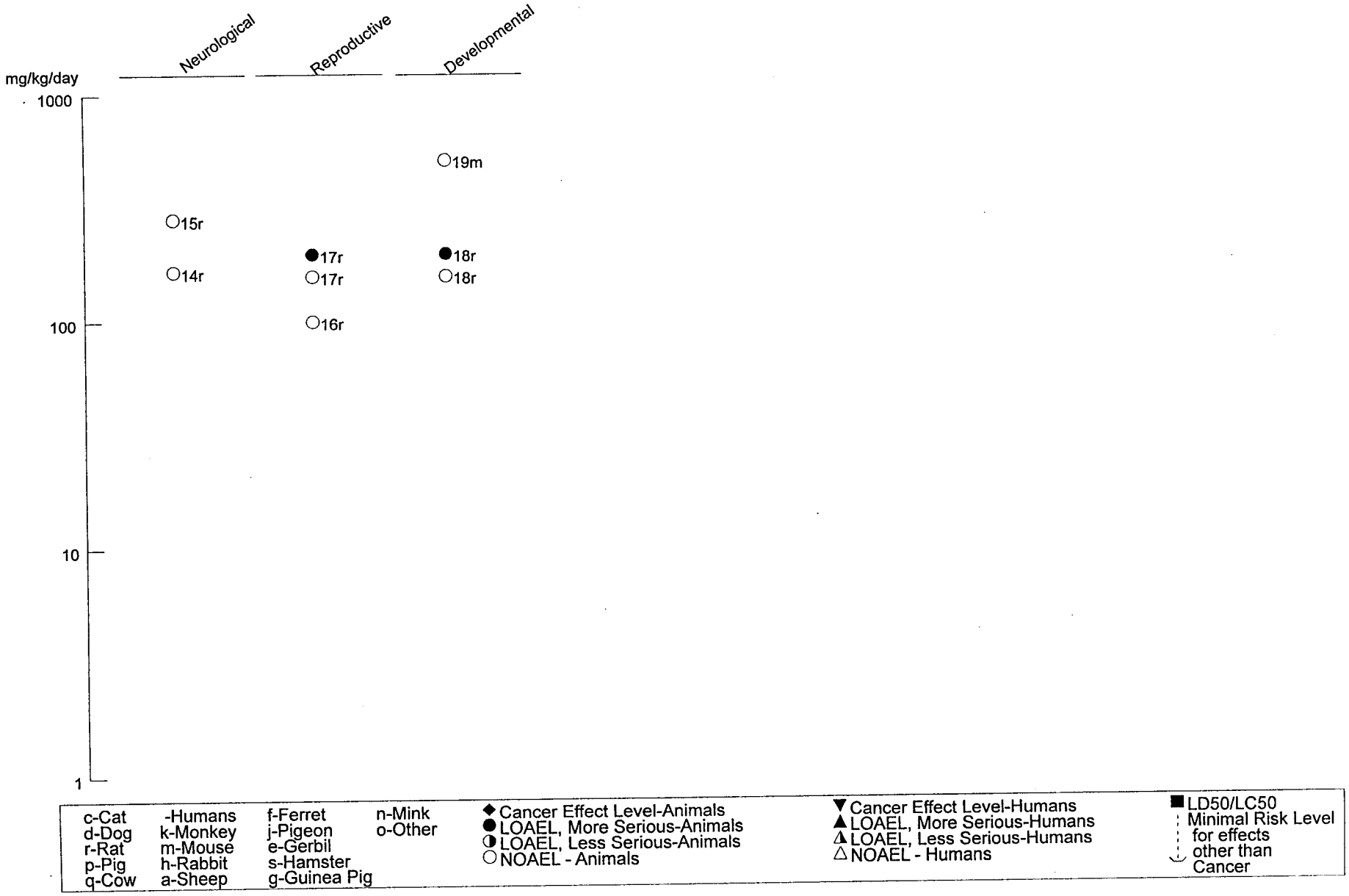


Figure 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (*continued*)

Intermediate (15-364 days)

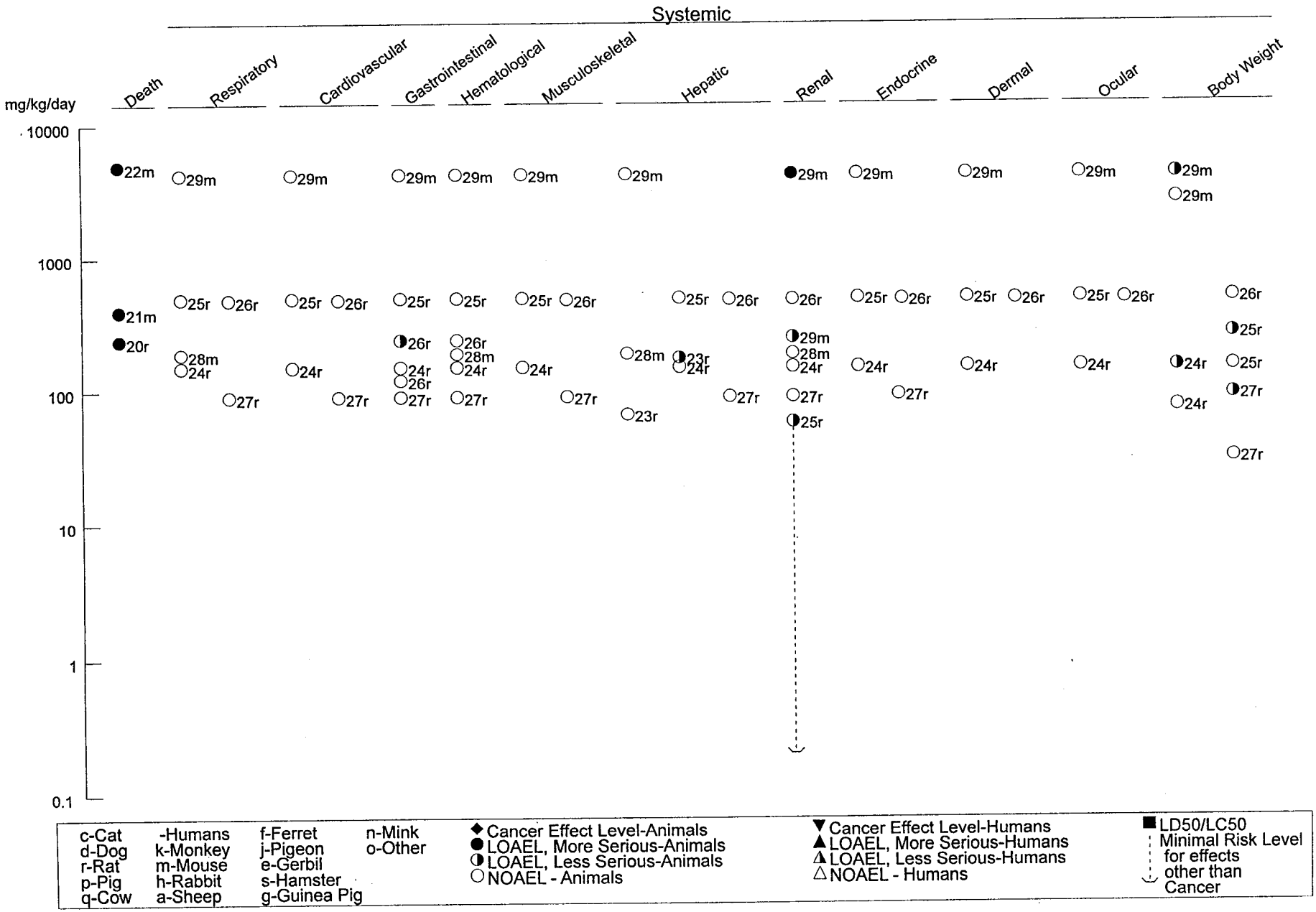
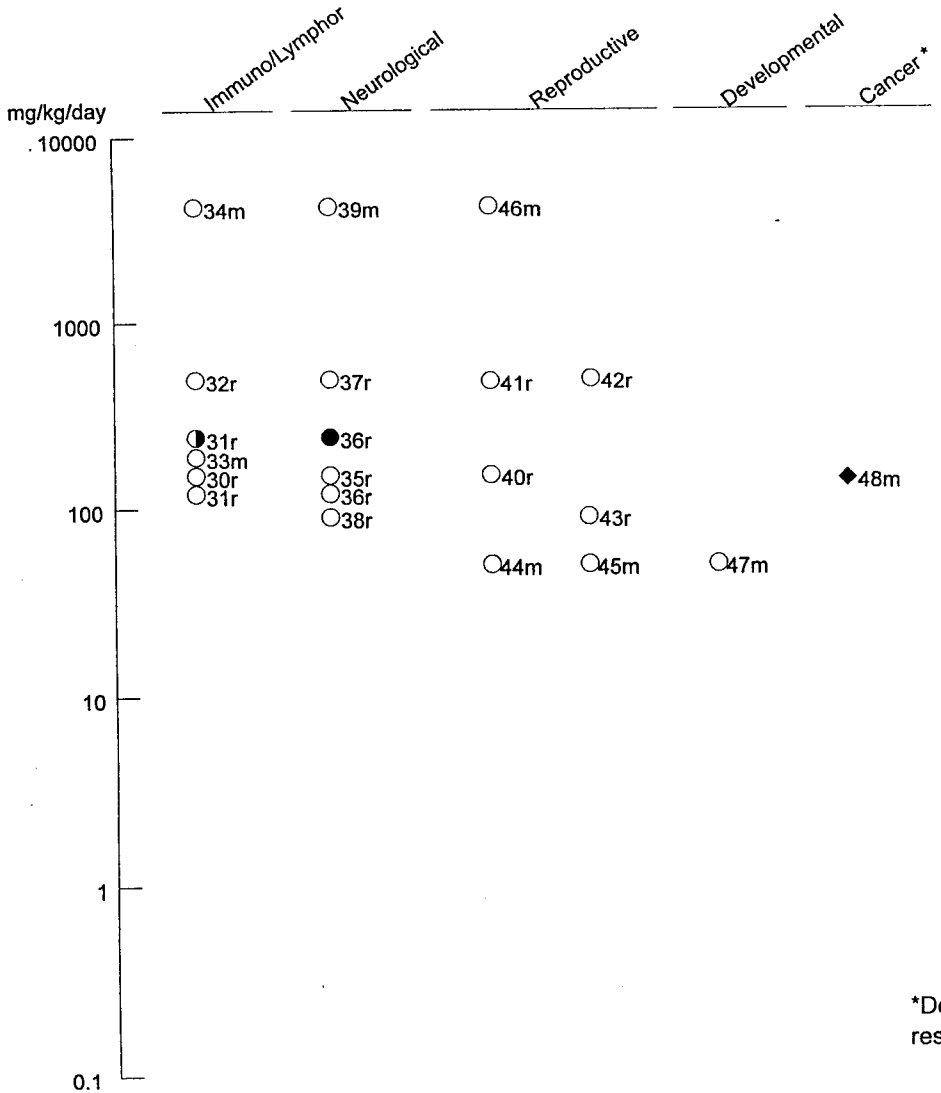


Figure 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (*continued*)

Intermediate (15-364 days)



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

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

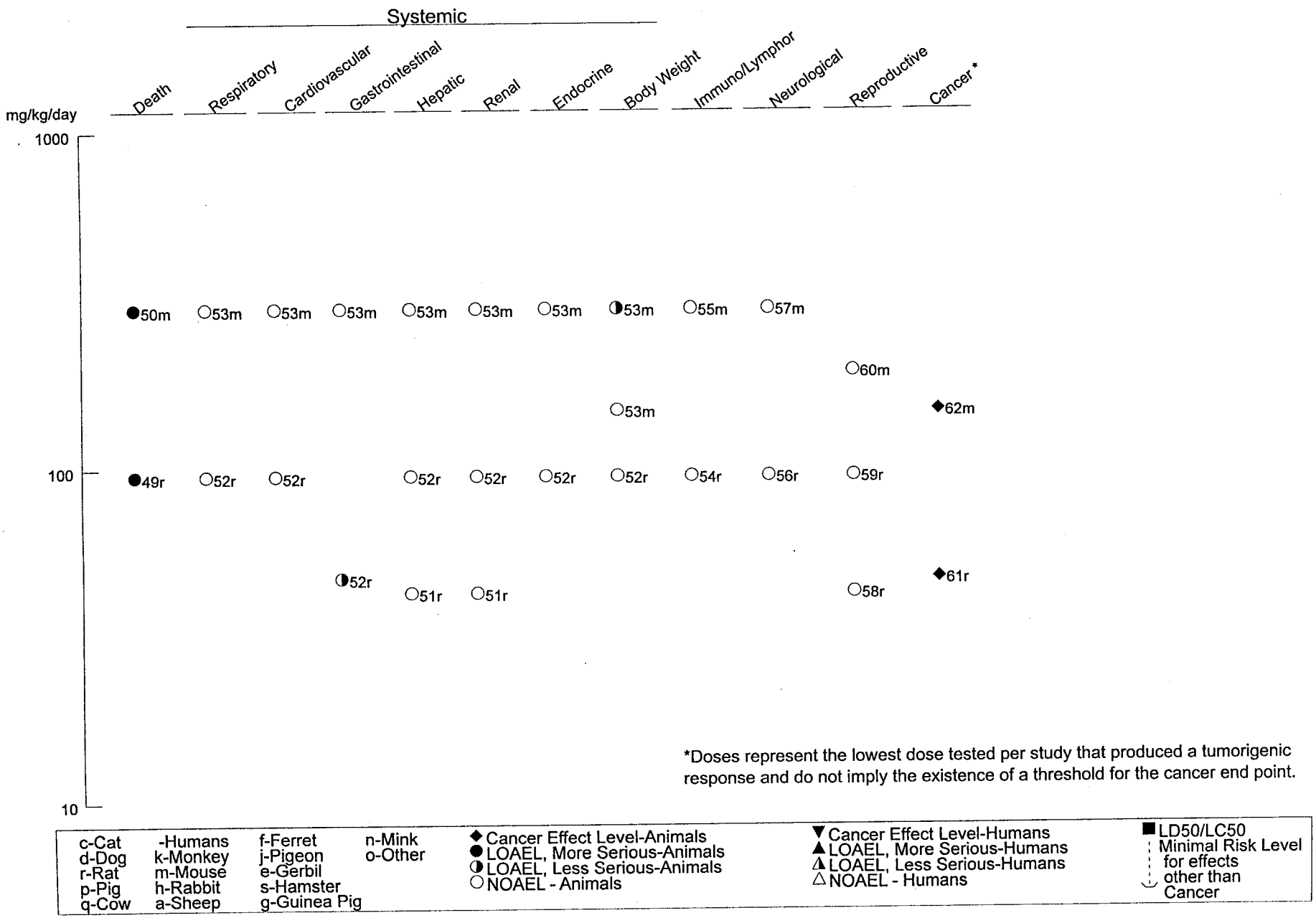
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

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

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

Figure 3-2. Levels of Significant Exposure to 1,2-Dichloroethane - Oral (*continued*)

Chronic (≥365 days)



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

Intermediate-duration studies in animals indicate that the lethality of 1,2-dichloroethane is much higher by gavage than by ingestion in drinking water. Complete mortality occurred at 398 mg/kg/day in male mice and at 631 mg/kg/day in female mice exposed to 1,2-dichloroethane by gavage for 6 weeks (NCI 1978). Similarly, in rats exposed by gavage for 6 or 13 weeks, doses $240 mg/kg/day caused deaths in all animals (NTP 1991a). However, much higher dose levels were required to produce death following drinking water exposure. No deaths occurred among rats exposed to doses #727 mg/kg/day in the drinking water for 13 weeks (NTP 1991a). Mice that were exposed to 1,2-dichloroethane in drinking water for 13 weeks experienced mortality only at the high dose of 4,930 mg/kg/day (NTP 1991a). The mortality in the NTP (1991a) drinking water studies began to increase during the first 2 weeks of exposure and approached or reached 100% after 13 weeks (NTP 1991a). In the 13-week gavage study, 240 and 480 mg/kg/day produced 100% mortality in male rats within 13 weeks and 3 days, respectively (NTP 1991a).

Chronic exposure to 1,2-dichloroethane by gavage caused reduced survival in rats and mice. Treatment with 95 mg/kg/day for 78 weeks caused 84% mortality in rats (NCI 1978). The mortality was seen as early as week 2 and became substantial after 15 weeks. The data suggest that the dose levels tested might be lethal to rats under both acute and chronic conditions. In mice, 72% mortality occurred in females exposed to 299 mg/kg/day by gavage for 78 weeks; mortality became evident after . 10 weeks (NCI 1978).

The LD_{50} values and all LOAEL values from each reliable study for death in each species and duration category are presented in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The systemic effects of 1,2-dichloroethane in humans and animals after oral exposure are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for systemic end points in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. The respiratory effects exhibited by individuals who died following acute oral exposure to 1,2-dichloroethane include congestion, pulmonary edema (at 570 mg/kg/day), dyspnea, and bronchitis (Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Yodaiken and Babcock 1973). The pulmonary edema reported in the case report by Yodaiken and Babcock (1973) may have been chemical pneumonitis due to aspiration of 1,2-dichloroethane.

The literature reviewed provided no evidence that 1,2-dichloroethane induces adverse effects on the respiratory system following acute, intermediate, or chronic oral exposure in animals. Gross and histological examinations showed no effects in the respiratory tract following gavage exposure in rats treated with #100 mg/kg/day for 10 or 14 days (Daniel et al. 1994; van Esch et al. 1977), rats treated with #480 mg/kg/day for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), or rats and mice treated with #95 and #299 mg/kg/day, respectively, for #78 weeks (NCI 1978). Similarly, no histopathological changes in the respiratory tract were found in rats and mice that ingested 1,2-dichloroethane in the drinking water at doses of #492 and #4,210 mg/kg/day, respectively, for #90 days (NTP 1991a). The histological examinations performed by NTP (1991a) were more complete than in the other studies because they included the nasal cavity and turbinates in addition to the lungs and bronchi. Other studies in mice found no changes in lung weight or gross appearance following exposure to #49 mg/kg/day by gavage for 14 days or #189 mg/kg/day in drinking water for #90 days (Munson et al. 1982), but these results are limited by lack of histological examinations.

Cardiovascular Effects. Clinical investigation of patients who died following acute ingestion of 1,2-dichloroethane determined that cardiovascular insufficiency and hemorrhage were major factors contributing to death (Garrison and Leadingham 1954; Hueper and Smith 1935; Martin et al. 1969; Schönborn et al. 1970). Numerous surficial petechial hemorrhages of the heart were observed at autopsy in a man who died from ingesting a “small” quantity of 1,2-dichloroethane (Hubbs and Prusmack 1955).

Cardiovascular histopathological effects were not found in animals orally exposed to 1,2-dichloroethane, even at lethal doses. Histological examinations showed no cardiovascular effects following gavage exposure in rats treated with #100 mg/kg/day for 10 days (Daniel et al. 1994), rats treated with #480 mg/kg/day for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), or rats and mice treated with #95 and #299 mg/kg/day, respectively, for #78 weeks (NCI 1978). Similarly, no histopathological changes in the heart were found in rats and mice that ingested 1,2-dichloroethane in the drinking water at doses of #492 and #4,210 mg/kg/day, respectively, for #90 days (NTP 1991a).

Gastrointestinal Effects. Gastrointestinal symptoms have been observed in humans prior to death following oral exposure to 570 or 714 mg/kg/day of 1,2-dichloroethane. These symptoms included nausea, vomiting, and diarrhea (Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Schönborn et al. 1970; Yodaiken and Babcock 1973). Hemorrhagic colitis, hemorrhagic gastritis, and focal hemorrhages of the gastrointestinal tract have also been reported upon autopsy (Garrison and

Leadingham 1954; Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Schönborn et al. 1970).

Gastrointestinal lesions have also been found in animals given bolus doses of 1,2-dichloroethane. Forestomach lesions developed in rats given gavage doses of 100 mg/kg/day for 10 days (minimal mucosal and submucosal inflammation), $240 mg/kg/day for #13 weeks (mild hyperplasia and inflammation), or $47 mg/kg/day for #78 weeks (acanthosis and hyperkeratosis) (Daniel et al. 1994; NCI 1978; NTP 1991a). Similar lesions were not found in rats exposed to corresponding doses (#492 mg/kg/day) in the drinking water for 13 weeks or mice exposed to much higher doses (#4,210 mg/kg/day) in the drinking water for 13 weeks (NTP 1991a). No increase in histopathologies in the stomach or intestines was observed in rats after intermittent gavage doses of up to 90 mg/kg/day over a 90-day period (van Esch et al. 1977). The incidences of non-neoplastic lesions of the stomach, large intestine, and colon were also not increased in mice intermittently administered up to 299 mg/kg/day by gavage for 78 weeks (NCI 1978). The gastrointestinal lesions observed in humans and animals ingesting bolus doses are probably produced by direct contact with concentrated 1,2-dichloroethane; the concentration in drinking water (8,000 mg/L) tested by NTP (1991a), although close to the solubility limit for this chemical (9,000 mg/L), was apparently too low to have this effect.

Hematological Effects. Adverse hematological effects, such as increased prothrombin time and reduction in blood clotting factors, were observed in 18- and 57-year-old men who had ingested approximately 40 mL ($570 mg/kg) of 1,2-dichloroethane (Martin et al. 1969; Schönborn et al. 1970) and in a 14-year-old boy who had ingested approximately 15 mL (360 mg/kg, using an approximate body weight of 51.3 kg [EPA 1988d]) of 1,2-dichloroethane (Yodaiken and Babcock 1973). These are only crude estimates of the ingested doses. The alterations in coagulation parameters described above may have been associated to some degree with liver dysfunction. The liver plays an important role in blood clotting homeostasis, and hepatic disorders may result in abnormalities in coagulation tests. The liver is the site of production of most of the plasma coagulant factors such as fibrinogen, prothrombin, and factors V, VII, IX, and X.

Similar effects have not been reported in animals following oral exposure. However, a 30% decrease in leukocytes was reported in mice given daily gavage doses of 49 mg/kg of 1,2-dichloroethane for 2 weeks (Munson et al. 1982). This effect may have had some relation to immunosuppressive effects reported in the same study. Mice that ingested #189 mg/kg/day in the drinking water for 90 days did not exhibit any differences from control animals with regard to hemoglobin, hematocrit, red or white blood cell counts, or

platelets (Munson et al. 1982). Similarly, there were no hematological changes in mice exposed to #4,210 mg/kg/day in the drinking water for up to 13 weeks (NTP 1991a). In order to explain the apparent contradiction in their results, Munson et al. (1982) suggested that more 1,2-dichloroethane may enter systemic circulation when the animals are given a concentrated solution in bolus form, than when they are allowed to drink water containing lower concentrations of 1,2-dichloroethane. They also suggested that, during the longer exposure time, 1,2-dichloroethane might induce its own metabolism and therefore be removed from the blood and other organs more rapidly. In rats, hematological parameters were unaffected by exposure to #100 mg/kg/day by gavage for 10 or 14 days (Daniel et al. 1994; van Esch et al. 1977), #480 mg/kg/day by gavage for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), or #492 mg/kg/day in drinking water for 90 days (NTP 1991a).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,2-dichloroethane.

There is no indication that ingested 1,2-dichloroethane produces musculoskeletal effects in animals. Histological changes in muscle and bone were not observed in rats administered #100 mg/kg/day by gavage for 10 days (Daniel et al. 1994), in rats administered #480 mg/kg/day by gavage for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), or in rats and mice exposed at #492 and #4,210 mg/kg/day, respectively, in drinking water for #90 days (NTP 1991a).

Hepatic Effects. 1,2-Dichloroethane has been implicated as a hepatotoxin in humans after acute oral poisoning (Przezdziak and Bakula 1975). Ingestion of $570 mg/kg/day of 1,2-dichloroethane resulted in severe hepatocellular damage and liver atrophy (Martin et al. 1969) and necrosis (Schönborn et al. 1970), although the degree to which these conditions were pre-existing is unknown. No gross changes were reported in the liver of a man who died from ingesting a “small” quantity of 1,2-dichloroethane, but hepatocellular fatty vacuolation and inflammation, “engorged” hepatic vasculature, and mild lymphocytic infiltration of portal spaces were observed microscopically (Hubbs and Prusmack 1955).

Studies in orally exposed animals have not found serious liver effects like those reported in humans. Hepatic biochemical changes consisting of a 15% increase in fat accumulation and increases in total triglycerides (indicative of liver damage), were observed in rats fed 80 mg/kg/day of 1,2-dichloroethane in the diet for 5–7 weeks (Alumot et al. 1976). Histological examinations were not performed, although liver weight was unchanged. The NOAEL for liver changes in this study was 30 mg/kg/day. Increased liver weight with no hepatic histological alterations occurred in intermediate-duration studies conducted

by NTP (1991a) in rats and mice. Following a 13-week gavage exposure in rats, both liver weight and liver-to-body-weight ratio were elevated in a dose-related fashion. The increase over controls was significant at 18–150 mg/kg/day in females and 120 mg/kg/day in males (liver weight was not measured in higher-dose animals because of mortality). Following a 13-week drinking water exposure, liver weight increases were noted at 60 mg/kg/day in rats (liver-to-body-weight ratio was significantly elevated at 60–518 mg/kg/day in Sprague-Dawley males without corresponding decreases in body weight), and at 249 mg/kg/day in mice (liver-to-body-weight ratio was significantly elevated in a dose-related manner at 249–4,210 mg/kg/day in males without corresponding decreases in body weight). Similarly, relative liver weights were increased with no accompanying histopathological changes in rats administered #150 mg/kg/day by gavage for #90 days (Daniel et al. 1994; van Esch et al. 1977). In the absence of histopathological or biochemical changes in the liver, the changes in liver weight are not considered to be adverse effects. Based on these findings, the liver does not appear to be a sensitive target organ for 1,2-dichloroethane toxicity in animals.

Other animal studies of 1,2-dichloroethane did not find hepatic effects. No changes in liver weight were observed in mice exposed to #49 mg/kg/day by gavage for 14 days or #189 mg/kg/day in drinking water for 90 days (Munson et al. 1982); histology was not evaluated. Rats administered single gavage doses (80 mg/kg) of 1,2-dichloroethane showed no effect on liver triglyceride, SDH, and ALT levels (Aragno et al. 1992; Danni et al. 1992). Chronic exposure of rats to 25 mg/kg/day in food for 2 years did not result in abnormalities in liver function, as measured by transaminases and cholesterol values (Alumot et al. 1976). In this chronic feeding study, the animals were not evaluated grossly or microscopically for liver lesions. There also were reported losses of 1,2-dichloroethane due to volatilization from the food; consequently, actual exposures would probably have been less than nominal exposures. No histological changes were observed in the liver of rats and mice that were administered #95 and #299 mg/kg/day, respectively, by gavage for #78 weeks (NCI 1978).

Renal Effects. Acute renal damage resulting from ingestion of 1,2-dichloroethane has been observed in humans. Bleeding and hyperemia of the kidney were observed in an 18-year-old man who ingested a single dose of 714 mg/kg (Schönborn et al. 1970), and in a male hospital patient who died after accidentally ingesting a “small” quantity of 1,2-dichloroethane (Hubbs and Prusmack 1955). Observations upon microscopic examination included swelling, vacuolation, and degeneration of the renal tubule epithelial cells and sloughing of the glomerular capsular epithelium, and nearly complete loss of the bladder epithelium (Hubbs and Prusmack 1955). In one case study, renal damage that resulted from acute oral poisoning of a 25-year-old man was not considered severe or permanent, and the patient fully

recovered (Przezdziak and Bakula 1975). The amount of 1,2-dichloroethane ingested was not reported. However, individuals who died following ingestion of 15–30 mL of 1,2-dichloroethane had severe kidney damage, primarily in the form of diffuse renal necrosis (Hueper and Smith 1935; Lochhead and Close 1951; Yodaiken and Babcock 1973). These are only crude estimates of ingested dose.

Renal effects reported in animals were limited to increases in kidney weight and minimal-to-moderate histopathological changes after longer-term exposures. Relative kidney weight was increased without altered histology in rats that were treated with 75–90 mg/kg/day by gavage for 90 days (Daniel et al. 1994; van Esch et al. 1977). An NTP (1991a) 13-week gavage study in rats found significant dose-related increases in kidney weight and kidney-to-body-weight ratio at 30–120 mg/kg/day in males and 75–150 mg/kg/day in females (kidney weight was not measured in higher-dose animals because of mortality). Exposure to 1,2-dichloroethane in the drinking water for 13 weeks caused significant dose-related increases in kidney weight and kidney-to-body-weight ratio in rats at $58 mg/kg/day and mice at $244 mg/kg/day (NTP 1991a). The increase in kidney weight is considered to be an early-stage adverse effect in a known target tissue because renal histopathological changes occurred at higher doses. Histopathological examination of the animals in the drinking water study showed dose-related increased incidences of minimal-to-moderate renal regeneration in female rats at $102 mg/kg/day and male mice at $249 mg/kg/day. These changes are indicative of previous tubular injury with subsequent repair. More severe renal effects including karyomegaly, dilation, protein casts, and mineralization occurred in male mice exposed at 4,210 mg/kg/day. Based on these results, NTP (1991a) concluded that the kidney was a target organ for 1,2-dichloroethane in mice. Using a LOAEL of 58 mg/kg/day based on kidney effects, an intermediate oral MRL of 0.2 mg/kg/day was calculated as described in the footnote in Table 3-2 and in Appendix A.

Other studies in animals failed to find evidence of kidney damage produced by 1,2-dichloroethane. Acute (10–14 days) gavage administration of up to 100 mg/kg/day did not result in treatment-related changes in kidney weight or in the incidence of gross or histopathological changes in the kidney in rats (Daniel et al. 1994; van Esch et al. 1977). There were no changes in kidney weight in mice after administration of 49 mg/kg/day by gavage for 14 days or exposure to 189 mg/kg/day in drinking water for 90 days (Munson et al. 1982), and kidney function, as measured by changes in serum levels of urea and uric acid, was normal in rats exposed to 25 mg/kg/day in food for 2 years (Alumot et al. 1976). Histological examination of the kidney was not performed in either of these studies. No histological changes were observed in the kidneys of rats and mice that were administered #95 and #299 mg/kg/day, respectively, by gavage for #78 weeks (NCI 1978). The discrepancy between the negative results of this bioassay and

the finding of kidney effects in the NTP (1991a) 13-week study may be related to animal strain. NTP (1991a) found compound-related renal changes in F344/N rats, whereas Osborne-Mendel rats were tested by NCI (1978); tests of Osborne-Mendel and Sprague-Dawley rats by NTP (1991a) were also negative.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to 1,2-dichloroethane.

Endocrine function has not been evaluated in oral toxicity studies in animals. Histological examinations of endocrine system tissues were performed in several studies with essentially negative results, but lack of histopathology does not necessarily indicate that there were no functional endocrinologic changes. Histopathological examinations failed to detect changes in endocrine tissues in rats administered #100 mg/kg/day by gavage for 10 or 14 days (Daniel et al. 1994; van Esch et al. 1977), in rats administered #480 mg/kg/day by gavage for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), in rats and mice exposed to #492 and #4,210 mg/kg/day, respectively, in drinking water for #90 days (NTP 1991a), or in rats and mice exposed to #95 and #299 mg/kg/day, respectively, by gavage for #78 weeks (NCI 1978). The examinations in the NCI (1978) and NTP (1991a) studies were the most extensive and included tissues from the adrenal, pancreas, pituitary, thyroid, and parathyroid glands.

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

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to 1,2-dichloroethane.

Histological examinations showed no changes in the skin of rats administered #100 mg/kg/day by gavage for 14 days (Daniel et al. 1994), in rats administered #480 mg/kg/day by gavage for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), or in rats and mice exposed to #492 and #4,210 mg/kg/day, respectively, in drinking water for #90 days (NTP 1991a).

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

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to 1,2-dichloroethane.

Ophthalmoscopic examinations showed no effects in rats that were treated with #150 mg/kg/day of 1,2-dichloroethane by gavage in a 90-day study; the exams were performed prior to treatment and during the last week of the study (Daniel et al. 1994). Other 90-day studies similarly found no gross ocular changes in the eyes of rats treated with #480 mg/kg/day by gavage, or in rats and mice exposed to #492 and #4,210 mg/kg/day, respectively, in drinking water (NTP 1991a).

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

Body Weight Effects. No studies were located regarding effects on body weight in humans after oral exposure to 1,2-dichloroethane.

Acute-duration animal studies found no effects on body weight in rats administered #100 mg/kg/day by gavage for 10 or 14 days (Daniel et al. 1994; van Esch et al. 1977), although gavage treatment with 198 mg/kg/day (but not #158 mg/kg/day) for 14 days during pregnancy caused a 30% reduction in maternal body weight gain (Payan et al. 1995). Reduced growth (10–30% decreases in body weight gain) has been observed in animals following intermediate- and chronic-duration oral exposures, including rats administered $90 mg/kg/day by gavage for 90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), rats and mice exposed to $259 and 4,210 mg/kg/day, respectively, in drinking water for 90 days (NTP 1991a), and mice administered 299 mg/kg/day by gavage for #78 weeks (NCI 1978). No effect on body weight was seen in rats administered up to 95 mg/kg/day by gavage for 78 weeks (NCI 1978).

The highest NOAEL values and all LOAEL values from each reliable study for body weight effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.3 Immunological and Lymphoreticular Effects

Limited information was located regarding immunological effects in humans after oral exposure to 1,2-dichloroethane. Gross findings at autopsy of a male patient who ingested a “small” quantity of 1,2-dichloroethane included a dark appearance of the spleen; hemorrhaging and congestion of the red pulp were observed microscopically (Hubbs and Prusmack 1955).

Evidence from animal studies suggests that the immune system is a target of 1,2-dichloroethane toxicity after oral exposure. In 5-week-old mice exposed for 14 days by gavage to 4.9 and 49 mg/kg/day, there

was a significant dose-related reduction in humoral immunity (measured by immunoglobulin M [IgM] response to sheep erythrocytes), and a significant, but not dose-related, reduction in cell-mediated immunity (measured by delayed-type hypersensitivity response to sheep erythrocytes) (Munson et al. 1982). In mice given 49 mg/kg/day, these effects were accompanied by a 30% decrease in total leukocyte number.

Mice given drinking water containing up to 189 mg/kg/day of 1,2-dichloroethane for 90 days displayed no treatment-related effects on either the antibody-forming cell response or the delayed-type hypersensitivity response after immunization with sheep erythrocyte antigens (Munson et al. 1982). The authors suggested that the conflicting results in mice treated by gavage and those exposed to 1,2-dichloroethane in drinking water may reflect differences in compound administration and exposure duration, as discussed earlier (see the discussion of hematological effects in Section 3.2.2.2). No increase in the incidences of gross or histopathological changes were observed in the spleen, lymph nodes, or thymus in rats administered up to 100 mg/kg/day by gavage for 10 days (Daniel et al. 1994).

Immune system function tests were not included in intermediate- and chronic-duration studies conducted by NTP (1991a). However, immune system tissues were examined for histopathological lesions in some of these studies. Thymic necrosis was observed in rats given $240 mg/kg/day of 1,2-dichloroethane by gavage #13 weeks (NTP 1991a). Because this lesion was found only in moribund animals, the study authors concluded that it was a result of generalized stress rather than a target organ effect. 1,2-Dichloroethane did not produce lesions in immune system tissues in rats and mice exposed to #492 mg/kg/day and #4,210 mg/kg/day, respectively, in drinking water for 13 weeks (NTP 1991a), in rats exposed by gavage to 150 mg/kg/day for 90 days (Daniel et al. 1994), or in rats and mice exposed to #95 and #299 mg/kg/day, respectively, by gavage for #78 weeks (NCI 1978).

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

3.2.2.4 Neurological Effects

Neurological effects, such as central nervous system depression, have been reported in humans following acute oral intoxication with 1,2-dichloroethane (Hubbs and Prusmack 1955; Lochhead and Close 1951; Yodaiken and Babcock 1973). Morphological alterations in the nervous system were observed in patients who died of acute oral poisoning by 1,2-dichloroethane. These alterations included vascular disorders,

diffuse changes in cerebellar cells, parenchymatous changes in brain and spinal cord, myelin degeneration, and hyperemia, swelling, edema, and hemorrhage of the brain (Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951). The morphological changes observed in the cerebellum may affect the coordination of muscular movements.

Neurological effects have also been observed in animals exposed to 1,2-dichloroethane by ingestion. Clinical signs in rats exposed to $240 mg/kg/day by gavage for #13 weeks included tremors, salivation, emaciation, abnormal posture, ruffled fur, and dyspnea (NTP 1991a). Upon microscopic examination, mild necrotic lesions were observed in the cerebellum of rats dosed with 240 or 300 mg/kg/day. These lesions were not found in rats dosed with 480 mg/kg/day, but these rats all died after only 3 days of treatment and may not have had time to develop the lesion. Intermittent gavage exposure to 90 mg/kg/day in female rats over a 90-day period induced a slight increase in relative brain weight (+8%) in female rats, but no clinical signs or histological changes in the brain or spinal cord were observed, and no neurological effects of any kind were seen in males at 90 mg/kg/day or in either sex at lower exposure levels (van Esch et al. 1977). Similarly, gavage administration of 75 and 150 mg/kg/day induced a significant increase in brain weight (+8 and +22%, respectively) in male rats without increases in the incidences of neurological clinical signs or lesions of the brain or sciatic nerve; no neurological effects of any kind were reported in females at $75 mg/kg/day or in either sex at lower exposure levels (Daniel et al. 1994). In the Daniel et al. (1994) study, the increase in relative brain weight may have been due to an observed dose-related decrease in body weight in the male rats, and may not necessarily be due to an actual change in brain weight; absolute organ weights were not reported. Exposure to 1,2-dichloroethane in the drinking water for 13 weeks did not produce increased brain weights, abnormal clinical signs, or lesions in nervous system tissues in rats (#492 mg/kg/day) or mice (#4,210 mg/kg/day) (NTP 1991a). (See the discussion of hematological effects in Section 3.2.2.2 regarding why effects that occur following bolus exposure might not occur following drinking water exposure). A 10-day gavage exposure to up to 100 mg/kg/day did not induce an increase in brain weight or an increase in the incidences of gross or microscopic lesions in nervous system tissues of rats (Daniel et al. 1994), and a single gavage exposure to 170 mg/kg in rats did not significantly alter neurotransmitter levels in various parts of the brain (Kanada et al. 1994).

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

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 1,2-dichloroethane.

Studies in animals suggest that reproductive effects of 1,2-dichloroethane may be induced at oral doses that are maternally toxic. One-and two-generation reproduction studies showed no dose-dependent effects on fertility, gestation, viability, or lactation indices in mice exposed to doses of 5–50 mg/kg/day in drinking water for 24–49 weeks (Lane et al. 1982). Similarly, there were no effects on fertility indices (e.g., percentage pregnant, percent bearing litters, and litter size) in five pregnancies throughout a 2-year study during which rats ingested dietary doses of 21.3 or 42.5 mg/kg/day (Alumot et al. 1976). In a study using higher doses of 1,2-dichloroethane, rats that were treated with $198 mg/kg/day for 14 days during gestation showed 30% reduced body weight gain and dose-related increased percentages of nonsurviving implants per litter (resorptions plus dead fetuses) and resorption sites per litter (Payan et al. 1995). These effects did not occur at #158 mg/kg/day, and no changes in mean number of implantation sites or live fetuses per litter were observed.

Histological examinations showed no changes in male or female reproductive tissues in rats administered #100 mg/kg/day by gavage for 10 days (Daniel et al. 1994), in rats administered #480 mg/kg/day by gavage for #90 days (Daniel et al. 1994; NTP 1991a; van Esch et al. 1977), in rats and mice exposed to #492 and #4,210 mg/kg/day, respectively, in drinking water for #13 weeks (NTP 1991a), or in rats and mice exposed to #95 and #299 mg/kg/day, respectively, by gavage for #78 weeks (NCI 1978). Reproductive performance was not evaluated in these studies.

The highest NOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans exposed solely to 1,2-dichloroethane by ingestion. A cross-sectional epidemiologic study investigated whether elevated levels of routinely sampled organic contaminants in New Jersey public water systems, including 1,2-dichloroethane, were associated with increased prevalences of adverse birth outcomes (Bove 1996; Bove et al. 1995). The study population consisted of all live births and fetal deaths that occurred during 1985–1988 to residents

of 75 towns in a four-county area where some municipal water supplies were contaminated. A total of 80,938 live births and 594 fetal deaths, excluding plural births, fetal deaths due to therapeutic abortions, and chromosomal anomalies, were studied. The comparison group comprised 52,334 (all) live births from the study population that had no birth defects and were not low birth weight, small for gestational age, or pre-term. A number of associations between various chemicals and birth outcomes were found, including a positive association between 1,2-dichloroethane and major cardiac defects for exposure levels >1 ppb compared to #1 ppb (OR=2.11). The odds ratio increased to 2.81 when exposure was recategorized as detected versus not detected. Croen et al. (1997) reported an increased crude odds ratio (OR=2.8; 95% CI 1.0–7.2; 14 exposed cases) for neural tube defects in offspring of residents within the census tract of NPL sites contaminated with 1,2-dichloroethane. The OR for residence within 1 mile of the NPL site was elevated, but was not significant (OR=1.7; 95% CI 0.8–3.6; 18 exposed cases). Although an association between 1,2-dichloroethane in drinking water and major birth defects was found in these epidemiological studies, concurrent mixed chemical exposures indicate that the results are only suggestive, do not establish a cause-and-effect relationship, and should be interpreted with caution. Primary routes of exposure in these epidemiological studies may have been both oral and inhalation (including inhalation of 1,2-dichloroethane volatilized from household water).

Developmental toxicity studies in animals have not shown 1,2-dichloroethane to be fetotoxic or teratogenic following oral exposure, although indications of embryolethality at maternally toxic doses have been reported. Drinking water studies in mice found no increased incidences of fetal visceral and skeletal abnormalities following exposure to 50 mg/kg/day on gestation days 0–18 (Lane et al. 1982) or #510 mg/kg/day on gestation days 7–14 (Kavlock et al. 1979). Rats that were treated with $198 mg/kg/day by gavage on gestation days 6–20 showed 30% reduced body weight gain and some embryolethal effects (increased nonsurviving implants and resorption sites per litter), but no fetotoxicity or teratogenicity as indicated by fetal sex ratio, fetal body weight, and incidences of visceral and skeletal variations and malformations (Payan et al. 1995). The highest NOAEL values from each reliable study for developmental effects in mice after acute and intermediate exposure are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

Little information is available concerning the development of cancer in humans following ingestion of 1,2-dichloroethane. Isacson et al. (1985) used indices of drinking water contamination to examine the relationship between cancer incidence and exposure to environmental pollutants in groundwater and

surface water samples. A statistically significant association was observed between the presence of 1,2-dichloroethane in drinking water and an increased incidence of colon ($p=0.009$) and rectal ($p=0.02$) cancer in men aged 55 years or older. However, it is highly likely that the study population was concomitantly exposed to other chemicals.

1,2-Dichloroethane was found to be carcinogenic in rats and mice that were exposed by gavage for up to 78 weeks (NCI 1978). Statistically significant increases in multiple tumor types (malignant and benign) were noted in treated animals of both species. An increased incidence of fibromas of the subcutaneous tissue and hemangiosarcomas of the spleen, liver, pancreas, and adrenal gland (as well as other organs and tissues) occurred in male rats of both exposure groups (47 and 95 mg/kg/day). In the high-dose group (95 mg/kg/day), male rats had increased squamous cell carcinomas of the forestomach, and female rats had increased frequencies of adenocarcinomas and fibroadenomas of the mammary gland. In mice, the incidence of hepatocellular carcinomas and pulmonary adenomas increased in males given 195 mg/kg/day. In female mice from both the 149- and 299-mg/kg/day exposure groups, there were increased incidences of pulmonary adenomas, adenocarcinomas of the mammary gland, and endometrial polyps and sarcomas. In conclusion, 1,2-dichloroethane administered by gavage produced tumors in rats and mice in tissues distant from the site of administration. The NCI (1978) study has a number of limitations including dosage adjustments throughout the course of the bioassay (because of the toxicity of 1,2-dichloroethane), testing of other volatile organic chemicals in the same room, small numbers of concurrent controls, poor survival of treated animals, imprecise reporting of 1,2-dichloroethane purity, and use of a corn oil vehicle, which can alter the disposition of lipophilic compounds and the incidence of some spontaneous tumors. Despite these study limitations, it is prudent to consider the possibility of tumor induction when the chemical is administered via other routes and absorbed into systemic circulation as well.

In another study, 1,2-dichloroethane was administered to $B6C3F_1$ mice in their drinking water using a two-stage (initiation/promotion) treatment protocol; no increase in tumorigenicity was found (Klaunig et al. 1986). In this study, mice were initiated with diethylnitrosamine (DENA) for 4 weeks and subsequently treated with 159 or 475 mg/kg/day 1,2-dichloroethane for 52 weeks. 1,2-Dichloroethane did not increase the incidence of lung or liver tumors either alone or as a tumor promoter following DENA initiation. However, severe study limitations (including short duration, high liver-tumor incidence in untreated controls [20%] and in DENA-initiated [100%] mice after 52 weeks, lack of positive controls, and failure to specify the compound purity) invalidate any conclusions about the lack of carcinogenicity of 1,2-dichloroethane. A shorter-term initiation/promotion study in rats, based on the use of enzyme-

altered liver foci as a marker for preneoplastic changes, also failed to confirm the carcinogenic potential of 1,2-dichloroethane (Milman et al. 1988), but was limited by use of a single dose level (100 mg/kg), short exposure duration (single dose in initiation study and 7 weeks in promotion study), and monitoring of an end point not firmly established as proof of carcinogenicity.

In another two-stage oral cancer assay (Pott et al. 1998), a 16-week co-administration of 1,2-dichloroethane and arsenic (in drinking water) with vinyl chloride and trichloroethylene (administered by gavage) (all of which are chemicals commonly found at hazardous waste sites) produced dose-related inhibition of the promotion of preneoplastic hepatic lesions and bronchoalveolar hyperplasia and pulmonary adenomas in male Fisher 344 rats, after a 4-week initiation with a series of three broad-spectrum initiators. The drinking water concentrations of 1,2-dichloroethane ranged from 3 ppm (approximately 0.47 mg/kg/day) in the low exposure group (with relatively low levels of the other test substances) to 300 ppm (approximately 47 mg/kg/day) in the high exposure group (with relatively high levels of the other test substances). The study has limited usefulness for understanding lifetime risk of cancer from 1,2-dichloroethane exposure because of co-exposure with other known carcinogens, the use of a short promotion exposure period (16 weeks), small numbers of test animals (15 per exposure group), and evaluation of effects to only one sex (males).

CEL values from the chronic NCI (1978) study in rats and mice are recorded in Table 3-2 and plotted in Figure 3-2.

EPA has derived a slope (potency) factor (q_1*) of 0.091 $(mg/kg/day)^{-1}$ for cancer risk associated with oral exposure to 1,2-dichloroethane based on the study by NCI (1978) in rats (IRIS 2001). This slope factor corresponds to a drinking water unit risk of $2.6x10^{-6}$ $(\mu g/L)^{-1}$ and an inhalation unit risk of $2.6x10^{-5}$ $(\mu g/m^3)^{-1}$. Based on this potency factor, oral doses of 1,2-dichloroethane associated with excess human lifetime cancer risks of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7} are $1x10^{-3}$, $1x10^{-4}$, $1x10^{-5}$, and $1x10^{-7}$ mg/kg/day, respectively. These risk levels correspond to one excess cancer death in 10,000, 100,000, 1 million, and 10 million persons, respectively, and are derived based on the assumption that individuals are exposed continuously for their entire lifetime (estimated as 70 years) to these oral doses of 1,2-dichloroethane. The range of doses associated with excess lifetime cancer risks of 10^{-4} to 10^{-7} is plotted in Figure 3-2. The estimated excess cancer risks are upper-bound risks (i.e., the true risks are not likely to exceed the upper-bound risk estimate and may be lower).

3.2.3 Dermal Exposure

No studies were located regarding effects after dermal exposure to 1,2-dichloroethane in humans. In animals, ocular effects were produced by direct contact between the eye and 1,2-dichloroethane vapor in the air. Skin lesions and benign pulmonary tumors were reported in animals exposed to liquid 1,2-dichloroethane dermally.

3.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to 1,2-dichloroethane.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or animals after dermal exposure to 1,2-dichloroethane. Dermal and ocular effects in animals dermally exposed to 1,2-dichloroethane are discussed below.

Dermal Effects. No studies were located regarding effects on the skin in humans after dermal exposure to 1,2-dichloroethane.

A single animal study was located that investigated dermal effects following direct application of 1,2-dichloroethane to the skin as a liquid. In guinea pigs, dermal exposure to unspecified amounts for 4 hours applied to the skin under a cover slip resulted in skin changes, including karyopyknosis (shrinkage of cell nuclei), perinuclear edema, spongiosis, and junctional separation (Kronevi et al. 1981); however, only one dose was tested and no control data were presented.

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to 1,2-dichloroethane.

Studies in animals reported direct-contact effects following exposure to 1,2-dichloroethane as a vapor in the air. Dogs exposed to 1,2-dichloroethane as a vapor in the air developed corneal opacity. This corneal clouding was observed in 3 dogs that died following intermittent exposure to 1,500 ppm for 6 days

(Heppel et al. 1945). Corneal opacity was not reported in other similarly exposed species studied by Heppel et al. (1945, 1946). However, lacrimation was reported in guinea pigs exposed to 1,500 ppm of 1,2-dichloroethane vapor in air intermittently for 4 days (Heppel et al. 1945).

No studies were located regarding the following health effects in humans or animals after dermal exposure to 1,2-dichloroethane:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding cancer in humans after dermal exposure to 1,2-dichloroethane.

The carcinogenicity of 1,2-dichloroethane following dermal exposure has been evaluated in mice (Van Duuren et al. 1979). In this study, a statistically significant increase ($p<0.0005$) in pulmonary papillomas was observed in mice treated with 126 mg of 1,2-dichloroethane 3 times/week for 428–576 days. These results, which indicate a significant increase in benign tumors remote from the site of application, provide suggestive or supportive evidence that 1,2-dichloroethane is carcinogenic and that it can penetrate through the skin into the circulatory system.

3.3 GENOTOXIC EFFECTS

No studies were located regarding genotoxic effects in humans after inhalation exposure to 1,2-dichloroethane. Inhalation of 1,2-dichloroethane has produced genotoxic effects in animals. Exposure to 1,000 ppm for 4 hours produced irreversible deoxyribonucleic acid (DNA) damage in mice as evidenced by single-stranded breaks in hepatocytes. This genetic damage was seen at a concentration that produced mortality in 80–100% of treated mice within 24 hours (Storer et al. 1984). A brief account of a mouse dominant lethal assay reported reduced impregnation rate, increased preimplantation loss, and increased ratio of total embryonic loss to number of corpora lutea compared to controls in female mice mated to males that had been exposed by inhalation to 200 ppm 1,2-dichloroethane for 4 hours/day for 2 weeks (Zhao et al. 1989). No effects were observed after exposure to 6.3 ppm for 2 weeks, nor at any

concentration after exposure durations of 1, 3, or 4 weeks. The reliability of the results is uncertain because of reporting deficiencies in the study design. In a study investigating the relationship between inhalation exposure to 1,2-dichloroethane and covalent binding to liver and lung DNA, female Fischer-344 rats were exposed either to 80 ppm of 1,2-dichloroethane for 4 hours ("constant-low" exposure) or 4,400 ppm for a few minutes ("peak" exposure) (Baertsch et al. 1991). The DNA covalent binding index was elevated, compared to controls, after both exposure scenarios. However, in both the liver and the lung, the effect was much greater (approximately 35 times greater) after peak exposure, suggesting that acute exposure to highly concentrated 1,2-dichloroethane may pose a greater genotoxic hazard than protracted low-level exposure. The results of this study support the hypothesis that toxicity of 1,2-dichloroethane is associated with saturation of mixed function oxidation (MFO) enzymes (see Section 3.4, Mechanisms of Action). Also consistent with this hypothesis is the fact that oral doses were more potent than comparable inhalation doses, and that a route-of-administration effect has been reported for 1,2-dichloroethane carcinogenicity.

No studies were located regarding genotoxicity in humans after oral exposure to 1,2-dichloroethane, although oral exposure has produced genotoxic effects in animals. A single oral dose of 100 mg/kg of 1,2-dichloroethane produced irreversible DNA damage in mice, as revealed by single-stranded breaks in hepatocytes (Storer et al. 1984). Hepatocytic DNA damage was also induced in female rats receiving two oral gavage doses of 1,2-dichloroethane (in corn oil) at 134 mg/kg each, but not in rats receiving two doses of 13.4 mg/kg (Kitchin and Brown 1994). A single oral dose of 150 mg/kg produced high levels of DNA binding in the liver of rats (Cheever et al. 1990). The level of binding produced was similar in rats that had previously been exposed via inhalation to 50 ppm of 1,2-dichloroethane vapor for 2 years, and in rats that had served as controls in the 2-year study.

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to 1,2-dichloroethane.

The results of *in vivo* genotoxicity studies by all routes of exposure are summarized in Table 3-3. As indicated in the table, the ability of 1,2-dichloroethane to bind DNA in rodents *in vivo* has been well established in the liver as well as in other organs such as the kidney and lung. DNA binding has been observed not only after inhalation and oral exposures, but also in rats (Banerjee 1988; Prodi et al. 1986) and mice (Banerjee 1988; Hellman and Brandt 1986; Prodi et al. 1986) administered a single intraperitoneal injection of 1,2-dichloroethane at dose levels as low as 6.35 µmol/kg (0.00635 mg/kg) (Prodi et al. 1986). Actual structural damage to DNA, in the form of single-stranded breaks and

Table 3-3. Genotoxicity of 1,2-Dichloroethane *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian assays:			
Mouse/spot test	Gene mutation	(+)	Gocke et al. 1983
Mouse bone marrow	Sister chromatid exchange	+	Giri and Hee 1988
Mouse	Micronuclei	–	Jenssen and Ramal 1980; King et al. 1979
Mouse	Micronuclei	–	Sasaki et al. 1994
Mouse, Eμ-PIM-1	Micronuclei	–	Armstrong and Galloway 1993
Mouse liver, kidney, lung, and stomach	DNA binding	+	Prodi et al. 1986
Mouse forestomach and kidney	DNA binding	+	Hellman and Brandt 1986
Mouse liver	DNA binding	+	Banerjee 1988
Rat liver, kidney, lung, and stomach	DNA binding	+	Prodi et al. 1986
Rat liver and kidney	DNA binding	+	Inskeep et al. 1986
Rat liver and lung	DNA binding	+	Baertsch et al. 1991
Rat liver	DNA binding	+	Banerjee 1988
Rat liver	DNA binding	+	Cheever et al. 1990
Mouse liver	DNA damage	+	Storer and Conolly 1983, 1985; Storer et al. 1984
Mouse liver	DNA damage	+	Taningher et al. 1991
Mouse liver, kidney, bladder, lung, brain, bone marrow	DNA damage	+	Sasaki et al. 1998
Insect assays:			
Drosophila melanogaster//somatic mutation	Gene mutation	+	Nylander et al. 1978
D. melanogaster/somatic mutation	Gene mutation	+	Romert et al. 1990
D. melanogaster/somatic mutation	Gene mutation	+	Kramers et al. 1991
D. melanogaster/somatic mutation	Gene mutation	+	Ballering et al. 1994
D. melanogaster/somatic mutation	Gene mutation	+	Vogal and Nivard 1993
D. melanogaster/sex-linked recessive	Gene mutation	+	King et al. 1979
D. melanogaster/sex-linked recessive	Gene mutation	+	Kramers et al. 1991
D. melanogaster/recessive lethal	Gene mutation	+	Ballering et al. 1993
D. melanogaster	Chromosomal recombination	(+)	Rodriguez-Arnaiz 1998
D. melanogaster/chromosome loss	Chromosomal aberration	+	Ballering et al. 1993
D. melanogaster	DNA binding	+	Fossett et al. 1995

Table 3-3. Genotoxicity of 1,2-Dichloroethane *In Vivo (continued)*

Species (test system)	End point	Results	Reference
Host-mediated assays:			
Escherichia coli K12/343/113 mouse host-mediated assay	Gene mutation	–	King et al. 1979

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acidtable 3-3

unwinding of the DNA molecule, has also been demonstrated in mice after single intraperitoneal injections of 45–360 mg/kg (Sasaki et al. 1998; Storer and Conolly 1983, 1985; Storer et al. 1984; Taningher et al. 1991). In one study, DNA binding was associated with decreased rates of DNA synthesis and transcription (Banerjee 1988). However, the results of this study are questionable. Genotoxicity assays for clastogenic effects obtained mixed results, with a positive effect on sister chromatid exchange (believed to be caused by strand breakage) in mouse bone marrow cells of mice administered a single intraperitoneal injection of up to 16 mg/kg, but no effect on micronucleus formation in mice after 14 weeks of daily gavage administrations of up to 300 mg/kg/day or in mice after a single intraperitoneal injection of between 45–400 mg/kg (Jenssen and Ramel 1980; King et al. 1979; Sasaki et al. 1994). The only *in vivo* assay for mutagenicity in mammalian cells produced only a marginal response after a single intraperitoneal injection of an unreported dose. However, there is abundant evidence that 1,2-dichloroethane produces both somatic and sex-linked recessive lethal mutations in *Drosophila melanogaster in vivo*.

The results of *in vitro* genotoxicity studies are presented in Table 3-4. The evidence from these studies overwhelmingly indicates that 1,2-dichloroethane is capable of interacting with DNA to produce genotoxic effects *in vitro*. Results were positive in assays for point mutations in human cells, animal cells, and bacteria, unscheduled DNA synthesis (i.e., DNA repair activity) in human and animal cells, DNA binding in animal cells, and mitotic segregation aberrations leading to aneuploidy in fungi. The results in bacterial mutagenicity assays suggest that 1,2-dichloroethane is a very weak, direct-acting mutagen that can be activated to a more effective species by glutathione and glutathione *S*-transferases (DeMarini and Brooks 1992). The presence of an exogenous mammalian metabolic system was not required, but increased mutagenic activity was observed in tests with a metabolic activation system supplemented with glutathione. Mutagenicity was increased in TA100 strain *Salmonella typhimurium* expressing the alpha class of human glutathione *S*-transferase via regulatable tac promoter expression, but not in bacteria expressing the pi class of human glutathione *S*-transferase (Simula et al. 1993). *S*-(Chloroethyl)-cysteine, an analog of the proposed intermediate product of the conjugation of 1,2-dichloroethane with glutathione, was a potent inducer of unscheduled DNA synthesis and micronucleus formation in mammalian cells *in vitro* (Vamvakas et al. 1988, 1989). *S*-(2-Chloroethyl)-glutathione itself was found to be a potent mutagen in *S. typhimurium*. Although it produced only intermediate levels of alkylation, the results indicate that the guanyl adduct that is formed appears to be unusually mutagenic (Humphreys et al. 1990). 1,2-Dichloroethane was found to be nonmutagenic in somatic cells and mature spermatozoa in *D. melanogaster*, further suggesting the lack of genotoxicity through a direct mechanism (Ballering et al. 1993).

Table 3-4. Genotoxicity of 1,2-Dichloroethane *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	+	+	Milman et al. 1988
S. typhimurium	Gene mutation	+	+	Barber et al. 1981
S. typhimurium	Gene mutation	+	+	Kanada and Uyeta 1978
S. typhimurium	Gene mutation	+	+	Nestmann et al. 1980
S. typhimurium	Gene mutation	+	+	Rannug et al. 1978
S. typhimurium	Gene mutation	+	+	Van Bladeren et al. 1981
S. typhimurium	Gene mutation	+	No data	Rannug and Beije 1979
S. typhimurium	Gene mutation	+	–	Cheh et al. 1980
S. typhimurium	Gene mutation	+	–	Moriya et al. 1983
S. typhimurium	Gene mutation	–	–	King et al. 1979
S. *typhimurium*	Gene mutation	No data	+	Thier et al. 1993
S. *typhimurium*	Gene mutation	No data	+	Simula et al. 1993
S. typhimurium/spot test	Gene mutation	No data	(+)	Brem et al. 1974
S. typhimurium/spot test	Gene mutation	No data	–	Buijs et al. 1984
S. typhimurium/Ara test (standard)	Gene mutation	+	–	Roldan-Arjona et al. 1991
S. typhimurium/Ara test (liquid)	Gene mutation	(+)	(+)	Roldan-Arjona et al. 1991
Escherichia coli K12/343/113	Gene mutation	–	–	King et al. 1979
E. coli WP2	Gene mutation	No data	(+)	Hemminki et al. 1980
E. coli WP2	Gene mutation	–	–	Moriya et al. 1983
E. coli Pol A	DNA damage	No data	(+)	Brem et al. 1974
Bacillus subtilis/rec-assay	DNA damage	No data	–	Kanada and Uyeta 1978

Table 3-4. Genotoxicity of 1,2-Dichloroethane *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Eukaryotic organisms:				
Fungi:				
Aspergillus nidulans	Gene mutation	No data	–	Crebelli and Carere 1988
A. nidulans	Mitotic segregation aberrations	No data	+	Crebelli et al. 1984
A. nidulans	Aneuploidy induction	No data	+	Crebelli et al. 1988
Animal cells:				
Hamster CHO/HGPRT	Gene mutation	+	(+)	Tan and Hsie 1981
Hamster Chinese SP5	Intrachromosomal	–	No data	Zhang and Jenssen 1994
Rat hepatocytes	recombination	No data	+	Williams et al. 1989
Mouse hepatocytes	Unscheduled DNA synthesis	No data	+	Milman et al. 1988
Mouse liver DNA	Unscheduled DNA synthesis	+	No data	Banerjee 1988
Calf thymus DNA	DNA binding	+	No data	Prodi et al. 1986
Salmon sperm DNA	DNA binding	+	–	Banerjee and Van Duuren 1979; Banerjee et al. 1980
	DNA binding			
Mouse BALB/c-3T3	Cell transformation	No data	–	Milmann et al. 1988
Human cells:				
Human lymphoblasts AHH-1	Gene mutation	No data	+	Crespi et al. 1985
Human lymphoblasts TK6	Gene mutation	No data	+	Crespi et al. 1985
Human lymphoblasts AHH-1	Micronuclei	No data	+	Doherty et al. 1996
Human lymphoblasts MCL-5	Micronuclei	No data	+	Doherty et al. 1996
Human lymphoblasts h2E1	Micronuclei	No data	+	Doherty et al. 1996
Human embryo epithelial-like EUE cells	Gene mutation	No data	+	Ferreri et al. 1983
Human peripheral lymphocytes	Unscheduled DNA synthesis	+	–	Perocco and Prodi 1981
Human peripheral lymphocytes	Micronuclei	–	+	Tafazoli et al. 1998
Human peripheral lymphocytes	DNA damage	–	+	Tafazoli et al. 1998

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

3.4 TOXICOKINETICS

1,2-Dichloroethane is well absorbed through the lungs following inhalation exposure, the gastrointestinal tract following oral exposure, and the skin following dermal exposure in humans. In animal studies, equilibrium blood concentrations of 1,2-dichloroethane were obtained 2–3 hours after inhalation exposure, 15–60 minutes after oral exposure, and 1–2 hours after aqueous dermal exposure. Absorption probably occurs by passive diffusion for all three routes of exposure. Upon absorption, 1,2-dichloroethane is widely distributed within the body. Experiments in animals exposed orally or by inhalation showed that the highest concentrations of 1,2-dichloroethane (7–17 times that of the blood) were found in adipose tissue. The liver and lung contained lower equilibrium levels of 1,2-dichloroethane than the blood.

1,2-Dichloroethane is readily metabolized in the body. The primary metabolic pathways for this chemical are MFO and glutathione conjugation. Oxidation products include chloroacetaldehyde, 2-chloroethanol, and 2-chloroacetic acid. MFO metabolism of 1,2-dichloroethane appears to be saturable at oral gavage doses $25 mg/kg and inhalation concentrations of $150 ppm (. 500 mg/kg), both of which correspond to blood levels of 5–10 µg/mL. Glutathione conjugation becomes relatively more important at larger doses, and increased metabolism by this pathway may be responsible for the toxic effects noted at these high doses.

Excretion of 1,2-dichloroethane and metabolites is rapid; in animal studies, excretion was essentially complete 48 hours after acute exposure. Following inhalation exposure to labeled 1,2-dichloroethane, excretion of 1,2-dichloroethane was primarily in the form of metabolites (thiodiglycolic acid and thiodiglycolic acid sulfoxide) in the urine (84%), and as carbon dioxide (CO_2) in the exhaled air (7%). Following oral exposure to labeled 1,2-dichloroethane, the amount of radioactivity excreted by these routes was reduced, and a large percentage of the dose (29%) was excreted as unchanged 1,2-dichloroethane in the exhaled air. The increased exhalation of unchanged 1,2-dichloroethane may reflect the saturation of biotransformation enzymes.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

1,2-Dichloroethane is readily absorbed through the lungs following inhalation exposure in both humans and experimental animals. This is expected, based on 1,2-dichloroethane's high vapor pressure and high serum/air partition coefficient. Thus, absorption occurs most likely via passive diffusion across alveolar membranes. Nursing women exposed to 15.6 ppm of 1,2-dichloroethane in the workplace air (with concurrent dermal exposure) accumulated the chemical in breast milk (Urusova 1953). The concentration of the chemical in milk gradually increased, reaching the maximum level 1 hour after work ended, although the validity of the results could not be assessed because of a lack of sufficient detail in reported methods and because the sample size was not provided. EPA (1980a) also found 1,2-dichloroethane in the milk of lactating women. These results indicate that 1,2-dichloroethane is absorbed through the lungs by humans and accumulates (because of its high lipid-water partition coefficient) in the breast milk of nursing women. Concurrent levels of 1,2-dichloroethane in blood were not measured (EPA 1980a; Urusova 1953).

Nouchi et al. (1984) reported a fatal case of 1,2-dichloroethane poisoning in a man exposed to 1,2-dichloroethane vapors for approximately 30 minutes in an enclosed space (concentration in air not specified), providing further evidence that this chemical is readily absorbed through the lungs by humans. However, adverse effects were seen at 20 hours postexposure, prompting the authors to suggest that the formation of reactive metabolites is a necessary first step in the expression of 1,2-dichloroethane-induced toxicity. An alternative explanation is that the 1,2-dichloroethane is, in part, slowly released from adipose tissue or other compartments after an initial rapid release (see Section 3.4.3)

The rapid absorption of 1,2-dichloroethane following inhalation exposure has also been demonstrated in experimental animals. Reitz et al. (1980, 1982) found that peak blood levels were constant 1–2 hours after the onset of a 6-hour inhalation exposure to 150 ppm of 1,2-dichloroethane in rats. The plateau concentration in blood was approximately 8 μg/mL and was reached within 2 hours. Similar results were obtained by Spreafico et al. (1980) at inhalation exposures of 50 ppm of 1,2-dichloroethane. However, at 250 ppm of 1,2-dichloroethane, equilibrium was not achieved until 3 hours from the start of exposure. It is likely that as the concentration of inspired 1,2-dichloroethane increases, the time required to reach an equilibrium concentration of 1,2-dichloroethane in the blood also increases. In rats that had been exposed to 1,2-dichloroethane vapor (50 ppm) intermittently for 2 years, blood levels of 1,2-dichloroethane

15 minutes after the end of a 7-hour exposure to 50 ppm were 0.26–0.28 µg/mL (Cheever et al. 1990). Blood levels were not increased, but rather only slightly reduced after an additional 2 hours, which suggests that equilibrium had been reached during the exposure period.

3.4.1.2 Oral Exposure

No studies were located regarding absorption in humans following oral exposure to 1,2-dichloroethane. However, it can be inferred from case studies, which described toxic effects (including death) subsequent to accidental (Hueper and Smith 1935) or intentional (Lochhead and Close 1951; Yodaiken and Babcock 1973) ingestion of 1,2-dichloroethane by humans, that 1,2-dichloroethane is rapidly absorbed into the systemic circulation following exposure by the oral route. 1,2-Dichloroethane is lipophilic and is expected, therefore, to be absorbed largely via passive diffusion across the mucosal membranes of the gastrointestinal tract.

Studies in experimental animals indicate that the oral absorption of 1,2-dichloroethane is rapid, complete, and essentially linear (Reitz et al. 1980, 1982; Spreafico et al. 1980). Reitz et al. (1982) reported that peak blood levels of 1,2-dichloroethane were reached within 15 minutes after oral administration of 150 mg/kg by gavage in corn oil to male Osborne-Mendel rats, attesting to the rapid nature of oral absorption. These investigators reported complete recovery of orally administered radioactivity (from [^{14}C]-1,2-dichloroethane) in exhaled air, urine, and carcass, thereby demonstrating that absorption of 1,2-dichloroethane from the gastrointestinal tract of rats is virtually complete (Reitz et al. 1980). The percentage of recovered radioactivity found in the feces following inhalation or oral exposure to [^{14}C]-1,2-dichloroethane was 1.7–2.1%; 7.0–7.7% of the recovered dose was found in the expired air following exposure by either route (Reitz et al. 1980). This implies that at least 90% of the inhaled or orally administered 1,2-dichloroethane was absorbed.

Data reported by Spreafico et al. (1980) supported the observation that absorption of 1,2-dichloroethane is rapid and complete. In Sprague-Dawley rats, peak blood levels were achieved within 30–60 minutes of oral administration at doses of 25, 50, and 150 mg/kg in corn oil. One-half of the low dose was absorbed within 3.3 minutes, and one-half of the high dose was absorbed within 6.4 minutes (Spreafico et al. 1980). Peak blood levels achieved were proportional to the dose administered, thus providing evidence that 1,2-dichloroethane is absorbed by passive transport across the gastrointestinal tract. Furthermore, comparison of blood levels attained after intravenous (i.e., reflective of 100% absorption) and oral

administration of 1,2-dichloroethane in rats indicates that oral absorption is 100%, if first-pass effects through the liver and lung are taken into consideration (Spreafico et al. 1980).

The vehicle used in oral administration studies appears to play a role in the time course of absorption. Withey et al. (1983) found that 1,2-dichloroethane is absorbed more readily by the gastrointestinal tract when administered in water than in corn oil. Peak blood concentrations of 1,2-dichloroethane were about four times higher following oral administration in water than when given in corn oil. This may relate to higher solubility vehicles regarding the absorption of xenobiotics. Furthermore, the time taken to reach peak levels was approximately three times longer when administered in corn oil, compared to water. This may have important implications with regard to human exposure to 1,2-dichloroethane. Since animal data and the available information in humans indicate that oral absorption of 1,2-dichloroethane in aqueous solutions is rapid and complete, ingestion of water contaminated with high levels of 1,2-dichloroethane is of particular concern and could result in adverse health effects in humans. However, no unequivocal information was available concerning health effects in humans after long-term exposure to low levels of 1,2-dichloroethane in drinking water.

3.4.1.3 Dermal Exposure

Urusova (1953) reported a gradual increase in the concentration of 1,2-dichloroethane in the breast milk of nursing women following both dermal and inhalation exposure to 1,2-dichloroethane at the workplace. Maximum levels were reached within 1 hour (2.8 mg/100 mL of milk) after skin contact and decreased over time. Eighteen hours later, the concentration of 1,2-dichloroethane in milk ranged between 0.195 and 0.63 mg/100 mL of milk. The findings of Urusova (1953) indicate that percutaneous absorption via contact with contaminated water or the chemical itself may be a significant route of exposure to 1,2-dichloroethane in humans. No details of analytical methodology were reported, and the sample size was not provided, and thus, the validity of these results cannot be assessed.

Studies in animals have shown that 1,2-dichloroethane is well absorbed through the skin following dermal exposure. Male rats exposed to 2 mL of 1,2-dichloroethane under cover on a shaved area of the back had blood 1,2-dichloroethane levels of 25 µg/mL after 30 minutes (Morgan et al. 1991). After 24 hours, blood levels were 135 µg/mL and a total of 1.08 mL had been absorbed. The continued build-up of blood levels throughout the 24-hour exposure period shows that the rate of absorption exceeded that of distribution and elimination throughout this entire period. When the experiment was repeated using solutions of 1,2-dichloroethane in water, blood levels peaked after 1–2 hours (at concentrations of

0.35–1.4 µg/mL, depending on degree of saturation of the applied solution) and then declined to control levels within 24 hours. Analysis of the aqueous solutions remaining in the exposure chamber after 24 hours showed that they contained <1% of the initial 1,2-dichloroethane concentration. This result suggests that 1,2-dichloroethane in water was rapidly and completely absorbed from solution, thus allowing elimination processes to reduce blood concentration to control levels within the 24-hour exposure period. 1,2-Dichloroethane was among the best absorbed of the 14 volatile organic compounds tested in this experiment.

Supporting data for the time course of absorption following neat exposure were obtained by Jakobson et al. (1982), who studied the dermal absorption of 1,2-dichloroethane in anesthetized guinea pigs. Blood concentrations rose rapidly during the first half-hour after application, followed by steadily increasing blood levels throughout the 12-hour exposure period. Tsuruta (1975) estimated the rate of percutaneous absorption of 1,2-dichloroethane. After a 15-minute exposure, the absorption rate through the abdominal skin of mice was 480 nmol/minute/cm^2. In contrast to the results of Morgan et al. (1991), comparisons of this absorption rate with those of other chlorinated hydrocarbons tested in the same study did not support the conclusion that 1,2-dichloroethane is among the more rapidly absorbed of these chemicals.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

1,2-Dichloroethane was detected in the breath (14.3 ppm) and breast milk (0.54–0.64 mg % [per 100 mL]) of nursing mothers 1 hour after leaving factory premises containing 15.6 ppm 1,2-dichloroethane in the air (Urusova 1953). This observation suggests a rapid distribution of 1,2-dichloroethane in humans following inhalation exposure.

The distribution of 1,2-dichloroethane in rats following a 6-hour inhalation exposure to 50 or 250 ppm occurred readily throughout body tissues; levels achieved in tissues were dose-dependent (Spreafico et al. 1980). The investigators measured 1,2-dichloroethane in blood, liver, lung, and fat, and found that blood and tissue levels reached equilibrium by 2 hours after exposure to 50 ppm and 3 hours after exposure to 250 ppm. Concentrations of 1,2-dichloroethane in liver and lung were lower than those in blood. The highest concentration of 1,2-dichloroethane was found in fat (8–9 times that seen in blood). 1,2-Dichloroethane was found in maternal blood (83.6±20.2 mg %), placental tissue (43.0±9.6 mg %), amniotic fluid (55.5±11.1 mg %), and fetal tissue (50.6±11.5 mg %) after inhalation exposure of female

rats to 247±10 ppm 1,2-dichloroethane during pregnancy (Vozovaya 1977), but the reliability of the data is unclear. The geometric mean concentration of 1,2-dichloroethane in maternal blood and in fetuses of rats that inhaled 150–2,000 ppm for 5 hours increased linearly with increasing exposure level (Withey and Karpinski 1985), indicating transplacental distribution of 1,2-dichloroethane. The slope and intercept of the relation between fetal concentration of 1,2-dichloroethane (µg/g) and exposure level were 0.035 and -3.95, respectively, and for concentration in maternal blood (µg/g), they were 0.092 and -10.4, respectively. However, details of the methods used to detect 1,2-dichloroethane and quantify its concentration in tissues were not provided in Withey and Karpinski (1985), so the validity of the results cannot be confirmed.

3.4.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to 1,2-dichloroethane. However, the wide variety of effects noted in humans following oral exposure suggest a wide distribution.

1,2-Dichloroethane was distributed readily throughout the body following oral administration of single doses to rats (Spreafico et al. 1980). As was seen following inhalation exposure, peak tissue levels were dose-dependent. Spreafico et al. (1980) reported that 1,2-dichloroethane absorbed through the gastrointestinal tract reached peak concentrations in the liver within 10 minutes. Again, equilibrium levels in liver and lung (achieved by 2 hours postexposure) were lower than in blood, while levels in fat were 7–17 times greater than in blood. This difference in tissue levels decreased with increasing dose. Thus, there is little difference between oral and inhalation exposure with regard to tissue distribution in animals, and specific target organ toxicity cannot be explained by differential distribution of 1,2-dichloroethane.

Payan et al. (1995) evaluated [^{14}C]-1,2-dichloroethane distribution in maternal rats following a single bolus dose of approximately 160 mg/kg on gestation day 12. At 1 hour after exposure, 50% of the orally administered dose was in gastrointestinal tract tissues, falling to 0.2% of the administered dose by 48 hours after exposure, while less than 1% was accounted for in the feces. Aside from the absorptive tissues, the liver and kidney accounted for most of the distributed radioactivity throughout the 48-hour postexposure observation period, although adipose tissue and brain and spinal cord tissues, possible sites of accumulation, were not included in the evaluation. The highest tissue concentrations were found in the liver, ovary, and kidney. Transplacental distribution of radiocarbon was demonstrated by the presence of radioactivity in the developing conceptus at 1 hour postexposure, with the highest amount in the

conceptus (0.057% of administered dose) occurring at approximately 4 hours postexposure. At 48 hours postexposure, most of the residual radioactivity was located in the liver (0.215% of administered dose). When 160 mg/kg was administered on gestation day 18, the pattern of distribution was similar, except greater accumulation occurred in the developing fetus and placenta. At 48 hours postexposure (the 20th day of gestation), the majority of residual radioactivity burden was located in the fetus (0.167% of administered dose) and the liver (0.156% of administered dose).

Spreafico et al. (1980) studied the distribution of 1,2-dichloroethane in rats following repeated oral administration (11 daily doses). They demonstrated that there was no difference between blood or tissue levels following either single or repeated exposure. This finding suggests that bioaccumulation of 1,2-dichloroethane does not occur with repeated oral exposure.

3.4.2.3 Dermal Exposure

1,2-Dichloroethane was detected in the breast milk of nursing mothers following dermal exposure (with probable concurrent inhalation exposure) to liquid 1,2-dichloroethane at the workplace (Urusova 1953). The concentration in milk gradually increased, with the maximum level (2.8 mg %) reached 1 hour after work ended. Eighteen hours later, the levels in milk ranged from 0.195 to 0.63 mg %. This study did not report the dermal exposure concentration of 1,2-dichloroethane. Because of the lack of details on methodology, the validity of these findings cannot be assessed.

No studies regarding distribution in animals following dermal exposure to 1,2-dichloroethane were located. Since the tissue distribution of this chemical did not appear to be route-dependent after either inhalation or oral exposure, and since it is well absorbed through the skin, the distribution pattern of 1,2-dichloroethane following percutaneous application may possibly resemble that observed following exposure via other routes.

3.4.2.4 Other Routes of Exposure

No studies were located regarding distribution in humans after parenteral exposure to 1,2-dichloroethane.

Mice exposed to radiolabeled 1,2-dichloroethane by a single intravenous injection had high levels of tightly bound radioactivity in the nasal mucosa and tracheo-bronchial epithelium within 1 minute of exposure; these levels persisted throughout the 4-day observation period (Brittebo et al. 1989). Lower

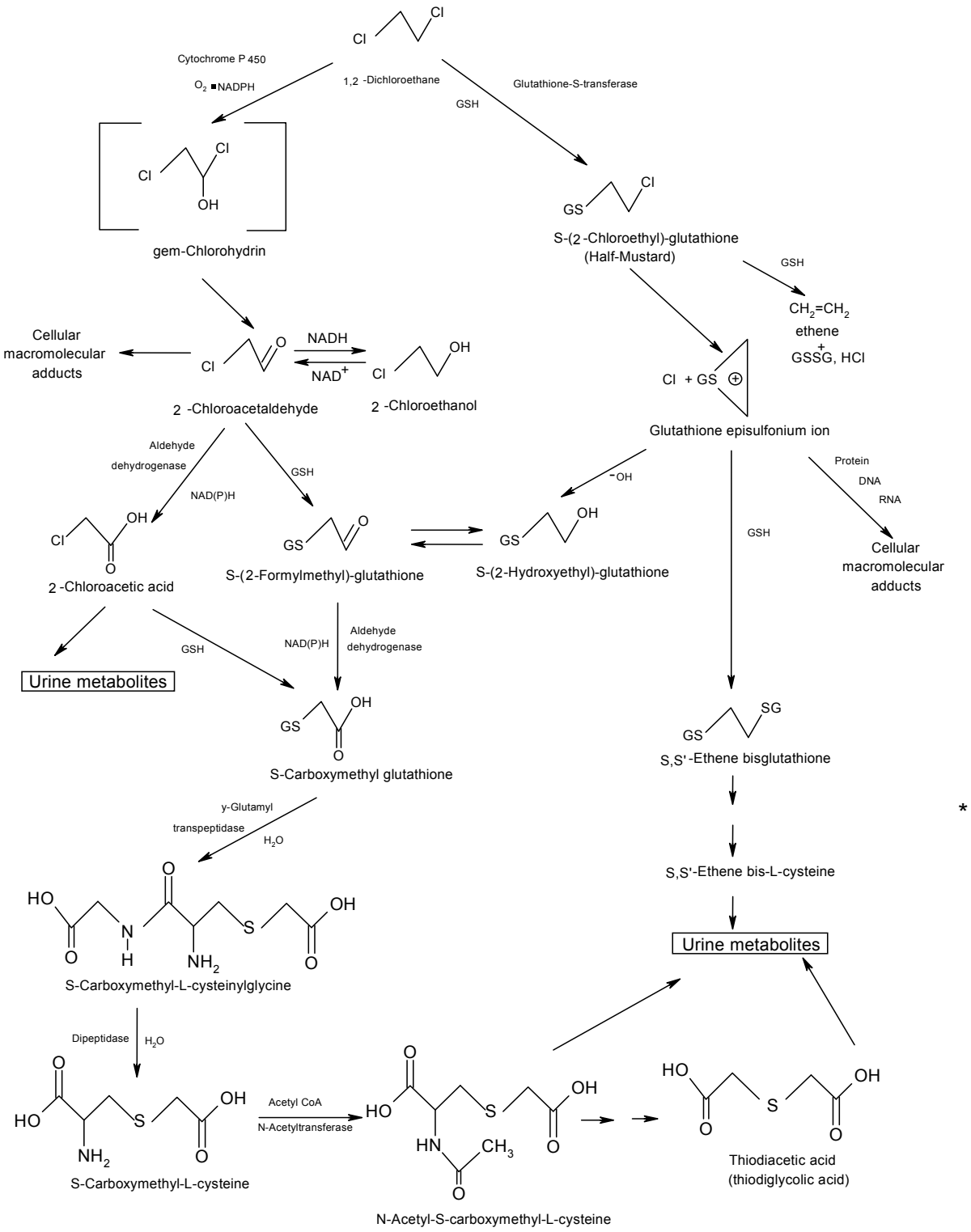
levels of radioactivity were bound to epithelia of the upper alimentary tract, eyelid, and vagina, as well as the liver, kidney, adrenal cortex, and submaxillary gland. The bound radioactivity was considered to represent nonvolatile reactive metabolites formed in the tissues where it was found. A study of tissue kinetics of 1,2-dichloroethane in rats after a single intravenous dose of 15 mg/kg reported preferential initial distribution to fat (Withey and Collins 1980) and first-order elimination from each tissue studied (except blood). The estimated initial concentration in fat was 36.9 µg/g, while for other soft tissues (including heart, lung, liver, spleen, kidney, and brain), the initial concentrations were relatively uniform, with estimates ranging from 4.2 to 9.2 µg/g. The study also showed that distributed 1,2-dichloroethane remained in fat longer than in other soft tissues, as indicated by a lower estimated elimination coefficient in fat (0.0088 min^{-1}) relative to other tissues (ranged from 0.0226 to 0.0514 $minute^{-1}$).

3.4.3 Metabolism

No studies regarding metabolism in humans following inhalation, oral, or dermal exposure to 1,2-dichloroethane were located. The biotransformation of 1,2-dichloroethane has been studied extensively in rats and mice both *in vivo* and *in vitro*. Proposed metabolic pathways for 1,2-dichloroethane are shown in Figure 3-3. The results of the *in vivo* studies indicate that 1,2-dichloroethane is readily metabolized in the body, the primary route of biotransformation involves conjugation with glutathione to yield nonvolatile urinary metabolites, and the enzymes involved in the biotransformation of 1,2-dichloroethane are saturable at approximately 25 mg/kg/day (gavage) and 150 ppm (inhalation) (D'Souza et al. 1988; Reitz et al. 1982). Metabolic saturation appears to occur sooner after oral (gavage) administration than after inhalation exposure. This will be discussed further below. A proposed physiological pharmacokinetic model explains the route-of-exposure difference in quantifying the amount of 1,2-dichloroethane-glutathione conjugate produced in target organs after oral and inhalation exposures (D'Souza et al. 1987, 1988).

No studies were located regarding metabolism specifically in children. However, the expression of certain enzymes is known to be developmentally regulated. An N-acetyltransferase (NAT) is thought to be involved in 1,2-dichloroethane metabolism at a step subsequent to a glutathione (GSH) conjugation (see Figure 3-3). There are two NATs (NAT1 and NAT2) that are expressed in humans (Parkinson 1996) and one, NAT2, is known to be developmentally regulated (Leeder and Kearns 1997). Some NAT2 activity is present in the fetus at 16 weeks. Activity is low in virtually 100% of infants, and reaches adult activity at 1 to 3 years of age (Leeder and Kearns 1997).

Figure 3-3. Proposed Pathways for 1,2-Dichloroethane Metabolism*



*

Derived from NTP 1991a

3.4.3.1 Inhalation Exposure

Reitz et al. (1982) studied the metabolism of 1,2-dichloroethane in male rats following a 6-hour exposure to 150 ppm of [^{14}C]-1,2-dichloroethane. The exact metabolic pathways were not determined, but an observed depression of hepatic nonprotein sulfhydryl groups may indicate that glutathione plays a major role in the metabolism of 1,2-dichloroethane following inhalation exposure. Saturation of biotransformation enzymes was not apparent at this dose since 84% of the administered ^{14}C was recovered as urinary metabolites and only 2% of the administered ^{14}C was recovered as parent compound in the expired air. However, the data of Spreafico et al. (1980) suggest that saturation does occur after inhalation exposure in rats, since peak blood levels of 1,2-dichloroethane rose 22-fold when the exposure concentration was increased from 50 to 250 ppm. Based on the data of these 2 groups of investigators, it appears that saturation of 1,2-dichloroethane metabolism occurs when blood levels reach 5–10 µg/mL blood or after exposure to 150–250 ppm 1,2-dichloroethane. When blood concentrations of 1,2-dichloroethane exceed these levels (i.e., at exposure concentrations $150 ppm), manifestations of toxicity became more apparent. For example, Maltoni et al. (1980) reported that most of the toxicity associated with inhalation exposure to 250 ppm 1,2-dichloroethane in rats and mice was alleviated when exposure levels were reduced to 150 ppm, and no treatment-related effects were noted at 50 ppm. These findings suggest that 1,2-dichloroethane-induced toxicity occurs once a threshold blood level has been exceeded.

3.4.3.2 Oral Exposure

Reitz et al. (1982) also studied the metabolism of 1,2-dichloroethane following the administration of single oral doses of 150 mg/kg [^{14}C]-1,2-dichloroethane. Again, the exact metabolic pathways were not determined, but the observation that hepatic nonprotein sulfhydryl groups were depressed indicated that glutathione may also play a major role in the metabolism of 1,2-dichloroethane following oral exposure. Saturation of biotransformation enzymes was apparent at this dose since only 60% of the administered radiolabel was recovered as urinary metabolites, and 29% of the administered radiolabel was associated with unchanged parent compound in the expired air. As with inhalation, it appeared that saturation of 1,2-dichloroethane metabolism occurred when blood levels reached 5–10 µg/mL blood or after administration of $25 mg/kg 1,2-dichloroethane (D'Souza et al.1988; Reitz et al. 1982; Spreafico et al. 1980). This blood threshold level again correlated with observed toxicity in animal studies (NCI 1978), as discussed above.

Although the saturable pathways appear to be the same for both oral and inhalation exposure, oral administration of 1,2-dichloroethane by gavage results in saturation at lower administered doses than inhalation exposure. Reitz et al. (1982) demonstrated that administration of 150 mg/kg 1,2-dichloroethane by gavage resulted in a 1.3-fold higher absolute dose to the animals than 150 ppm via inhalation (which is approximately equal to 502 mg/kg). Gavage administration produced approximately twice as much total metabolite as inhalation, and peak levels of 1,2-dichloroethane in blood were almost five times higher following gavage versus inhalation. Gavage administration may not represent typical oral exposure in humans. Gavage administration results in large bolus doses absorbed at one time thereby leading to spikes in blood levels and a more pronounced expression of toxicity. Oral exposure to 1,2-dichloroethane by humans will most likely occur via ingestion of contaminated drinking water in small doses spread out over the course of a day. In such instances, biotransformation processes will probably not become saturated; thus, the risk for adverse effects is not as high as would be predicted from gavage administration of equivalent doses.

3.4.3.3 Intraperitoneal Exposure

In female albino mice given 1,2-dichloroethane intraperitoneally, the metabolism of 1,2-dichloroethane appeared to be initiated by hydrolytic dehalogenation followed by reduction to yield 2-chloroethanol (Yllner 1971b). This was then converted to 2-chloroacetic acid by microsomal oxidation. Final metabolites identified in the urine of these animals in percent radioactivity recovered included *S*-carboxymethyl-L-cysteine (44–46% free; 0.5–5% conjugated), thiodiacetic acid (33–34%), *S,S'*-ethylene-*bis*-cysteine (1.0%), which are indicative of glutathione conjugation, in addition to chloroacetic acid (6–23%) and 2-chloroethanol (0–0.8%) (see Figure 3-3).

3.4.3.4 Other Routes of Exposure

The pathways of 1,2-dichloroethane metabolism have been elucidated primarily by *in vitro* studies in isolated rat hepatic microsomes.

In one *in vitro* study, 1,2-dichloroethane was metabolized mainly to chloroacetaldehyde by hepatic nuclear cytochrome P-450 (Casciola and Ivanetich 1984). Guengerich et al. (1980) proposed a pathway involving microsomal cytochrome P-450 (in the presence of oxygen and nicotinamide adenine dinucleotide phosphate [reduced form] [NADPH]) and MFO to explain the production of chloroacetaldehyde. 1,2-Dichloroethane undergoes oxygen insertion to yield an unstable chlorohydrin,

which spontaneously dechlorinates to form 2-chloroacetaldehyde that can react with macromolecules. 2-Chloroacetaldehyde can also be reduced to chloroethanol or be further oxidized to chloroacetic acid. Guengerich et al. (1991) demonstrated that cytochrome P-450 2E1 is the primary oxidation catalyst of 1,2-dichloroethane in humans.

Conjugation of 1,2-dichloroethane with glutathione is proposed to be a major metabolic pathway *in vivo* (Yllner 1971b); this has been confirmed by the *in vitro* studies of Livesey and Anders (1979), Anders and Livesey (1980), and Jean and Reed (1989). This pathway is outlined on the right side of Figure 3-3. The depletion of hepatic glutathione by 1,2-dichloroethane has been demonstrated *in vitro* (Albano et al. 1984). Johnson (1967) demonstrated that, *in vitro*, conjugation of 2-chloroacetic acid with glutathione also proceeded by a nonenzymatic process, yielding *S*-carboxymethylglutathione. This compound subsequently degraded to yield glycine, glutamic acid, and *S*-carboxymethylcysteine. *S*-carboxymethylcysteine may then be further oxidized to thiodiglycolic acid. Both *S*-carboxymethylcysteine and thiodiglycolic acid were found as urinary metabolites in rats and mice given 1,2-dichloroethane *in vivo* (Spreafico et al. 1980; Yllner 1971b). This scheme is also supported by studies with 1,2-dibromoethane (Nachtomi et al. 1966; Van Bladeren 1983).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Women inhaling approximately 15.6 ppm 1,2-dichloroethane present in the workplace air eliminated the compound unchanged in the expired air. Similar observations were also reported in women exposed via dermal contact to liquid 1,2-dichloroethane. In both cases, the amount of 1,2-dichloroethane in the expired air was greater immediately following exposure and decreased gradually with time (Urusova 1953).

Elimination of 1,2-dichloroethane following inhalation exposure in rats occurred primarily via the excretion of soluble metabolites and unchanged parent compound in the urine and carbon dioxide in the expired air (Reitz et al. 1982; Spreafico et al. 1980). Urinary metabolites accounted for 84% of the absorbed dose, unchanged fecal 1,2-dichloroethane accounted for 2%, and carbon dioxide accounted for 7% of the absorbed dose following the inhalation of 150 ppm by rats (Reitz et al. 1982). The primary urinary metabolites identified in rats following inhalation exposure were thiodiacetic acid (70%) and thiodiacetic acid sulfoxide (26–28%). The rapidity of elimination is demonstrated by the fact that a few

hours after exposure, 1,2-dichloroethane was not detected in blood and was detected only to a small extent 48 hours after exposure in various tissues (liver, kidney, lung, spleen, forestomach, stomach, carcass) (Reitz et al. 1982).

Spreafico et al. (1980) studied the kinetics of 1,2-dichloroethane excretion in rats following inhalation exposure of 50 or 250 ppm 1,2-dichloroethane for 5 hours. They determined that elimination was monophasic with the half-times of 12.7 and 22 minutes at 50 and 250 ppm exposure, respectively. The disappearance of 1,2-dichloroethane was dose-dependent since the percentage of parent compound recovered in the expired air increased exponentially with dose. This was presumably a reflection of the saturable metabolic processes. Spreafico et al. (1980) also determined that elimination of 1,2-dichloroethane from adipose tissue was slower than elimination of 1,2-dichloroethane from the blood, liver, and lung.

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to 1,2-dichloroethane.

Elimination of 1,2-dichloroethane following oral administration in rats was also rapid and occurred primarily via excretion of soluble metabolites in the urine, and unchanged parent compound and carbon dioxide in the expired air (Mitoma et al. 1985; Payan et al. 1993; Reitz et al. 1982; Spreafico et al. 1980). Reitz et al. (1982) conducted a complete ^{14}C-balance study in male Osborne-Mendel rats and found that urinary metabolites accounted for 60% of the radioactivity administered as a single oral dose of 150 mg ^{14}C-1,2-dichloroethane/kg body weight. Unchanged 1,2-dichloroethane in the breath accounted for 29% and carbon dioxide in the breath accounted for 5% of the administered radioactivity. The remaining 6% of the administered radioactivity was recovered in the carcass, feces, and cage washes. The primary urinary metabolites identified were the same as those seen following inhalation exposure—thiodiacetic acid (70%) and thiodiacetic acid sulfoxide (26–28%). Elimination of 1,2-dichloroethane was 96% complete within 48 hours. The results were similar in rats given a single gavage dose of 150 mg/kg following 2 years of intermittent inhalation exposure to 50 ppm of 1,2-dichloroethane (Cheever et al. 1990).

Mitoma et al. (1985) studied the elimination of single gavage doses of ^{14}C-labeled 1,2-dichloroethane from rats and mice (doses of 100 and 150 mg/kg, respectively, in corn oil) after pretreatment with unlabeled compound 5 days per week for 4 weeks. At 48 hours after administration of the radiolabeled

compound, expired volatile metabolites, CO_2, excreta (feces and urine), and the carcass accounted for approximately 11.5, 8.2, 69.5, and 7% of administered radioactivity in rats, and 7.7, 18.2, 81.9, and 2.4% of the administered dose in mice.

Spreafico et al. (1980) studied the kinetics of 1,2-dichloroethane excretion in rats following the oral administration of 50 mg/kg 1,2-dichloroethane (in corn oil), and found that kinetics were best described by a two-compartment model. Withey et al. (1983) reported that administration in water resulted in a shorter elimination half-time than administration in vegetable oil. Reitz et al. (1982) also reported a two-compartment model of elimination following the gavage administration of 150 mg/kg 1,2-dichloroethane. The initial elimination phase had a half-time of .90 minutes, but elimination became more rapid when blood levels fell to 5–10 µg/mL, characterized by a half-life of approximately 20–30 minutes. This is in contrast, however, to what was observed following inhalation exposure. Spreafico et al. (1980) suggested that the oral profile represented both an absorption-distribution phase and an elimination phase, whereas the inhalation profile reflected only elimination. This elimination of 1,2-dichloroethane was also dose-dependent following oral administration in rats, as the percentage of parent compound recovered in the expired air increased exponentially with dose. Again, this is a reflection of saturable metabolic processes. The rate of elimination from adipose tissue was similar to that from blood and other tissues, in contrast to the results for inhalation exposure.

These results indicate that 1,2-dichloroethane will most likely not accumulate in nonlipid components of the human body following repeated exposure by any route, as elimination of the compound is rapid and complete. Available data also suggest that 1,2-dichloroethane is not particularly persistent in adipose tissue following oral exposure (Spreafico et al. 1980), but it may accumulate to some extent in adipose tissue after inhalation exposure (Spreafico et al. 1980) and/or in breast milk of nursing women (Urusova 1953).

3.4.4.3 Dermal Exposure

1,2-Dichloroethane was eliminated unchanged in the expired air following dermal exposure of nursing mothers to liquid 1,2-dichloroethane in the workplace (Urusova 1953). The amount of 1,2-dichloroethane in the expired air was greatest immediately after skin contact and gradually decreased with time.

No studies were located regarding excretion in animals after dermal exposure to 1,2-dichloroethane.

3.4.4.4 Other Routes of Exposure

Studies conducted in animals in which 1,2-dichloroethane was administered via other routes (e.g., intraperitoneal or intravenous) support the findings of the studies discussed above; excretion of 1,2-dichloroethane via urine and expired air was rapid and complete, and the route of excretion as well as the form of the chemical excreted were dose-dependent (Spreafico et al. 1980; Yllner 1971b).

Estimates of an elimination constant (k_e) for 1,2-dichloroethane were similar between two- and three-compartment pharmacokinetic models fitted to a time-series of blood concentration data that were obtained from rats given single intravenous doses (Withey and Collins 1980). The k_e values for elimination from blood were roughly inversely related to dose; mean values of 0.143, 0.122, 0.091, 0.096, or 0.097 were obtained at dose levels of 3, 6, 9, 12, or 15 mg/kg, respectively.

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

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

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen 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.

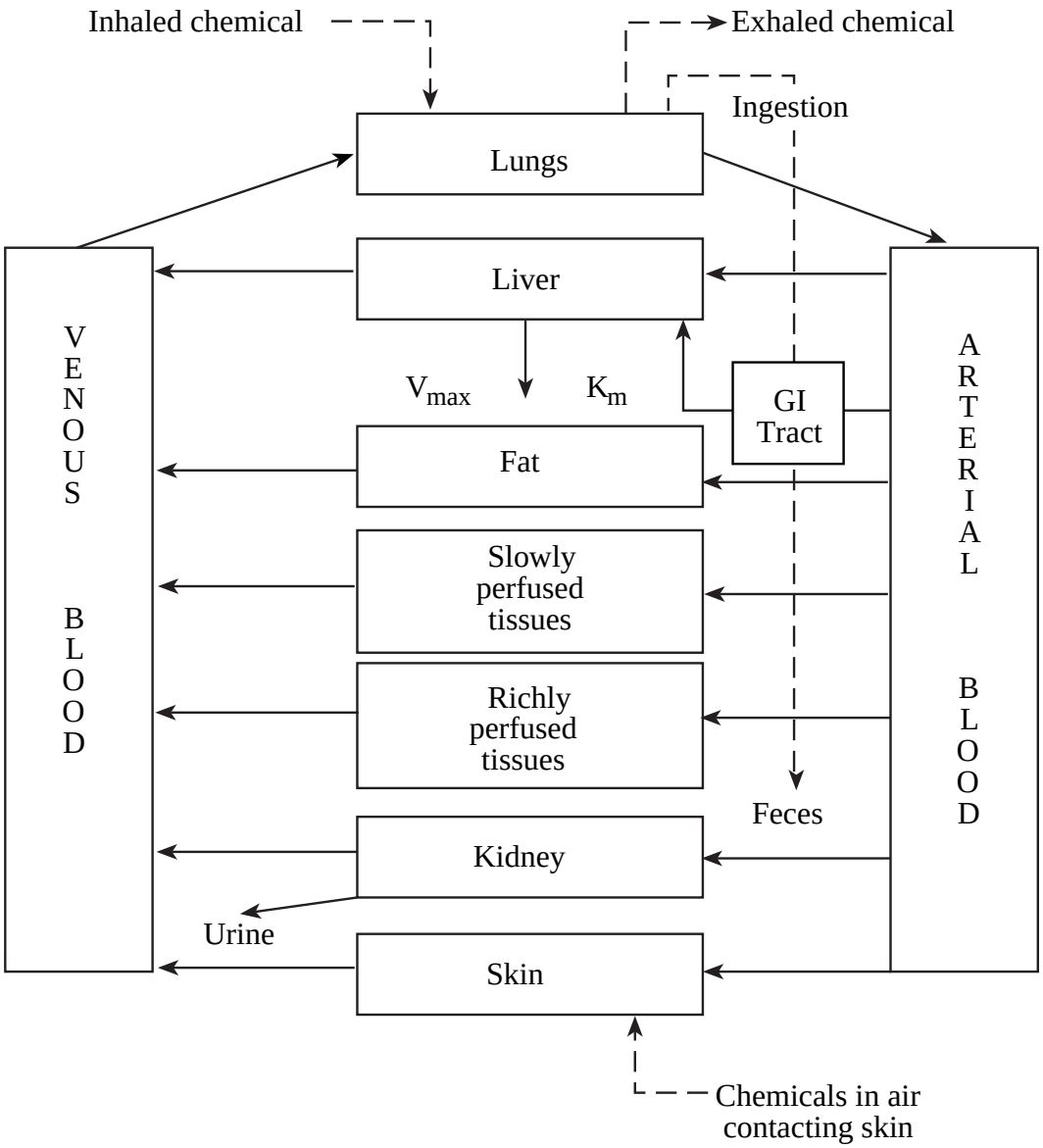
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically 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 3-4 shows a conceptualized representation of a PBPK model.

A PBPK model has been developed that quantitates the amount of 1,2-dichloroethane and its metabolites that reach the blood and target tissues following different exposure routes (D'Souza et al. 1987, 1988). As discussed in Section 3.4.3, 1,2-dichloroethane is metabolized by a saturable oxidation pathway and direct conjugation with glutathione. The model predicts that inhalation exposures to 1,2-dichloroethane produce less glutathione-conjugate metabolites in the liver and lung of rats than equivalent oral exposures. This prediction offers a possible explanation for why 1,2-dichloroethane is carcinogenic in rats by the oral route (NCI 1978), but not following inhalation exposures (Maltoni et al. 1980). This may have important implications for extrapolating cancer risk from high doses (above MFO saturation) to environmental exposures (below MFO saturation). The PBPK model may also be useful for extrapolating toxicity data

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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.

from animals to humans because the level of glutathione in the liver appears to modulate the toxic effects of 1,2-dichloroethane (see discussion in Section 3.5). However, this model needs to be tested and validated.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

The physical properties of 1,2-dichloroethane, particularly its lipophilic nature, high vapor pressure, and high serum/air partition coefficient, suggest that it is likely to be absorbed across the alveolar membranes of the lung, mucosal membranes of the gastrointestinal tract, and the skin by passive diffusion. Once in the body, it is widely distributed, with the greatest amounts accumulating in the more lipophilic tissues; this probably also occurs by passive diffusion.

There is compelling evidence that the toxicity and carcinogenicity of 1,2-dichloroethane are associated with its metabolism to active intermediates. Studies in rats and mice indicate that 1,2-dichloroethane is metabolized to 2-chloroacetaldehyde, *S*-(2-chloroethyl)glutathione, and other putative reactive intermediates capable of binding covalently to cellular macromolecules (Fabricant and Chalmers 1980; Jean and Reed 1989). The ability of a chemical to bind covalently to cellular macromolecules is often correlated with the induction of toxic and carcinogenic effects. In addition, 1,2-dichloroethane has been shown to promote lipid peroxidation *in vitro* (Sano and Tappel 1990; Tse et al. 1990). Lipid peroxidation is also associated with tissue damage. The lag time between inhalation exposure and onset of effects reported by Nouchi et al. (1984) in an occupationally exposed 51-year-old male may have been a reflection, in part, of the time required to metabolize 1,2-dichloroethane to active intermediates.

The level of glutathione present in the liver appears to modulate effects of 1,2-dichloroethane in animals. Glutathione is believed to be heavily involved in the biotransformation of 1,2-dichloroethane (Anders and Livesey 1980; Yllner 1971b). The metabolic pathway of 1,2-dichloroethane is linear at low doses, but at higher concentrations, as the P-450 enzymes become saturated, the amount of glutathione conjugate produced rises disproportionately with increasing administered dose; at very high doses, the GSH pathway is also saturated, and the glutathione conjugate produced declines disproportionately with increasing dose (D'Souza et al. 1987). It has been suggested that 1,2-dichloroethane-induced toxicity occurs when the biotransformation processes are saturated, thereby allowing higher levels of

1,2-dichloroethane to circulate throughout the body and conjugate with glutathione instead of being detoxified and eliminated (D'Souza et al. 1987; Reitz et al. 1982).

This might explain the observation that large drinking water doses fail to produce the same toxic effects as smaller gavage doses (Munson et al. 1982). Gavage administration involves the placement of large bolus doses in the stomach that are absorbed at one time, thereby leading to spikes in blood levels and the subsequent expression of toxicity. However, drinking water exposure results in ingestion of contaminated water in small doses spread out over the course of a day. In such instances, biotransformation processes are not as likely to become saturated, and the risk of adverse effects is not as high as would be predicted from gavage administration of equivalent doses. The time required for saturation of biotransformation processes to occur might have contributed to the lag time, observed by Nouchi et al. (1984), between exposure and onset of toxic effects in an exposed human male, since the exposure dose (unknown) was undoubtedly high.

3.5.2 Mechanisms of Toxicity

Specific mechanisms for 1,2-dichloroethane-induced toxicity have not been elucidated. Studies in rats and mice indicate that 1,2-dichloroethane may be metabolized to 2-chloroacetaldehyde, *S*-(2-chloroethyl)glutathione, and other putative reactive intermediates capable of binding covalently to cellular macromolecules in the liver, kidney, and other tissues (Fabricant and Chalmers 1980; Jean and Reed 1989; Lock 1989). 1,2-Dichloroethane promoted lipid peroxidation in rat liver cells (Sano and Tappel 1990) and arterial endothelial and aortic smooth muscle cells (Tse et al. 1990) *in vitro*, suggesting another possible mechanism by which this chemical might produce toxic effects.

Available evidence suggests that toxicity of 1,2-dichloroethane in various tissues is largely mediated by reactive intermediates formed by conjugation with glutathione (Lock 1989). High levels of glutathione-*S*-transferases, the family of enzymes that catalyze the conjugation of xenobiotics with glutathione, are present in liver, kidney, intestine, testis, adrenal, and lung, primarily (>95%) in the cytoplasm (Parkinson 1996). Putative glutathione-dependent metabolites, such as *S*-(2-chloroethyl)glutathione and *S*-(2-chloroethyl)-L-cysteine, are thought to spontaneously rearrange to form electrophilic episulfonium ions that can bind to cellular macromolecules (Peterson et al. 1988). Rapid depletion of hepatocellular glutathione and binding of *S*-(2-chloroethyl)glutathione and *S*-(2-chloroethyl)-L-cysteine to liver DNA and protein have been demonstrated *in vitro* (Jean and Reed 1989). Similarly, the renal cortex contains substantial amounts and high activity of glutathione *S*-transferases that perform the initial conjugation

reaction (Lock 1989), and the conjugates *S*-(2-chloroethyl)glutathione and *S*-(2-chloroethyl)-L-cysteine have been identified as nephrotoxic in rats. Cytochrome P-450, which catalyzes competing metabolic reactions, has relatively low activity in the kidney, thus shifting the metabolism of 1,2-dichloroethane in the kidney toward production of toxic metabolites.

Differences in carcinogenic response have been observed between the positive oral gavage study (NCI 1978) and the negative inhalation study (Maltoni et al. 1980) summarized in Sections 3.2.1.7 and 3.2.2.7. These inconsistent cancer findings could be attributed to a number of factors, including different strains of rats and inhalation study limitations, including intermittent exposures, an MTD that was exceeded at the highest dose tested, and poor survival rates. The route-related difference in carcinogenic response may also be explained on the basis of metabolic differences and the saturation of the detoxification/ excretion mechanism occurring between the gavage dose and the longer-term inhalation dose, as proposed by Reitz et al. (1982) and discussed in Section 3.5.1. At lower doses, metabolic saturation appeared to occur sooner after oral administration than after inhalation exposure. Reitz et al. (1982) also suggested that the expression of 1,2-dichloroethane-induced toxicity occurred when the biotransformation processes were saturated, thereby allowing higher levels of 1,2-dichloroethane to circulate throughout the body instead of being detoxified and eliminated. The 1,2-dichloroethane inhalation study therefore may not have produced peak blood levels high enough to saturate the detoxification mechanisms and produce a detectable incidence of tumors. Route-related differences in immunologic and several other toxic responses have similarly been observed, which may also be due to the saturation of the detoxification/ excretion mechanism as a result of the bolus gavage dosing.

3.5.3 Animal-to-Human Extrapolations

The metabolism of 1,2-dichloroethane has not been studied in humans. The lack of this information precludes a nonspeculative attempt to discuss potential interspecies differences or similarities in the toxicity of 1,2-dichloroethane, as well as a determination of which animal species is the most appropriate model for humans. Extrapolations of 1,2-dichloroethane oral toxicity data from animals to humans should consider the type of exposure because, as discussed in Section 3.5.1, some of the differences in toxic and carcinogenic responses in animal studies can be explained on the basis of saturation of the detoxification/excretion mechanism due to bolus (gavage) administration.

3.6 ENDOCRINE DISRUPTION

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies regarding endocrine disruption in humans and animals after exposure to 1,2-dichloroethane were located.

No *in vitro* studies regarding endocrine disruption of 1,2-dichloroethane were located.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when 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 resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

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

Children sometimes differ from adults in their susceptibility to 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 prenatal and postnatal 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 (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). 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. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their

alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Data on the health effects of 1,2-dichloroethane exposure in children are limited to a single case report of a 14-year-old boy who swallowed 15 mL of the compound (Yodaiken and Babcock 1973). The most immediate signs of toxicity were headache and staggering gait within 2 hours of exposure, followed soon after by lethargy and vomiting. During the next few days, the boy developed symptoms of toxicity, increasing in variety and severity, that involved several organ systems, including adverse hematological effects, pulmonary edema, cardiac arrest (he was resuscitated), and eventual death on the 5th day after exposure from massive hepatic necrosis and renal tubular necrosis. Data from this case report and from reports of adult humans who died following acute exposure to high levels by inhalation or ingestion are consistent with animal studies indicating that the main targets of acute toxicity include the central nervous system, respiratory tract, stomach, liver, and kidneys. Considering the consistency of effects in acutely exposed humans and animals, and data showing that the liver, kidney, and immune system are sensitive targets of lower-dose and longer-term inhalation and oral exposures in animals, it is reasonable to assume that effects in these tissues would also be seen in similarly exposed adults and children.

No studies that provide reliable information on adverse developmental effects in humans exposed to 1,2-dichloroethane are available. A cross-sectional epidemiologic study that investigated whether elevated levels of routinely sampled organic contaminants in New Jersey public water systems, including 1,2-dichloroethane, were associated with increased prevalences of adverse birth outcomes (Bove 1996; Bove et al. 1995) was located. A number of associations between various chemicals and birth outcomes were found, including a positive association between ingestion of 1,2-dichloroethane in drinking water and major cardiac birth defects; however, the mixed chemical exposures indicate that the results are only suggestive, do not establish a cause-and-effect relationship, and should be interpreted with caution.

Studies in rats, mice, and rabbits indicate that 1,2-dichloroethane is not developmentally toxic following inhalation or oral gestational exposure, although indications of embryolethality at maternally toxic doses have been reported (Kavlock et al. 1979; Lane et al. 1982; Payan et al. 1995; Rao et al. 1980).

Evidence from mouse studies suggests that the specific nature of oral exposure may play a role in the degree of immunotoxicity expressed in young animals. Bolus doses of 1,2-dichloroethane appear to be more effective in eliciting an immunotoxic response than drinking-water exposures in 5-week-old mice. There was a significant, dose-related reduction in IgM response to sheep erythrocytes, and a significant,

but not dose-related, reduction in delayed-type hypersensitivity response to sheep erythrocytes in 5-week-old CD-1 mice exposed for 14 days by gavage to 4.9 and 49 mg/kg/day (Munson et al. 1982). In mice provided 49 mg/kg/day, these effects were accompanied by a 30% decrease in total leukocyte number. In contrast, mice given drinking water containing 189 mg/kg/day of 1,2-dichloroethane for 90 days beginning at 5 weeks of age displayed no treatment-related effects on either the antibody-forming cell response or the delayed-type hypersensitivity response after immunization with sheep erythrocyte antigens (Munson et al. 1982). The fact that the animal evidence for oral immunotoxicity of 1,2-dichloroethane includes decreased immune responses in 5-week-old mice provides a limited indication of the potential susceptibility of children to immunotoxic effects, particularly after bolus ingestion by children, that could occur, for example, with accidental ingestion of older household products that contain 1,2-dichloroethane.

Young mice were also susceptible to reduced immune function after brief inhalation exposure to 1,2-dichloroethane. A single 3-hour exposure to 5–11 ppm of 1,2-dichloroethane induced increased susceptibility to *S. zooepidemicus* (i.e., increased mortality following infection) in 4- to 5-week-old female mice, suggesting reduced pulmonary immunological defenses in the exposed mice (Sherwood et al. 1987). No immunological effects were observed at 2.3 ppm. Young female mice exposed to 11 ppm also had reduced bactericidal activity in the lungs 3 hours after inhalation challenge with *K. pneumoniae*. In contrast, young male rats (ages ranging from 4 to 5 weeks) that were exposed once to 200 ppm for 5 hours or 100 ppm 5 hours/day for 12 days did not exhibit any increased susceptibility to infection from these microbes, suggesting that rats may be less susceptible to the detrimental immunological effects of 1,2-dichloroethane than mice and/or that male rodents are less susceptible than females (Sherwood et al. 1987). The relevance of the young mouse inhalation data to child susceptibility is unknown, particularly in the light of the observed interspecies differences. However, the data do suggest that it would be prudent to prevent 1,2-dichloroethane inhalation exposures in children such as those that might occur during, and for several days after, using old wallpaper or carpet adhesives that contain 1,2-dichloroethane.

No studies that evaluated for the distribution of 1,2-dichloroethane or its metabolites across the placenta in humans were located. However, there is some evidence that 1,2-dichloroethane and/or its metabolites crosses the placenta after inhalation and oral exposures in animals. 1,2-Dichloroethane was found in maternal blood (83.6±20.2 mg %), placental tissue (43.0±9.6 mg %), amniotic fluid (55.5±11.1 mg %), and fetal tissue (50.6±11.5 mg %) after inhalation exposure of female rats to 247±10 ppm 1,2-dichloroethane during pregnancy (Vozovaya 1977). Additional evidence of transplacental distribution of 1,2-dichloroethane after inhalation exposure is provided by Withey and Karpinski (1985), who found that

the geometric mean concentration of 1,2-dichloroethane in the fetuses of rats that inhaled 150–2,000 ppm for 5 hours increased linearly with increasing exposure level. However, the reliability of the Vozovaya data is unclear, and the methods for evaluating 1,2-dichloroethane tissue concentrations were not reported in Withey and Karpinski (1985).

There is clearer evidence for transplacental distribution of 1,2-dichloroethane and/or its metabolites after maternal oral exposure. Payan et al. (1995) evaluated [^{14}C]-1,2-dichloroethane distribution in maternal rats following a single oral bolus dose of approximately 160 mg/kg on gestation day 12 or 18. In both cases, transplacental distribution of radiocarbon was demonstrated by the presence of radioactivity in the developing conceptus. A greater accumulation occurred in the developing fetus and placenta 48 hours after the gestation-day 18 administration than after the gestation-day 12 administration. At 48 hours after the gestation-day 18 dosing, the majority of residual radioactivity burden was located in the fetus (0.167% of administered dose) and the liver (0.156% of administered dose).

No studies regarding 1,2-dichloroethane metabolism in children were located. The metabolism of 1,2-dichloroethane is well described (see Figure 3-3), and it is reasonable to assume that the metabolic pathways are, for the most part, the same between adults and children. However, the expression of certain enzymes is known to be developmentally regulated, and one of these enzymes may be involved in 1,2-dichloroethane metabolism. NAT is involved in 1,2-dichloroethane metabolism at a step subsequent to GSH conjugation (see Figure 3-3). NAT performs the N-acetylation of S-carboxymethyl-L-cysteine to N-acetyl-S-carboxymethyl-L-cysteine, a major urinary metabolite. There are, however, two NATs (NAT1 and NAT2) that are expressed in humans with separate but overlapping substrate specificities (Parkinson 1996). NAT2 is apparently expressed only in the liver and the gut (Parkinson 1996), and is known to be developmentally regulated (Leeder and Kearns 1997). Some NAT2 activity is present in the fetus at 16 weeks, but NAT2 activity is low in virtually 100% of infants, not reaching adult activity levels until 1 to 3 years of age (Leeder and Kearns 1997). It is not clear in NTP (1991a), the source of the metabolism information in Figure 3-3, whether the NAT involved in 1,2-dichloroethane metabolism is NAT1 or NAT2, although both enzymes N-acetylate some xenobiotics equally well (Parkinson 1996).

1,2-Dichloroethane has been detected in human milk (EPA 1980a; Urusova 1953), indicating that developing children could possibly be exposed to 1,2-dichloroethane from breast-feeding mothers. The importance of this route of developmental exposure is unclear because current data on the concentration of 1,2-dichloroethane in breast milk are not available. 1,2-Dichloroethane also accumulated in the adipose tissue of rats after inhalation exposure and was eliminated from fat more slowly than from blood,

liver, and lung (Spreafico et al. 1980), suggesting the possibility that the maternal body burden of 1,2-dichloroethane in fat could be available for exposure to the fetus or nursing infant for a somewhat extended period after maternal exposure. Supporting data for relatively slow elimination of 1,2-dichloroethane from fat are provided in an intravenous exposure study in rats (Withey and Collins 1980).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

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 1,2-dichloroethane are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,2-dichloroethane are discussed in Section 3.8.2.

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

3.8.1 Biomarkers Used to Identify or Quantify Exposure to 1,2-Dichloroethane

Levels of 1,2-dichloroethane in breath, blood, and urine may be used to indicate exposure to this chemical. However, these measurements would have to be made soon after exposure, since 1,2-dichloroethane is rapidly eliminated from the body (see Section 3.4.4). In addition, it is not possible to establish from such measurements the precise environmental levels of 1,2-dichloroethane to which these individuals were exposed. A number of studies have investigated the relationship between tissue and environmental levels of 1,2-dichloroethane. In general, small amounts of 1,2-dichloroethane detected in the breath and urine (trace–0.2 ppb and 50–140 ng/L, respectively) were associated with exposure to 1,2-dichloroethane in air and water (Barkley et al. 1980; Conkle et al. 1975). In 2 studies conducted by Wallace et al. (1984, 1986), levels of 1,2-dichloroethane in breath samples from 350 residents of New Jersey were consistently below the detection limit; therefore, no conclusions could be drawn from these studies. 1,2-Dichloroethane was also detected in the breath (14.3 ppm) and breast milk (0.54–0.64 mg %) of nursing women working in factory premises containing 15.6 ppm 1,2-dichloroethane in air (Urusova 1953). These data are insufficient to characterize the relationship between environmental exposure to 1,2-dichloroethane and resultant tissue and fluid levels.

Urinary excretion of thioethers is another potentially useful biomarker of exposure to 1,2-dichloroethane. Payan et al. (1993) showed that total excreted urinary thioethers increased linearly with increasing oral dose (for doses between 0.25 and 4.04 mmol/kg [11.9 mg/kg/d and 400 mg/kg/d, respectively]) in male Sprague-Dawley rats during a 24-hour postadministration period, at a rate of 0.028 mmol thiol group eliminated per millimole of 1,2-dichloroethane administered. This occurred in spite of the fact that the total percentage of orally administered radioactivity excreted in the urine decreased with increasing dose (possibly due to saturation of certain metabolic pathways leading to urinary metabolites). Thioethers are commonly produced by conjugation reactions involving glutathione and comprise the primary urinary metabolites of 1,2-dichloroethane (see Sections 3.4.3 and 3.4.4). Increased urinary excretion of thioethers following exposure to 1,2-dichloroethane has been demonstrated in rats (Igwe et al. 1988; Payan et al. 1993), showing that this end point is sensitive to 1,2-dichloroethane exposure. As discussed above for the

parent compound, rapid excretion of 1,2-dichloroethane and metabolites (essentially complete after 48 hours in animal studies) means that measurements would have to be made soon after exposure to be of any value. There is an additional problem with use of increased urinary thioether excretion as a biomarker for 1,2-dichloroethane exposure. Since many xenobiotics form conjugates with glutathione, exposure to any number of compounds may increase urinary excretion of total thioethers (Monster 1986). Therefore, its use as a biomarker of 1,2-dichloroethane exposure is limited unless exposure to other compounds can be ruled out. Payan et al. (1993), however, found that urinary thiodiglycolic acid (measured by gas chromatography), a thioether compound that is not extractable by alkaline hydrolysis, is a more sensitive marker of 1,2-dichloroethane exposure than total thioethers.

Kim and Guengerich (1989) found that urinary mercapturic acid was linearly dose-related to intraperitoneally injected 1,2-dibromoethane in rats, and the urinary excretion of mercapturic acid was correlated with formation of hepatic and renal DNA adducts. It is possible that a similar relationship exists for relevant 1,2-dichloroethane exposures, although the methods proposed by Kim and Guengerich (1989) would not discriminate between the halogens.

Erve et al. (1996) investigated whether human hemoglobin, alkylated with the episulfonium ion of *S*-(2-chloroethyl)glutathione (a 1,2-dichloroethane metabolite via the glutathione-conjugation metabolic pathway), could be a useful biomarker for human exposure to 1,2-dichloroethane. They found that the method was not a very sensitive indicator for exposure, since an approximately 100-fold molar excess of *S*-(2-chloroethyl)glutathione over the hemoglobin concentration was required before alkylation was detectable *in vitro*.

3.8.2 Biomarkers Used to Characterize Effects Caused by 1,2-Dichloroethane

The health effects observed in humans exposed to 1,2-dichloroethane are all nonspecific effects and may be produced from any number of causes, including other causes that do not involve environmental exposure to xenobiotics such as 1,2-dichloroethane. Therefore, these effects would not be useful as indicators of exposure to 1,2-dichloroethane. Even if other causes could be ruled out, the specific levels that produce the various effects in humans are not known, so it would not be possible to quantify exposure based on the observed effects.

The primary targets of 1,2-dichloroethane identified in humans are probably the central nervous system, liver, and kidney (for a detailed description of the health effects of 1,2-dichloroethane, see Section 3.2).

Another likely target is the immune system, for which very limited information was available in humans but was the most sensitive target of 1,2-dichloroethane in animals. The effect on the immune system is immunosuppression. The observed biomarkers for this effect are reduced ability to fight induced bacterial infection, reduced immunoglobulin response to sheep erythrocytes, and reduced delayed-type hypersensitivity response to sheep erythrocytes, all of which show reduced immune system response to a challenge. The neurological effects observed included a variety of symptoms such as headache, irritability, drowsiness, tremors, partial paralysis, and coma. These effects were accompanied by histopathological changes in the brain in both humans and animals. The symptoms that occur at the lowest levels (such as headache, irritability, drowsiness, and tremors) may be considered biomarkers for the neurological effects of 1,2-dichloroethane. However, these suggested biomarkers of effects are nonspecific to 1,2-dichloroethane-induced toxicity.

Liver damage is a prominent feature of 1,2-dichloroethane exposure. Biomarkers for hepatotoxicity observed in humans and animals were alkylation of hepatocellular macromolecules, increased liver weight, and elevated levels of serum enzymes (ALT, AST, SDH). Kidney damage is another major effect of 1,2-dichloroethane; kidney failure has been reported in humans following high-level exposure. Biomarkers of renal effects in humans and animals included binding of macromolecules in renal cells and increased kidney weight. Glomerular involvement may be indicated by urinary excretion of the glomerular structural protein fibronectin (Bundschuh et al. 1993). Discussions of additional biomarkers of immunological, neurological, hepatic, and renal effects that may be relevant for 1,2-dichloroethane-induced toxicity can be found in the CDC/ATSDR (1990) and OTA (1990) reports referenced in Chapter 9.

3.9 INTERACTIONS WITH OTHER CHEMICALS

No studies regarding interactions of 1,2-dichloroethane with other chemicals in humans were located. Based on metabolic data resulting from animal studies, various interactions can be expected to occur. Inducers and inhibitors of cytochrome P-450 enzymes, glutathione precursors and depleting agents, and dietary/nutritional status can all influence the rate of formation and excretion of the various toxic intermediates resulting from exposure to 1,2-dichloroethane.

Induction of hepatic cytochrome P-450 enzymes by phenobarbital and/or Aroclor 1254 increases the rate of MFO metabolism of 1,2-dichloroethane *in vitro* (Hayes et al. 1973; Sipes and Gandolfi 1980). Alterations in metabolism could potentially produce profound effects on toxicity. Enhanced enzymatic

metabolism of 1,2-dichloroethane also occurs after treatment with ethanol *in vitro* (Sato et al. 1981). Ethanol is an inducer of cytochrome P-450 2E1, the major MFO enzyme involved in 1,2-dichloroethane metabolism (Guengerich et al. 1991). However, the effect of the consumption of ethanol before *in vitro* exposure to 1,2-dichloroethane varies greatly depending on the actual tissue concentration of ethanol reached during the metabolism of 1,2-dichloroethane (Sato et al. 1981). At low tissue ethanol concentration, cytochrome P-450 activity is stimulated. At high tissue ethanol concentrations, especially just before exposure to 1,2-dichloroethane, suppression of 1,2-dichloroethane metabolism occurs (Sato et al. 1981). Metabolism of 1,2-dichloroethane (50 ppm in air) was unaffected by chronic co-exposure to ethanol (5% in drinking water) in a 2-year study in rats (Cheever et al. 1990). Toxicity was also unaffected in this study.

Concurrent administration of 0.15% disulfiram in the diet and inhaled 1,2-dichloroethane (10, 153–304, 455 ppm) in animals markedly increased hepatotoxicity much more than would occur with exposure to 1,2-dichloroethane alone (Igwe et al. 1986a, 1988). Similarly, after chronic co-treatment with 50 ppm of 1,2-dichloroethane by inhalation and 0.05% disulfiram in the diet for 2 years, a series of neoplastic lesions were produced in rats that were not produced by 1,2-dichloroethane (or disulfiram) alone (Cheever et al. 1990). The lesions included intrahepatic bile duct cholangiomas, subcutaneous fibromas, hepatic neoplastic nodules, interstitial cell tumors in the testes, and mammary adenocarcinomas.

Metabolism studies on rats co-exposed to 1,2-dichloroethane and disulfiram for 2 years showed that following a 7-hour exposure, blood levels of 1,2-dichloroethane were elevated five-fold by co-treatment with disulfiram (Cheever et al. 1990). In addition, the amount of ^{14}C eliminated as unchanged 1,2-dichloroethane in the breath was elevated by disulfiram co-treatment, with a corresponding decrease in the amount of radioactivity excreted as metabolites in the urine. These results support the suggestion that disulfiram reduces the MFO metabolism of 1,2-dichloroethane, leading to accumulation of 1,2-dichloroethane in the blood and toxic effects. Diethyldithiocarbamate, the reduced form of disulfiram, is a relatively selective inhibitor of cytochrome P-450 2E1, the primary MFO enzyme involved in 1,2-dichloroethane metabolism (Guengerich et al. 1991).

Conjugation with glutathione is an important metabolic pathway for 1,2-dichloroethane. However, glutathione conjugation with 1,2-dichloroethane has also been hypothesized to produce reactive sulfur half-mustard metabolites, such as *S*-(2-chloroethyl) glutathione (D'Souza et al. 1987; Igwe et al. 1986b; Jean and Reed 1989; Lock 1989; Reitz et al. 1982). There is considerable evidence supporting the hypothesis that reactive intermediates formed by glutathione conjugation are responsible for 1,2-dichloro-

ethane toxicity. However, studies also show a protective effect of glutathione. The administration of glutathione, precursors of glutathione, or amino acids capable of donating a sulfhydryl group for the biosynthesis of glutathione all decrease the toxic effects and mortality in rats given 1,2-dichloroethane orally (Heppel et al. 1947). This protective action of glutathione and precursors also occurs in young rats exposed to 1,2-dichloroethane by inhalation (Johnson 1967). It is not clear how the protective effect of glutathione reported in these studies may be reconciled with the hypothesis that reactive intermediates formed by glutathione conjugation are responsible for 1,2-dichloroethane-induced toxicity. By analogy to 1,2-dibromoethane, however, the protective effect of co-administered glutathione in 1,2-dichloroethane exposures might be explained by the reaction of S-(2-chloroethyl)glutathione with glutathione, which is a nonenzymatic reaction occurring at physiological glutathione concentrations (Cmarik et al. 1990), although work with 1,2-dibromoethane indicates that levels of DNA adducts are correlated with glutathione content (Kim and Guengerich 1990). Methionine, p-aminobenzoic acid, aniline, and sulfanilamide have been shown to protect against toxicity of 1,2-dichloroethane (Heppel et al. 1945). A good correlation has been found between the urinary excretion of mercapturic acid and the formation of DNA adducts in liver and kidney DNA of 1,2-dibromoethane-treated rats (Kim and Guengerich 1989). This finding suggests that the extent of formation of adducts may be correlated with the toxic effects of 1,2-dichloroethane.

Nutritional status affects the rate of metabolic formation of toxic intermediates; liver from fasted animals showed an increased rate of 1,2-dichloroethane metabolism *in vitro* (Nakajima and Sato 1979) because fasting induces the formation of cytochrome P-450 2E1 (Johansson et al. 1988), the primary MFO enzyme involved in oxidation of 1,2-dichloroethane (Guengerich et al. 1991). Fasting also may lower hepatic levels of glutathione. According to the hypothesis that reactive intermediates formed by glutathione conjugation are responsible for 1,2-dichloroethane-induced toxicity, toxicity would be reduced under these conditions. However, the actual effect of fasting on 1,2-dichloroethane toxicity is unknown.

A few studies that investigated the toxic interactions between 1,2-dichloroethane and other xenobiotic toxicants were located. Pretreatment with orally administered 2-hexanone did not potentiate the nephrotoxicity of 1,2-dichloroethane administered by intraperitoneal injection in rats (Raisbeck et al. 1990). Co-treatment with 1,1-dichloroethylene produced only a slightly greater-than-additive effect on lipid droplet changes in rat hepatocytes (EPA 1989b). A mixture of 1,2-dichloroethane (80 mg/kg) and carbon tetrachloride (200 mg/kg) administered in a single oral dose to rats produced lower liver triglyceride levels than observed with carbon tetrachloride alone. These levels were still increased above

1,2-dichloroethane-only levels (Aragno et al. 1992). Studies of *in vitro* interactions produced more positive results. *tert*-Butyl hydroperoxide potentiated lipid peroxidation induced by 1,2-dichloroethane in rat liver slices *in vitro* (Sano and Tappel 1990). The occurrence of lipid peroxidation is associated with physical damage to tissues. There was a synergistic inactivation of plasma alpha-1 proteinase inhibitor when 1,2-dichloroethane was tested together with the cigarette smoke components acrolein and pyruvic aldehyde *in vitro* (Ansari et al. 1988b). Inactivation of plasma alpha-1 proteinase inhibitor has been proposed as an important factor in the development of lung emphysema.

Oral administration of 1,2-dichloroethane in drinking water for 16 weeks together with 3 other chemical carcinogens commonly found at hazardous waste sites (arsenic, vinyl chloride, and trichloroethylene) resulted in inhibition of the promotion of preneoplastic hepatic lesions and pulmonary hyperplasia and adenomas (Pott et al. 1998). The four chemicals, including 1,2-dichloroethane, have been shown to be individually carcinogenic in laboratory animals, yet they interacted antagonistically to inhibit promotion of precancerous lesions. The study is limited, however, by a short exposure duration, small numbers of test animals, and the use of only male rats; the interactive effect of lifetime exposure to the four chemicals cannot be inferred with confidence from these results. The mechanism for this interactive effect has not been elucidated, but Pott et al. (1998) hypothesized that decreased cell proliferation, increased apoptosis, or enhanced remodeling of preneoplastic lesions may play a role.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,2-dichloroethane than will most persons exposed to the same level of 1,2-dichloroethane 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 result in reduced detoxification or excretion of 1,2-dichloroethane, or compromised function of organs affected by 1,2-dichloroethane. Populations who are at greater risk due to their unusually high exposure to 1,2-dichloroethane are discussed in Section 6.7, Populations With Potentially High Exposures.

The synergistic effect of disulfiram (tetraethylthiuram disulfide) on 1,2-dichloroethane hepatotoxicity and carcinogenicity in animal studies suggests that individuals exposed concurrently to 1,2-dichloroethane and disulfiram, either in the rubber industry or medically (disulfiram is used as an anti-alcohol-abuse drug), have increased risk for liver toxicity (Cheever et al. 1990; Igwe et al. 1986a). Disulfiram and its reduced form, diethyldithiocarbamate, are known inhibitors of microsomal MFO enzyme, particularly

cytochrome P-450 2E1 (Guengerich et al. 1991; Igwe et al. 1985). It is possible that people exposed to other MFO inhibitors of like specificity would be at similar risk.

Inactivation of plasma alpha-1-proteinase inhibitor has been proposed to be an important factor in the development of lung emphysema. The occurrence of a synergistic inactivation of plasma alpha-1 proteinase inhibitor by 1,2-dichloroethane and cigarette smoke components (acrolein and pyruvic aldehyde) *in vitro* suggests that smokers as well as those exposed to passive smoke may be more susceptible to lung emphysema following repeated exposure to 1,2-dichloroethane (Ansari et al. 1988b). Further, those with genetically reduced plasma alpha-1-proteinase inhibitor, who are predisposed to emphysema, may be at increased risk.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,2-dichloroethane. 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 1,2-dichloroethane. 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 1,2-dichloroethane:

> Ellenhorn, M.J. 1997. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisons. (2^{nd} ed). Williams and Wilkins, Baltimore. 2047 pp.

The following discussion is based on suggested treatments provided in Ellenhorn (1997) for patients who were exposed to halogenated solvents, including 1,2-dichloroethane. Treatment is largely supportive. After dermal or ocular exposure, the exposed surface should be washed immediately with large amounts of water; for the eye, a 15- to 20-minute rinse is suggested. Appropriate and timely administration of ipecac to induce vomiting may help to reduce absorption from the gut if administered within 1 or 2 hours after the halogenated solvent is ingested. However, the risk of aspiration of the chemical during vomiting should be considered, particularly for infants and small children. After inhalation exposure, provide oxygen and watch for the need to provide mechanical respiration.

After exposures to high levels of a halogenated solvent, including 1,2-dichloroethane, the patient should be monitored for respiratory depression, hypoxic encephalopathy, cardiac dysrhythmias, hepatotoxicity, and renal toxicity (Ellenhorn 1997). Blood gases should be monitored and good ventilation maintained.

Observe for cardiac arrhythmias for a minimum of 24 hours. In the event of a ventricular arrhythmia, lidocaine or beta-blockers could be administered. Monitor serum creatinine, hepatic aminotransferase, electrolytes, and fluid balance for signs of hepatic or renal failure. Dialysis may be helpful in the event of renal failure. Hepatic failure may be treated with fresh frozen plasma, vitamin K, low protein diet, neomycin, and lactulose.

A major metabolic pathway of 1,2-dichloroethane involves conjugation with glutathione. In apparent opposition to the observation that conjugation with glutathione mediates 1,2-dichloroethane toxicity, some evidence from animal studies (Heppel et al. 1947; Johnson 1967) suggests that, after acute oral or inhalation exposure to 1,2-dichloroethane, prompt oral administration of glutathione, precursors of glutathione, or amino acids involved in donating a sulfhydryl group for the biosynthesis of glutathione may help to reduce the toxic effects of 1,2-dichloroethane exposure (further details of the animal studies are provided in Section 3.9). Ellenhorn (1997) suggested that treatment with N-acetylcysteine may help to restore depleted glutathione after exposure to a halogenated solvent, although he noted that no clinical trials had been conducted to confirm the efficacy or safety of this treatment.

3.11.1 Reducing Peak Absorption Following Exposure

Methods for reducing peak absorption of 1,2-dichloroethane after oral exposure include gastric lavage with activated charcoal, administration of ipecac to induce emesis, and the use of cathartics (Ellenhorn and Barceloux 1988). No information regarding ways to reduce absorption after exposure by other routes was located.

3.11.2 Reducing Body Burden

1,2-Dichloroethane is rapidly eliminated from the body after exposure. In animals, excretion of 1,2-dichloroethane and its metabolites was essentially complete within 48 hours of exposure (see Section 3.4.4). Following inhalation or oral exposure, elimination of 1,2-dichloroethane occurred primarily via excretion of soluble metabolites in the urine and excretion of unchanged parent compound and carbon dioxide in the expired air (Reitz et al. 1982). Increasing the volume of urine production by consuming a large volume of fluids beginning shortly after exposure may enhance the rate of urinary excretion of soluble 1,2-dichloroethane metabolites. The available data suggest that 1,2-dichloroethane will not accumulate in nonlipid components of the human body, but that it may accumulate to some extent in adipose tissue and in the breast milk of nursing women. Excretion of 1,2-dichloroethane may be

facilitated in nursing women by removing milk using either manual expression or a breast pump. The expressed breast milk should be discarded and not fed to infants. Methods (not specified) to enhance removal of 1,2-dichloroethane from the body have not been successful (Ellenhorn and Barceloux 1988).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism by which 1,2-dichloroethane produces toxic effects is not entirely understood. The two important metabolic pathways for 1,2-dichloroethane both lead to the formation of potentially reactive intermediates—chloroacetaldehyde by MFO and *S*-(2-chloroethyl)glutathione by glutathione conjugation (see Section 3.4.3). These reactive intermediates could produce toxic effects by binding covalently to cellular macromolecules. The MFO biotransformation pathway is saturable, and it has been suggested that 1,2-dichloroethane-induced toxicity occurs when MFO metabolism is saturated and large amounts of 1,2-dichloroethane conjugate with glutathione (see Section 3.5.1).

If this hypothesis is correct, then stimulation of MFO metabolism might prove effective in reducing toxicity. Cytochrome P-450 2E1 is the specific MFO enzyme that catalyzes metabolism of 1,2-dichloroethane (Guengerich et al. 1991). Theoretically, a drug that very rapidly induces this enzyme and is administered in a timely manner might have the ultimate effect of reducing 1,2-dichloroethane toxicity. Although experimental data are lacking that show that rapid P-450 2E1 induction by another chemical reduces 1,2-dichloroethane toxicity, available data do provide indirect support of this argument. Co-treatment with disulfiram, an inhibitor of MFO metabolism (especially P-450 2E1), enhances the toxicity of 1,2-dichloroethane (see Section 3.10). Alternatively, administration of drugs that would compete for glutathione and reduce the amount of glutathione available to conjugate with 1,2-dichloroethane might also mitigate the toxicity of 1,2-dichloroethane.

However, as evidence of the complexity of 1,2-dichloroethane biotransformation and uncertainty regarding toxic mechanisms, it may be noted that co-administration of glutathione and precursors with 1,2-dichloroethane had a protective effect (Heppel et al. 1947; Jaeger et al. 1974; Johnson 1967). These results are the opposite of those expected from the hypothesis that glutathione-dependent metabolites are responsible for 1,2-dichloroethane-induced toxicity. Clearly, a greater understanding of 1,2-dichloroethane bioactivation is necessary to develop methods to interfere with the process.

3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,2-dichloroethane 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 1,2-dichloroethane.

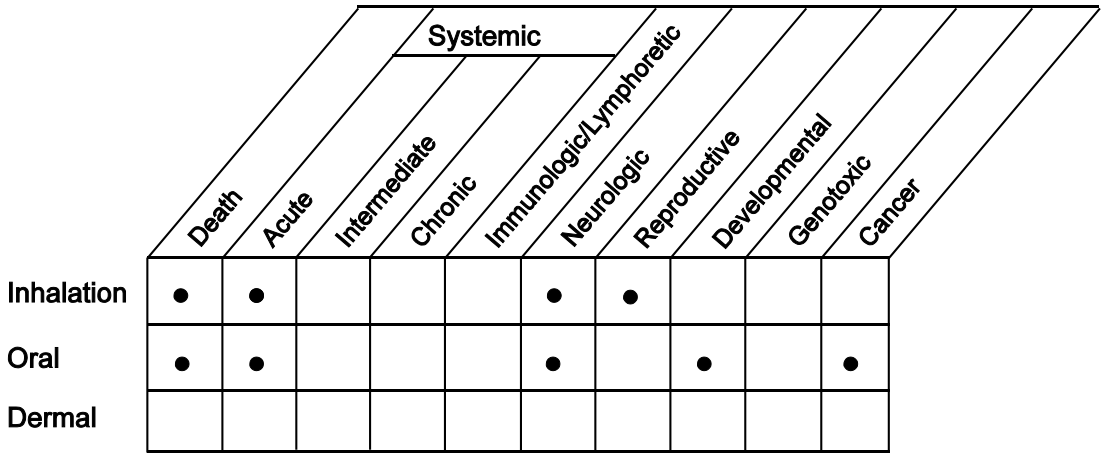
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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.

3.12.1 Existing Information on Health Effects of 1,2-Dichloroethane

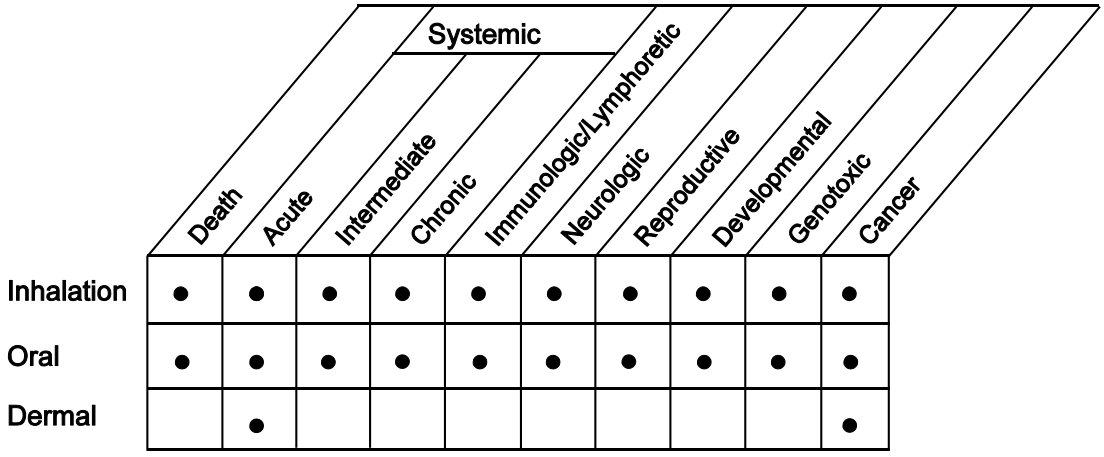
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2-dichloroethane are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,2-dichloroethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Limited information is available on the effects of inhaled 1,2-dichloroethane in humans. Most of the information consists of case reports of accidental or occupational exposure to 1,2-dichloroethane vapor. These studies are difficult to interpret because exposure concentration usually was not quantified, dermal exposure to 1,2-dichloroethane was also likely to occur concurrently with inhalation exposure, thereby contributing to total dose, or co-exposure to other chemicals occurred. The human health effects associated with ingested 1,2-dichloroethane are reported in case studies of individuals who drank 1,2-dichloroethane either intentionally or accidentally. In almost all of the case studies, death occurred

Figure 3-5. Existing Information on Health Effects of 1,2-Dichloroethane



Human



Animal

● Existing Studies

within a few days following exposure, and many of the systemic effects observed were found upon autopsy. No evidence of a relationship between 1,2-dichloroethane and cancer has been reported in epidemiological studies of petrochemical and other chemical industry workers, but the relevance of these studies to 1,2-dichloroethane is limited because exposure to various other chemicals also occurred. Similarly, evidence that 1,2-dichloroethane in drinking water is associated with colon and rectal cancer is also limited by the co-exposure to other chemicals. No information regarding human health effects following dermal exposure to 1,2-dichloroethane, except for ocular effects produced by direct contact with the vapor during inhalation exposure was located.

The lethal and systemic effects of 1,2-dichloroethane following acute- and intermediate-duration inhalation exposures have been studied in a variety of species. Excessive mortality was noted in most species examined under these exposure durations. Health effects associated with chronic-duration inhalation exposure to 1,2-dichloroethane have been investigated only in rats. Lethal and systemic effects of oral exposure have been studied mainly in rats and mice exposed for acute, intermediate, and chronic durations. Animal health effects data for dermal exposure to 1,2-dichloroethane are only available for acute-duration exposure. The carcinogenic effects of 1,2-dichloroethane have been investigated in rats and mice following inhalation, oral, and dermal exposure. Based on the results of available animal studies, EPA has classified 1,2-dichloroethane as a possible human carcinogen (Group B2) (IRIS 2001).

3.12.2 Identification of Data Needs

Acute-Duration Exposure. A data need to conduct additional studies via inhalation, oral, and dermal exposure has been identified. Information on 1,2-dichloroethane toxicity in humans comes primarily from a few case reports of humans who died following acute exposure to high levels of 1,2-dichloroethane by inhalation or ingestion (Garrison and Leadingham 1954; Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Nouchi et al. 1984; Schönborn et al. 1970; Yodaiken and Babcock 1973). Information that may be obtained from such studies is limited, but for 1,2-dichloroethane, the data were sufficient to identify the central nervous system, liver, kidney, and possibly cardiovascular system as target organs of high-level exposure from both oral and inhalation exposure. Results from acute inhalation and oral exposure studies in animals generally support the observations in humans. The dose spacing in these animal studies, however, was wide and resulted in identification of NOAELs and serious LOAELs for these effects.

The immune system was identified as the most sensitive target in mice for acute gavage exposure (Munson et al. 1982) and acute inhalation exposure (Sherwood et al. 1987) to 1,2-dichloroethane, but was not affected in rats by acute inhalation exposure to up to 20-fold higher concentrations of 1,2-dichloroethane (Sherwood et al. 1987). The lack of species concordance in the inhalation study in mice and rats (Sherwood et al. 1987) suggested that extrapolation from animals to humans is uncertain. The massive streptococcal challenge and lethality end point used to measure immune response in the mice exposed by inhalation does not appear to be suitable as the basis for MRL derivation. Therefore, an acute-duration inhalation MRL was not derived. Only one end point showed a significant dose-related immunotoxic effect in the acute gavage study in mice (Munson et al. 1982), and the higher doses of 1,2-dichloroethane administered in the drinking water for 90 days were not immunosuppressive in mice (Munson et al. 1982). These findings precluded acute-duration oral MRL derivation. Additional studies are needed to characterize the thresholds for acute immunologic effects and for other end points (e.g., central nervous system, liver, kidney, cardiovascular) to determine the most sensitive effects of inhalation and oral exposure and to investigate whether the immunologic effects in mice can be extrapolated across species. The additional data would establish the most appropriate basis for deriving an acute inhalation or oral MRL.

In addition, the reason for the discrepancy in results for immunotoxicity between the acute gavage and the intermediate drinking water study (Munson et al. 1982) is unknown. Although the discrepancy may have been related to the methods of dosing (gavage versus drinking water), another possible explanation is that younger mice are more susceptible than fully adult mice. As discussed in more detail in the section on children's susceptibility, the mice in the acute study were much younger at the time of immune testing than were the mice in the intermediate study.

The primary exposure routes for populations surrounding hazardous waste sites are ingestion of contaminated water and inhalation of air contaminated by volatilization of 1,2-dichloroethane from waste sites and from contaminated water used as household water. Studies to determine acute thresholds for effects induced by oral exposure, especially via drinking water instead of gavage, and to determine acute thresholds for effects of inhalation exposure are needed as populations near hazardous waste sites may be exposed to this chemical for brief periods by these routes.

Very little information was located regarding acute toxicity following dermal exposure in humans or animals. 1,2-Dichloroethane is well absorbed by this route, both as undiluted chemical and from aqueous solution (Morgan et al. 1991), and is expected to produce effects in the same tissues affected by exposure

via other routes. Acute dermal toxicity data are needed because acute dermal exposure to 1,2-dichloroethane (in household water used for bathing and showering) is a likely route of exposure for humans who live near hazardous waste sites.

Intermediate-Duration. A data need to conduct additional studies via inhalation and dermal exposure has been identified. There is no information on the health effects of intermediate-duration exposure to 1,2-dichloroethane in humans. Available inhalation studies in animals (Heppel et al. 1946; Spencer et al. 1951) are adequate for identifying main target organs (essentially the same as those affected by acute inhalation and oral exposure in humans and animals), but do not provide a fully adequate basis for identifying the most sensitive end points. Limitations in the intermediate-duration inhalation studies preclude considering them in MRL derivation. Additional studies to identify toxicity thresholds following intermediate-duration inhalation exposure are needed to derive an inhalation MRL specifically for intermediate-duration exposure.

The MRL for intermediate oral exposure is based on a LOAEL of 58 mg/kg/day for kidney effects in rats from an adequate 13-week drinking water study in rats and mice (NTP 1991a). In the same drinking water study, the most sensitive effect in mice was also renal, but it occurred at a much higher exposure level, 249 mg/kg/day (NTP 1991a). A 90-day immunotoxicity study in mice of 1,2-dichloroethane in drinking water found no effects on the immune system and no effects on liver or kidney weight at the highest exposure level, 189 mg/kg/day. Thus, the rat appears to be more sensitive than the mouse to 1,2-dichloroethane exposure in drinking water. Although few immune-related end points were evaluated in the rat subchronic drinking water study (leukocyte counts, thymus histology), acute inhalation exposure did not result in immune effects in rats at exposure levels as much as 20-fold higher than the effect levels in mice in the same study (Sherwood et al. 1987). Additional oral studies could identify a NOAEL, as well as determine if the kidney is the most sensitive target for intermediate-duration exposure to 1,2-dichloroethane (see data needs sections for acute-duration exposure and for immunotoxicity). Because the data were adequate for derivation of an intermediate oral MRL, a data need is not identified for this route and duration.

Dermal data were not located, but are needed because absorption by this route is expected (Morgan et al. 1991), and intermediate-duration dermal exposure is a likely exposure scenario for humans who live in the vicinity of a hazardous waste site.

Chronic-Duration Exposure and Cancer. A data need to conduct additional studies via oral and dermal exposure has been identified. There is no information on the noncancer health effects of chronic-duration exposure to 1,2-dichloroethane by any route in humans. Chronic studies in animals are limited to one inhalation study in rats (Cheever et al. 1990) and one oral study in rats and mice (NCI 1978) that were primarily designed to assess carcinogenicity, but provided some information on systemic toxicity.

The inhalation study (Cheever et al. 1990) was used to derive an MRL for chronic-duration exposure but is limited by the use of a single exposure level (a NOAEL), use of a single species, and lack of sensitive immunotoxicity end points. Because the inhalation information was considered adequate for MRL derivation, there is no data need for additional chronic inhalation studies.

The oral study (NCI 1978) provided an insufficient basis for derivation of an MRL due to limitations such as dosage adjustments, possible contamination by other chemicals tested in the same laboratory, and poor survival and small numbers of control animals, as well as concerns regarding the method of exposure, since it may not be appropriate to base an MRL on an effect level from a gavage oil study due to toxicokinetic considerations (bolus saturation of the detoxification/excretion mechanism, discussed elsewhere in this document). Additional chronic oral toxicity studies are needed because they could identify critical targets that are different than those detected in shorter-term studies and because toxicity levels may be considerably lower than in shorter-term studies.

The only chronic dermal study in animals was a carcinogenicity study that did not investigate noncancer end points (Van Duuren et al. 1979).

Epidemiological studies that have investigated associations between occupational or oral exposure to 1,2-dichloroethane and increased incidences of cancer are inadequate for assessing carcinogenicity of 1,2-dichloroethane in humans due to complicating co-exposures to various other chemicals, as discussed in the section on epidemiology. The carcinogenic potential of 1,2-dichloroethane has been examined in rats and mice following inhalation, oral, and dermal exposure. No tumors were produced in rats and mice exposed to 1,2-dichloroethane via inhalation (Cheever et al. 1990; Maltoni et al. 1980). Limitations of the inhalation studies included the use of a single, subthreshold exposure level in one study (Cheever et al. 1990) and exceedance of the maximum tolerated dose in rats, less-than-lifetime study duration, and poor survival in mice in the other study (Maltoni et al. 1980).

1,2-Dichloroethane was carcinogenic after gavage administration (of 97–195 mg/kg/day to rats and 97–299 mg/kg/day to mice), inducing statistically significant increases in forestomach squamous cell carcinomas, hemangiosarcomas, and subcutaneous fibromas in male rats; mammary gland adenocarcinomas and hemangiosarcomas in female rats; hepatocellular carcinomas and alveolar/bronchiolar adenomas in male mice; and alveolar/bronchiolar adenomas, mammary carcinomas, and endometrial tumors in female mice (NCI 1978). Limitations of this oral study include the nonnatural method of administration (gavage) and dosage adjustments during the study.

1,2-Dichloroethane induced lung papillomas following lifetime dermal exposure of female mice (Van Duuren et al. 1979). The results showed an apparent dose-response, with statistical significance at the high dose. This study appears adequate to demonstrate the carcinogenic potential of dermal exposure to 1,2-dichloroethane. In addition, pulmonary adenomas have been induced in mice by intraperitoneal injection (Stoner 1991; Theiss et al. 1977), and, as discussed previously, by oral administration of 1,2-dichloroethane.

It has been suggested that the route-related differences in carcinogenicity between inhalation and oral exposure may be associated with saturation of the detoxification/excretion mechanism by gavage dosing. Reitz et al. (1982) proposed that 1,2-dichloroethane-induced toxicity occurred when the biotransformation processes were saturated, thereby allowing higher levels of 1,2-dichloroethane to circulate throughout the body instead of being detoxified and eliminated. The 1,2-dichloroethane inhalation study, therefore, may not have produced peak blood levels that were high enough to saturate the detoxification mechanisms and produce a detectable incidence of tumors. Metabolic saturation apparently occurs at lower doses after oral administration (particularly by gavage) than after inhalation exposure. Additional information on 1,2-dichloroethane from well-conducted animal bioassays using the natural routes of exposure expected for populations surrounding hazardous waste sites (i.e., drinking water ingestion and inhalation exposure) are needed to better predict the likelihood of carcinogenicity in humans.

The positive and suggestive carcinogenicity results from animal bioassays (NCI 1978; Stoner 1991; Theiss et al. 1977; Van Duuren et al. 1979), along with data indicating that 1,2-dichloroethane and certain metabolites are mutagenic and capable of forming DNA adducts as discussed in the preceding section, provide sufficient evidence to suggest that 1,2-dichloroethane is a probable human carcinogen. Because oral, dermal, and intraperitoneal exposure of experimental animals to 1,2-dichloroethane is associated with the induction of tumors remote from the site of administration, 1,2-dichloroethane should be considered potentially carcinogenic by the inhalation route of exposure as well. The DHHS has

determined that 1,2-dichloroethane may reasonably be anticipated to be a human carcinogen (NTP 2000). IARC has placed 1,2-dichloroethane in Group 2B (possibly carcinogenic to humans) (IARC 2001). EPA has classified 1,2-dichloroethane as a Group B2 carcinogen (probable human carcinogen) (IRIS 2001). This EPA category applies to chemical agents for which there is sufficient evidence of carcinogenicity in animals.

Genotoxicity. A data need to conduct additional genotoxicity studies has been identified. No information regarding the genotoxicity of 1,2-dichloroethane in humans following oral, inhalation, dermal, or parenteral exposure is available. However, a great deal of data are available regarding the genotoxic effects of 1,2-dichloroethane in human cells *in vitro*; prokaryotic organisms, fungi, and nonhuman mammalian cells *in vitro*; and insects, rats, and mice *in vivo*.

The ability of 1,2-dichloroethane to bind to DNA in rats and mice *in vivo* has been well established, not only in the liver, but also in other organs such as the kidney and lung (Baertsch et al. 1991; Banerjee 1988; Cheever et al. 1990; Hellman and Brandt 1986; Inskeep et al. 1986; Prodi et al. 1986). DNA binding has also been reported in *D. melanogaster in vivo* (Fossett et al. 1995). DNA damage has been demonstrated *in vivo* in mice (Sasaki et al. 1998; Storer and Conolly 1983, 1985; Taningher et al. 1991). Genotoxicity assays for clastogenic effects in mice *in vivo* obtained mixed results, with a positive effect on sister chromatid exchange in bone marrow cells (Giri and Hee 1988), but no effect on micronucleus formation (Armstrong and Galloway 1993; Jenssen and Ramel 1980; King et al. 1979; Sasaki et al. 1994), and in *D. melanogaster,* gave positive results for chromosomal aberration (Ballering et al. 1993) and a marginally positive response for chromosomal recombination (Rodriguez-Arnaiz 1998). Negative results were obtained in a cell transformation assay (Milmann et al. 1988).

The only *in vivo* assay for the mutagenicity of 1,2-dichloroethane in mammalian cells (mouse/spot test) produced a marginal response (Gocke et al. 1983), and a mouse host-mediated assay produced negative results in *Escherichia coli* (King et al. 1979). However, there is abundant evidence that 1,2-dichloroethane produces both somatic and sex-linked recessive lethal mutations in *D. melanogaster in vivo* (Ballering et al. 1994; King et al. 1979; Kramers et al. 1991; Nylander et al. 1978; Romert et al. 1990; Vogel and Nivard 1993). In addition, *in vitro* studies provide strong support for the mutagenicity of 1,2-dichloroethane. Results of *in vitro* assays for point mutations were positive in human cells (Crespi et al. 1985; Ferreri et al. 1983), marginally positive in a single assay in animal cells (Tan and Hsie 1981), and positive in nearly all of the assays in bacteria, with or without metabolic activation (Barber et al. 1981; Brem et al. 1974; Buijs et al. 1984; Cheh et al. 1980; Hemminki et al. 1980; Kanada and Uyeta

1978; King et al. 1979; Milman et al. 1988; Moriya et al. 1983; Nestmann et al. 1980; Rannug and Beije 1979; Rannug et al. 1978; Roldan-Arjona et al. 1991; Simula et al. 1993; Thier et al. 1993; Van Bladeren et al. 1981), although not in a single assay in fungi (Crebelli and Carere 1988). The results of these bacterial mutagenicity assays suggest that 1,2-dichloroethane is a very weak, direct-acting mutagen that can be activated to a more effective species by glutathione and glutathione *S*-transferases (DeMarini and Brooks 1992).

Additional evidence from *in vitro* studies supports the *in vivo* results regarding the DNA binding, DNA damaging, and clastogenic effects of 1,2-dichloroethane. Results were positive for DNA binding in animal cells (Banerjee 1988; Banerjee and Van Duuren 1979; Banerjee et al. 1980; Prodi et al. 1986), unscheduled DNA synthesis (i.e., DNA repair activity) in human (Perocco and Prodi 1981) and animal cells (Milman et al. 1988; Williams et al. 1989), and mitotic segregation aberrations leading to aneuploidy in fungi (Crebelli et al. 1984). Negative results were obtained for intrachromosomal recombination in a single assay in animal cells (Zhang and Jenssen 1994, but positive results were reported for micronucleus formation in human cells (Doherty et al. 1996; Tafazoli et al. 1998). Thus, both *in vitro* and *in vivo* genotoxic effects of 1,2-dichloroethane include gene mutations, DNA binding and damage, and clastogenic effects.

The DNA binding is an alkylation of DNA that occurs following biotransformation of 1,2-dichloroethane. Inhalation exposure of rats to very high concentrations of 1,2-dichloroethane for short durations produced greater amounts of DNA binding in liver and lung than do longer-duration inhalation to low concentrations (Baertsch et al. 1991), and oral gavage doses were more potent in causing DNA damage in liver than were comparable inhalation doses in mice (Storer et al. 1984). These observations are consistent with the hypothesis that the toxicity of 1,2-dichloroethane is associated with saturation of MFO enzymes. The major identified DNA adduct is *S*-[2-(N^7-guanyl)ethyl]glutathione in rat liver following a single intraperitoneal injection of ^{14}C-1,2,-dichloroethane, and it is one of several DNA adducts found in the kidney, after a single intraperitoneal injection (Inskeep et al. 1986).

Although genotoxicity in humans could be investigated directly by examining peripheral lymphocytes obtained from exposed workers for clastogenic effects, the utility of such studies is likely to be limited due to the workers' exposures to other chemicals. Additional *in vivo* studies examining the importance of the route of administration on 1,2-dichloroethane-induced quantitative genotoxicity data (i.e., adducts) in animals are needed since the available information indicates route-dependent effects (inhalation doses are less potent than oral gavage) (Storer et al. 1984). DNA adduct and monoclonal antibody dosimetry work

also are needed to provide quantitative genotoxicity data, and perhaps could be used as a biomarker of exposure to 1,2-dichloroethane.

Reproductive Toxicity. A data need to conduct additional reproductive studies via dermal exposure has been identified. A single study on reproductive effects of exposure to 1,2-dichloroethane in humans is suggestive of a decrease in duration of gestation (Zhao et al. 1989), but should be interpreted with caution since co-exposure to other chemicals occurred in most cases and the adequacy of the study design could not be evaluated because of reporting deficiencies. Results of animal studies indicate that this chemical is unlikely to cause female reproductive impairment at doses that are not maternally toxic. Although some inhalation studies found that exposure to 1,2-dichloroethane prior to mating and continuing into gestation caused pre-implantation loss and embryolethality in rats (Vozovaya 1974, 1977; Zhao et al. 1989), the methods used by these investigators were not well reported and the reliability of the data is uncertain. In contrast to these findings, a well-designed and reported study of reproductive toxicity found no adverse effects on the fertility of rats exposed by inhalation to 10-fold higher concentrations of 1,2-dichloroethane in a one-generation reproduction study (Rao et al. 1980). In the absence of an apparent explanation for the discrepancy, greater credence should be given to the well-designed and reported study. One- and two-generation reproduction studies found no chemical-related effects on fertility indices in long-term oral studies in mice and rats (Alumot et al. 1976; Lane et al. 1982), but exposure to higher oral doses caused increases in nonsurviving implants and resorptions in rats that also experienced maternal toxicity (30% decreased body weight gain) (Payan et al. 1995). Histological examinations of the testes, ovaries, and other male and female reproductive system tissues were performed in intermediate- and chronic-duration inhalation and oral animal studies with negative results (Cheever et al. 1990; Daniel et al. 1994; NCI 1978; NTP 1991a; van Esch et al. 1977), although reproductive performance was not evaluated in these studies.

Although 1,2-dichloroethane appears to have induced embryotoxic effects in one adequate animal study conducted by the oral route, the overall indication of the data is that this chemical is unlikely to impair reproduction at doses that are not highly toxic. No data are available regarding the potential reproductive toxicity of dermal exposure, so there is a need for studies.

Developmental Toxicity. A data need to conduct additional developmental studies via inhalation, oral, and dermal exposure has been identified. The only studies regarding developmental effects in humans are epidemiologic investigations of adverse birth outcomes that found increased OR for exposure to 1,2-dichloroethane in public drinking water and major cardiac defects (but not neural tube defects)

(Bove 1996; Bove et al. 1995), and for residence within the census tract of NPL sites contaminated with 1,2-dichloroethane and neural tube defects (but not heart defects) (Croen et al. 1997). Primary routes of exposure in these epidemiologic studies may have been both oral and inhalation (including inhalation of 1,2-dichloroethane volatilized from household water). The OR for cardiac defects for 1,2-dichloroethane (detected versus not detected in drinking water) was 2.8 (95% CI 1.11–6.65; 6 exposed cases) (Bove 1996; Bove et al. 1995). The crude odds ratio for neural tube defects was 2.8 (95% CI 1.0–7.2; 14 exposed cases) (Croen et al. 1997). In these studies, the study populations were also simultaneously exposed to elevated levels of other contaminants. Because of the mixed chemical exposure, lack of dose-response information, and inconsistency between the findings of the two studies, the associations with 1,2-dichloroethane are only suggestive, do not establish a cause-and-effect relationship, and should be interpreted with caution.

The weight of evidence from available inhalation and oral studies in rats, mice, and rabbits indicates that 1,2-dichloroethane is not fetotoxic or teratogenic, although indications of embryo and fetal lethality at maternally toxic doses have been reported (Kavlock et al. 1979; Lane et al. 1982; Payan et al. 1995; Rao et al. 1980). The reliability of the reports of increased embryo and pup mortality following intermediate-duration inhalation of lower (not maternally toxic) concentrations of 1,2-dichloroethane (Vozovaya 1977; Zhao et al. 1989) is uncertain, due to the lack of statistical analysis, inadequate description of methods, and uncertainties in the reported results. The possibility of induction of cardiac malformations by 1,2-dichloroethane, as suggested by the epidemiologic data, was not adequately addressed in the animal studies because their conventional teratology protocols did not include detailed examinations of dissected hearts. Given the suggestive evidence of an association between exposure to 1,2-dichloroethane in drinking water and major cardiac defects in human offspring, and evidence of heart malformations in epidemiology and animal cardiac teratogenicity studies of dichloroethylene and trichloroethylene (Dawson et al. 1993; Goldberg et al. 1990), which are metabolized to some of the same reactive intermediates as is 1,2-dichloroethane, it would be informative to have studies specifically designed to investigate the potential for induction of developmental heart malformations by 1,2-dichloroethane. In addition, the possibility of neurodevelopmental effects, also suggested by the epidemiological data, needs to be investigated, particularly because 1,2-dichloroethane is known to affect the central nervous system.

Immunotoxicity. A data need to conduct additional immunotoxicity studies via inhalation, oral, and dermal exposure has been identified. Immunological effects reported in humans exposed to 1,2-dichloroethane are limited to splenic lesions in a single case of accidental ingestion (Hubbs and Prusmack 1955). In mice, this chemical had immunosuppressive effects following both acute inhalation and acute oral

exposure. A single 3-hour inhalation exposure to 5 or 11 ppm increased the susceptibility of female mice to bacterial infection, and to 11 ppm decreased the bactericidal activity of the lungs. No change in bactericidal activity was seen in male rats after a single 5-hour inhalation exposure to 200 ppm or 12 5-hour exposures to 100 ppm (Sherwood et al. 1987). Other immune function end points studied in the rats were also negative. The relevance of the end point (lethality due to massive streptococcal challenge) in mice to immune function is known, but its suitability as a basis for MRL derivation is uncertain. Gavage administration of 4.9 and 49 mg/kg/day of 1,2-dichloroethane to mice for 14 days reduced humoral (immunoglobulin response to sheep red blood cells) and cell-mediated (delayed-type hypersensitivity response to sheep erythrocytes) immunity. Only the humoral response was dose-related. In addition, the leukocyte number was decreased by 30% at the high dose (Munson et al. 1982). The immune system was the most sensitive target for short-term exposure to 1,2-dichloroethane by both the inhalation and gavage routes in mice, as compared with end points in other studies in mice and in other species. The other studies, however, had limitations including wide spacing of the exposure concentrations, such that only NOAELs and serious LOAELs were identified.

In contrast to the acute oral study, higher doses of 1,2-dichloroethane (189 mg/kg/day) administered to mice in their drinking water for 90 days did not affect humoral and cell-mediated immunity (Munson et al. 1982), as assessed by some of the Tier I and Tier II procedures from the immunotoxicity testing battery (Luster et al. 1988). Immune function has not been evaluated in chronic-duration studies of 1,2-dichloroethane, but histopathological examinations failed to detect immune system lesions or immune-related changes in rats and mice exposed to 1,2-dichloroethane by inhalation or oral (gavage or drinking water) routes for intermediate or chronic durations (Cheever et al. 1990; NCI 1978; NTP 1991a). Leucocyte counts were not affected in intermediate-duration drinking water and gavage studies in rats (NTP 1991a). The acute data provide limited evidence that the immune system is a sensitive target of 1,2-dichloroethane in mice, but not rats. Because of the apparent interspecies differences in animal immunotoxicity, it is unclear whether the immune system could be a target of 1,2-dichloroethane in humans following acute exposure by inhalation or ingestion.

The mechanism by which 1,2-dichloroethane may produce immunological effects is not known, but it is possible that these effects were produced by reactive intermediates resulting from conjugation with glutathione (Reitz et al. 1982). Glutathione conjugation and MFO metabolism are the two primary pathways of 1,2-dichloroethane metabolism. It has been shown that MFO metabolism of 1,2-dichloroethane is saturable and that direct glutathione conjugation occurs to a much greater extent after saturation of MFO metabolism. Gavage administration, which involves the placement of large bolus doses in the

stomach that are absorbed at one time, could lead to saturation of MFO metabolism and the subsequent expression of toxicity. Drinking water exposure, which results in multiple daily ingestions of small doses, may not provide large enough doses to saturate MFO metabolism, even when the aggregate daily dose is fairly large. Therefore, even though immunological effects might be expected in humans ingesting large doses of undiluted 1,2-dichloroethane, it is uncertain whether immunological effects would occur in humans exposed to 1,2-dichloroethane in the drinking water at hazardous waste sites. Another possible explanation for the different outcomes of acute and intermediate oral exposure is that 1,2-dichloroethane may induce its own metabolism during the longer exposure period, thus reducing the dose to the immune cells. An additional possibility, related to age of the mice at the time of immune function testing, was mentioned in the section on acute exposure and is discussed in detail in the section on children's susceptibility.

Both the oral and the inhalation acute immunotoxicity studies found immunosuppressive effects at levels of 1,2-dichloroethane low enough to enable identification of the immune system as the most sensitive target for acute exposure by both routes of exposure, but neither study provided the data sufficient for deriving an MRL (the lethality assay in the inhalation study was not considered suitable, and the oral study showed a dose-response in only one end point and was limited by use of gavage). In addition, dose-response information for other potential targets of toxicity was not adequate. Additional studies are needed to determine the immunologic potential of acute inhalation and oral (drinking water) exposure and to better characterize the threshold for immunologic effects by both routes of exposure relative to thresholds for other effects in order to provide the data needed to establish the most appropriate basis for deriving acute inhalation and oral MRLs.

No data were located regarding the potential immunotoxicity of dermal exposure.

Neurotoxicity. A data need to conduct additional neurotoxicity studies via inhalation, oral, and dermal exposure has been identified. Neurological symptoms and signs in people acutely exposed to high levels of 1,2-dichloroethane by inhalation (Nouchi et al. 1984) or ingestion (Hubbs and Prusmack 1955; Lochhead and Close 1951; Yodaiken and Babcock 1973) included headache, irritability, drowsiness, tremors, partial paralysis, and coma. Autopsies of people who died following acute exposure to this chemical revealed morphological changes in the brain, such as hyperemia, edema, hemorrhage, myelin degeneration, diffuse changes in the cerebellum, shrunken appearance and pyknotic nuclei in the Purkinje cell layer of the cerebellum, and parenchymous changes in the brain and spinal cord (Hubbs and

Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Nouchi et al. 1984). The results of animal studies confirm that the central nervous system is a target of high concentrations of 1,2-dichloroethane. Symptoms similar to those reported in humans, such as tremors, abnormal posture, uncertain gait, and narcosis, were observed after high-level acute vapor exposures (Heppel et al. 1945; NTP 1991a; Spencer et al. 1951). In addition, clinical signs of neurotoxicity and mild necrosis in the cerebellum were found in rats administered 240–300 mg/kg/day of 1,2-dichloroethane by gavage for 13 weeks (NTP 1991a). No clinical signs or neurological lesions were seen in rats exposed through their drinking water up to 492 mg/kg/day or mice exposed up to 4,210 mg/kg/day for 13 weeks (NTP 1991a), and no brain lesions were seen in rats intermittently exposed to 50 ppm for 2 years (Cheever et al. 1990). No studies regarding the potential neurotoxicity of dermal exposure were located. The discrepancy in results between gavage and drinking water administration may be due to saturation of the detoxification/excretion mechanism by the bolus gavage dosing. These data do not sufficiently characterize the potential for 1,2-dichloroethane to induce more subtle neurotoxic effects following low-level prolonged exposure by inhalation, oral, or dermal exposure. Intermediate-duration neurotoxicity studies in animals, using sensitive functional and neuropathological tests at inhalation and oral exposure levels significantly lower than those resulting in morbidity and death, would assist in the characterization of the neurotoxic potential of 1,2-dichloroethane.

Epidemiological and Human Dosimetry Studies. A data need has been identified. Most of the available information on the adverse noncancer effects of 1,2-dichloroethane in humans comes from cases of acute poisoning by inhalation or ingestion (Garrison and Leadingham 1954; Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Nouchi et al. 1984; Schönborn et al. 1970; Yodaiken and Babcock 1973) and epidemiological studies of exposure to drinking water contaminants, residence near hazardous waste sites, or employment in the chemical industry (discussed later in this section). Limitations inherent in the case studies include unquantified exposure and the high-dose nature of the exposures. Despite their inadequacies, the available human case studies indicate that 1,2-dichloroethane can cause neurotoxic, nephrotoxic, and hepatotoxic effects, and death due to cardiac arrhythmia. These observations are similar to those in high-dose animal studies, but other, more sensitive effects seen in animals at low levels of exposure have not been investigated in humans.

Epidemiologic investigations of adverse birth outcomes found an increased OR for exposure to 1,2-dichloroethane in public drinking water and major cardiac defects (but not neural tube defects) (Bove 1996; Bove et al. 1995), and an increased OR for residence within the census tract of NPL sites contaminated with 1,2-dichloroethane and neural tube defects (but not heart defects) (Croen et al. 1997).

The study populations also were simultaneously exposed to elevated levels of other contaminants. Because of the mixed chemical exposure, lack of dose-response information, and inconsistency between the findings of the two studies, the associations with 1,2-dichloroethane are only suggestive, and do not establish a cause-and-effect relationship. The animal data do not indicate that 1,2-dichloroethane is teratogenic, but conventional teratology protocols were used that do not include detailed examinations of dissected hearts. Increased rates of premature births were reported in workers exposed in a Chinese synthetic fiber factory (Zhao et al. 1989). The study included women exposed throughout pregnancy and unexposed wives of men exposed for at least 1 year before their wives became pregnant, and included relatively small numbers of exposed workers. It was generally deficient in reporting of study design and accounting for possible confounders, including other chemicals in the factory. In general, the adequate one- and two-generation reproductive studies in animals did not report effects except at high, maternotoxic exposure levels.

Epidemiological studies of workers in the chemical industry suggest that exposure to chemical manufacturing processes that involve 1,2-dichloroethane is associated with an increased incidence of brain tumors (Austin and Schnatter 1983a, 1983b; Reeve et al. 1983; Teta et al. 1989; Waxweiler et al. 1983), nonlymphatic leukemia (Ott et al. 1989), stomach cancer, and leukemia (Hogstedt et al. 1979), and with increased deaths due to pancreatic cancer and lymphatic and hematopoietic cancers (Benson and Teta 1993) among chemical plant workers. Increased risk of breast cancer was reported among men working at jobs associated with exposure to gasoline or gasoline combustion products containing 1,2-dichloroethane (Hansen 2000), and the risk of several cancer types was increased in residents living proximal to a Montreal municipal waste site that emitted volatile organic substances including 1,2-dichloroethane (Goldberg et al. 1995). These studies involved exposure to other chemicals and did not deal with 1,2-dichloroethane exposure exclusively. Isacson et al. (1985) reported an association between the presence of 1,2-dichloroethane in drinking water and an increased incidence of colon and rectal cancer in men aged 55 years or older, but other organic chemicals were present in the drinking water. Studies in animals are adequate to support the determination that 1,2-dichloroethane may reasonably be anticipated to be a human carcinogen.

Well-controlled epidemiological studies of people living in areas where 1,2-dichloroethane has been detected in water or near industries or hazardous waste sites releasing 1,2-dichloroethane, and/or of people exposed in the workplace, could add to and clarify the existing database on 1,2-dichloroethane-induced human health effects. In the United States, however, about 98% of the 1,2-dichloroethane produced is used (usually captively) to manufacture vinyl chloride (Anonymous 1998), which is a more

potent toxicant and carcinogen than is 1,2-dichloroethane. Other uses of 1,2-dichloroethane also involve manufacture of other chemicals. Therefore, it may not be possible to identify a cohort of workers exposed predominantly to 1,2-dichloroethane. Previous studies of 1,2-dichloroethane from hazardous waste sites or drinking water have not been able to establish anything more than a weak association between a health effect and 1,2-dichloroethane due to the presence of many other chemicals at the sites or in the water, small numbers of cases with the health effect, and difficulties in controlling for all of the variables that may confound the results for a general population study. At present, the only known health effects of 1,2-dichloroethane in humans, seen in cases of acute high exposure, are neurotoxicity, nephrotoxicity, hepatotoxicity, and effects on the cardiovascular system. A particularly sensitive end point of acute inhalation or gavage exposure to 1,2-dichloroethane in mice (but not rats) is immunological effects. No data regarding this end point are available for humans.

Biomarkers of Exposure and Effect.

Exposure. A data need has been identified. Proposed biomarkers for exposure to 1,2-dichloroethane include levels of parent compound in the breath, blood, urine, and breast milk; levels of thioethers in the urine; and levels of thiodiglycolic acid in the urine (Igwe et al. 1988; Payan et al. 1993; Spreafico et al. 1980; Urusova 1953). However, use of the parent compound as a biomarker would only be possible soon after exposure, and the other proposed biomarkers are not specific for 1,2-dichloroethane. If epidemiological studies are conducted in which there is a correlation between 1,2-dichloroethane exposure and specific adverse health effects, then it may be possible to correlate these health effects quantitatively with changes in tissue and/or body levels of 1,2-dichloroethane.

Effect. Biomarkers of effect for 1,2-dichloroethane include serum enzyme levels indicative of liver damage (ALT, AST, SDH), increased liver or kidney weight (size), and DNA adduct formation for liver and kidney effects (Brondeau et al. 1983; Inskeep et al. 1986; Nouchi et al. 1984; Prodi et al. 1986). Another potential biomarker would be tests for immunosuppression, but immune effects have been demonstrated only in mice in acute exposure studies (Munson et al. 1982; Sherwood et al. 1987). Because they have not been seen in humans, rats, or even mice exposed for an intermediate duration, the relevance of these effects to humans is uncertain. None of these biomarkers are specific for 1,2-dichloroethane. These biomarkers are indicative of effects, but dosimetry has not been worked out for any of them. Because immunological effects of 1,2-dichloroethane have been seen only in mice, it is uncertain whether immunosuppression would occur in humans exposed to this chemical.

Absorption, Distribution, Metabolism, and Excretion. A data need to assess the toxicokinetics of 1,2-dichloroethane following inhalation, oral, and dermal exposure has been identified. Case reports of toxic effects subsequent to inhalation or oral exposure suggest that 1,2-dichloroethane is absorbed following exposure by these routes (Garrison and Leadingham 1954; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Nouchi et al. 1984; Schönborn et al. 1970; Yodaiken and Babcock 1973). Inhalation exposure of lactating women in the workplace resulted in distribution of 1,2-dichloroethane to their milk (Urusova 1953). Animal studies were sufficient to characterize the rate and extent of absorption following inhalation, oral, and dermal exposure (Morgan et al. 1991; Reitz et al. 1980, 1982; Spreafico et al. 1980). Distribution, metabolism, and excretion have also been well studied in animals exposed by the inhalation or oral routes (D'Souza et al. 1987, 1988; Reitz et al. 1982; Spreafico et al. 1980), and are qualitatively similar across these routes. Metabolism is saturable in animals, but the precise levels at which saturation phenomena come into play have not been determined and appear to differ between oral (gavage) and inhalation exposures (Reitz et al. 1982). Additional studies investigating the saturation of MFO metabolism by inhaled and ingested 1,2-dichloroethane would enable better understanding of the metabolism of this compound. Based on the elimination of virtually all radiolabel from inhalation or gavage administration of 1,2-dichloroethane to rats within 48 hours, Reitz et al. (1982) concluded that the potential for 1,2-dichloroethane to accumulate with repeated exposure is minimal. The rate of elimination of the parent compound from adipose tissue was similar to that from blood following gavage administration to rats, but was slower following a single inhalation exposure or intravenous injection (Spreafico et al. 1980; Withey and Collins 1980), raising the possibility that 1,2-dichloroethane may accumulate to some extent in adipose tissue and in breast milk of nursing women. More quantitative information on the presence of 1,2-dichloroethane in fat and breast milk would be useful to assess the ability of 1,2-dichloroethane to accumulate in fat and the potential hazard to nursing infants. Further study into the long-term fate of low-level 1,2-dichloroethane exposure in humans and animals and the potential for accumulation in humans would also provide valuable information.

Toxicity data in humans and animals suggest similar target organs in each. Toxicokinetic studies have not been performed in humans. The database with regard to comparative toxicokinetics across species is limited as most studies have been performed in rats (D'Souza et al. 1987, 1988; Morgan et al. 1991; Reitz et al. 1980, 1982; Spreafico et al. 1980). Only one set of studies included mice (D'Souza et al. 1987, 1988), and these studies were conducted to validate PBPK modeling, primarily for levels of the direct GSH conjugate in selected tissues of concern for carcinogenicity (liver and lung). More information on the toxicokinetics of 1,2-dichloroethane in other animal species would be useful for more fully assessing interspecies differences and the implications for human exposure. The database with regard to

comparative toxicokinetics across routes does include comparative toxicokinetics across acute inhalation and gavage (oil) administration (Reitz et al. 1980; Spreafico et al. 1980). The vehicle used in oral administration studies appears to play a role in the time course of absorption. Withey et al. (1983) reported that 1,2-dichloroethane is absorbed more rapidly by the gastrointestinal tract following gavage administration in water than in corn oil; the estimated area under the curve (based on data for up to 300 minutes postdosing) was also much greater for the water than the oil vehicle). Information on toxicokinetics for repeated or longer-term continuous exposure is not available.

Comparative Toxicokinetics. Toxicity data in humans and animals suggest similar target organs in each. Toxicokinetic studies have not been performed in humans. The database with regard to comparative toxicokinetics consists primarily of studies in rodents (D'Souza et al. 1987, 1988; Morgan et al. 1991; Reitz et al. 1980, 1982; Spreafico et al. 1980). More information on the toxicokinetics of 1,2-dichloroethane in other animal species would be useful for more fully assessing interspecies differences and the implications for human exposure.

Methods of Reducing Toxic Effects. A data need has been identified. It appears that 1,2-dichloroethane is absorbed across the alveolar membrane, gastrointestinal epithelium, and skin by passive means. Methods to reduce absorption following oral and dermal exposure are available, but must be applied soon after exposure (Ellenhorn and Barceloux 1988). The available data suggest that 1,2-dichloroethane does not accumulate in the nonlipid components of the human body, but that it may accumulate to some extent in adipose tissue and in the breast milk of nursing women. Methods to enhance removal of 1,2-dichloroethane from the body have not been successful (Ellenhorn and Barceloux 1988); determination of successful methods is needed. The mechanism of action of 1,2-dichloroethane is not clearly understood but involves complex toxifying and detoxifying reactions with glutathione (Jaeger et al. 1974; NTP 1991a). Reactive metabolites of P-450 metabolism are detoxified by conjugation with glutathione, but direct conjugation of unmetabolized 1,2-dichloroethane with glutathione produces reactive and toxic intermediates, which are in turn detoxified through additional reaction or conjugation with glutathione. Nevertheless, limited evidence that administration of glutathione and its precursors may have a protective effect against 1,2-dichloroethane toxicity in animals has been reported (Heppel et al. 1947; Jaeger et al. 1974; Johnson 1967). Further elucidation of the toxic mechanisms might enable identification of methods for reducing the toxic effects.

Endocrine Disruption. A data need to conduct additional studies on the endocrine system via dermal exposure has been identified.

A human study that reported increased rates of premature births in female workers and in wives of male workers at a Chinese synthetic fiber factory (Zhao et al. 1989) should be viewed with caution because of the deficient reporting of design, apparent lack of control for possible confounding environmental and behavioral factors, small number of subjects, and co-exposure to other chemicals. No assays of endocrine function are available. Some studies in animals, however, provide data regarding a lack of effect of 1,2-dichloroethane on the histology of endocrine tissues and on reproduction. Histological examinations of endocrine tissues were performed in animals exposed by inhalation or oral administration with essentially negative results (Cheever et al. 1990; Daniel et al. 1994; Heppel et al. 1946; NCI 1978; NTP 1991a; Spencer et al. 1951; van Esch et al. 1977). The examinations in these studies were generally limited to the adrenal gland and/or pancreas, although the pituitary, thyroid, and parathyroid glands were also evaluated following chronic inhalation and oral exposures. The only endocrine-related finding was calcification of the adrenal medulla in one of two monkeys exposed to 1,2-dichloroethane by inhalation in an intermediate-duration study (Heppel et al. 1946), but no controls were examined, and adrenal effects have not been reported in other long-term inhalation studies by these and other investigators. Histological examinations of pertinent reproductive tissues in animals in inhalation and oral studies revealed no changes (Cheever et al. 1990; Daniel et al. 1994; NCI 1978; NTP 1991a; van Esch et al. 1977), and adequately conducted studies of reproductive function in animals exposed to 1,2-dichloroethane by inhalation or oral routes (Alumot et al. 1976; Lane et al. 1982; Rao et al. 1980), although not definitive, strongly indicate that 1,2-dichloroethane is unlikely to impair reproduction at levels that are not maternally toxic. In an early NCI (1978) bioassay that had a number of limitations including dosage adjustments, possible contamination by other chemicals tested in the same laboratory, poor survival, and small control groups, gavage treatment with 1,2-dichloroethane in corn oil was associated with statistically significant increases in multiple tumor types, including mammary gland adenocarcinoma in female rats and mice and endometrial tumors in female mice. The finding of tumors in two endocrine-sensitive tissues is suggestive. On the other hand, the mechanism of carcinogenicity for 1,2-dichloroethane appears to involve alkylation of DNA, and statistically significant increased incidences were also observed for tumors of the forestomach, circulatory system, subcutaneous tissue, liver, and lung in the NCI (1978) study. The oral and inhalation data for noncancer effects in animals do not suggest that 1,2-dichloroethane has endocrine disrupting activity. No data are available for the dermal route, so there is a need for screening data (e.g., reproductive and other endocrine histopathology in a dermal study).

Children's Susceptibility. A data need to conduct additional studies relevant to children's susceptibility via oral, inhalation, and dermal exposure has been identified. Data on the effects of 1,2-dichloroethane exposure in children are limited to a single case report of a 14-year-old boy who

swallowed 15 mL of the compound (Yodaiken and Babcock 1973). The most immediate signs of toxicity were headache and staggering gait within 2 hours of exposure, followed soon after by lethargy and vomiting. During the next few days, the boy developed symptoms of toxicity, increasing in variety and severity, that involved several organ systems, including adverse hematological effects, pulmonary edema, cardiac arrest (he was resuscitated), and eventual death on the 5th day after exposure from massive hepatic necrosis and renal tubular necrosis. Data from this case report and from reports of adult humans who died following acute exposure to high levels by inhalation or ingestion are consistent with animal studies indicating that main targets of acute toxicity include the central nervous system, respiratory tract, stomach, liver, and kidneys. Considering the consistency of effects in acutely exposed humans and animals, and data showing that the liver and kidney are sensitive targets of lower-dose and longer-term inhalation and oral exposures in animals, it is reasonable to assume that effects in these tissues would also be seen in similarly exposed adults and children.

Evidence from mouse studies suggests that the specific nature of oral exposure or the age of the animals at the time of the immune testing may play a role in the degree of immunotoxicity expressed in young animals. Repeated gavage administration for 14 days of 1,2-dichloroethane appears to be more effective in eliciting an immunotoxic response than 90-day drinking-water exposure in 5-week-old mice (Munson et al. 1982). While this difference could be due to the saturation of detoxifying/excretion pathways by bolus gavage dosing, an alternative explanation is that young mice may be more sensitive to 1,2-dichloroethane than adult mice. The mice used for both the acute (14-day) and the 90-day studies were 5 weeks old at the start of dosing, so at the time of testing, the mice in the 14-day study were 7 weeks old, but the mice in the 90-day study were 17 weeks old. The decreased immune response in mice exposed at 5–7 weeks of age provides a limited indication of the potential susceptibility of children to immunotoxic effects. Because no immunotoxic effects were seen in young rats exposed to much higher inhalation concentrations of 1,2-dichloroethane than those that produced immunosuppression in mice (Sherwood et al. 1987), and because there are no reports of immune effects in humans exposed to this chemical, the relevance of the data in young mice to children is uncertain. Studies that also evaluate for other toxicological end points after exposures in immature animals are needed, particularly for known targets of toxicity such as the liver and kidney. Appropriate comparative studies are needed to document the toxicological potential and metabolism of 1,2-dichloroethane and to assess whether children and adults are equally susceptible, especially after longer-term exposures.

No studies that provide reliable information on adverse developmental effects in humans exposed to 1,2-dichloroethane are available. A cross-sectional epidemiologic study that investigated whether

elevated levels of routinely sampled organic contaminants in New Jersey public water systems, including 1,2-dichloroethane, were associated with increased prevalences of adverse birth outcomes (Bove 1996; Bove et al. 1995) was located. A number of associations between various chemicals and birth outcomes were found, including a positive association between ingestion of 1,2-dichloroethane in drinking water and major cardiac birth defects (but not neural tube defects). Similarly, a study that investigated residence within the census tract of NPL sites contaminated with 1,2-dichloroethane reported an association with neural tube (but not heart defects) (Croen et al. 1997). The mixed chemical exposures in these studies, and the lack of concordance on end point, indicate that the results are only suggestive, do not establish a cause-and-effect relationship, and should be interpreted with caution.

Studies in rats, mice, and rabbits indicate that 1,2-dichloroethane is not developmentally toxic following inhalation or oral gestational exposure, although fetolethality has been reported at maternolethal exposure levels following inhalation exposure (Kavlock et al. 1979; Lane et al. 1982; Payan et al. 1995; Rao et al. 1980). Embryolethality was reported at relatively low exposure levels in another inhalation study (Vozovaya 1977), but the reliability of these results cannot be evaluated due to limitations in reporting and data analysis.

No studies that evaluated for the distribution of 1,2-dichloroethane or its metabolites across the placenta in humans were located. However, there is some evidence that 1,2-dichloroethane and/or its metabolites crosses the placenta after inhalation and oral exposures in animals. 1,2-Dichloroethane was found in maternal blood (83.6±20.2 mg %), placental tissue (43.0±9.6 mg %), amniotic fluid (55.5±11.1 mg %), and fetal tissue (50.6±11.5 mg %) after inhalation exposure of female rats to 247±10 ppm 1,2-dichloroethane during pregnancy (Vozovaya 1977). Additional evidence of transplacental distribution of 1,2-dichloroethane after inhalation exposure is provided by Withey and Karpinski (1985), who found that the geometric mean concentration of 1,2-dichloroethane in the fetuses of rats that inhaled 150–2,000 ppm for 5 hours increased linearly with increasing exposure level. However, the reliability of the Vozovaya data is unclear, and the methods for evaluating 1,2-dichloroethane tissue concentrations were not reported in Withey and Karpinski (1985).

There is clearer evidence for transplacental distribution of 1,2-dichloroethane and/or its metabolites after maternal oral exposure. Payan et al. (1995) evaluated [^{14}C]-1,2-dichloroethane distribution in maternal rats following a single oral bolus dose of approximately 160 mg/kg on gestation day 12 or 18. In both cases, transplacental distribution of radiocarbon was demonstrated by the presence of radioactivity in the developing conceptus. A greater accumulation occurred in the developing fetus and placenta 48 hours

after the gestation day 18 administration than after the gestation day 12 administration. At 48 hours after the gestation day 18 dosing, the majority of residual radioactivity burden was located in the fetus (0.167% of administered dose) and the liver (0.156% of administered dose).

No studies regarding 1,2-dichloroethane metabolism in children were located. The metabolism of 1,2-dichloroethane is well described (NTP 1991a; WHO 1995), and it is reasonable to assume that the metabolic pathways are, for the most part, the same between adults and children. However, the expression of certain enzymes is known to be developmentally regulated, and one of these enzymes may be involved in 1,2-dichloroethane metabolism. NAT is involved in 1,2-dichloroethane metabolism at a step subsequent to GSH conjugation. NAT performs the N-acetylation of *S*-carboxymethyl-L-cysteine to N-acetyl-*S*-carboxymethyl-L-cysteine, a major urinary metabolite. There are, however, two NATs (NAT1 and NAT2) that are expressed in humans with separate but overlapping substrate specificities (Parkinson 1996). NAT2 is apparently expressed only in the liver and the gut (Parkinson 1996), and is known to be developmentally regulated (Leeder and Kearns 1997). Some NAT2 activity is present in the fetus at 16 weeks, but NAT2 activity is low in virtually 100% of infants, not reaching adult activity levels until 1–3 years of age (Leeder and Kearns 1997). It is not clear in NTP (1991a) or WHO (1995) whether the NAT involved in 1,2-dichloroethane metabolism is NAT1 or NAT2, although both enzymes N-acetylate some xenobiotics equally well (Parkinson 1996). The impact of lower rates of N-acetylation of S-carboxymethyl-L-cysteine in terms of potential health effects also is unclear.

1,2-Dichloroethane has been detected in human milk (EPA 1980a; Urusova 1953), indicating that developing children could possibly be exposed to 1,2-dichloroethane from breast-feeding mothers. The importance of this route of developmental exposure is unclear because current data on the concentration of 1,2-dichloroethane in breast milk are not available. 1,2-Dichloroethane was also accumulated in the adipose tissue of rats after inhalation exposure and was eliminated from fat more slowly than from blood, liver, and lung (Spreafico et al. 1980), suggesting the possibility that the maternal body burden of 1,2-dichloroethane in fat could be available for exposure to the fetus or nursing infant for a somewhat extended period after maternal exposure. Supporting data for relatively slow elimination of 1,2-dichloroethane from fat are provided in an intravenous exposure study in rats (Withey and Collins 1980). Nevertheless, 1- and 2-generation reproductive studies of 1,2-dichloroethane, administered by inhalation or drinking water exposure to rats and mice, in which the pups were exposed through the milk of the treated dams, showed no adverse effects on survival, body weight, gross appearance of tissues and organs (Lane et al. 1982; Rao et al. 1980), or histological appearance of the liver, kidneys, ovaries, uterus, and testes (Rao et al. 1980) in the pups at 21 days of age.

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

3.12.3 Ongoing Studies

The role of 1,2-dichloroethane and two other common groundwater contaminants, individually and in combination, in the development of hepatic angiosarcoma will be studied by Dr. Wendy A. Pott at the Foothills Campus of Colorado State University (FEDRIP 2000). The long-term objectives of this project are (1) to evaluate the carcinogenic effects of subchronic exposure to 1,2-dichloroethane, arsenic, and vinyl chloride, which are implicated as etiologic agents in the development of angiosarcoma; and (2) to use data from these studies with PBPK/PD models and statistical and mathematical modeling techniques for the purpose of health-risk characterization. Specific aims of the project include (1) evaluating whether synergistic carcinogenic activity may result when arsenic is combined with 1,2-dichloroethane; (2) developing PBPK/PD models for target tissue dosimetry of single chemicals and combinations of chemicals following exposure to arsenic, vinyl chloride, and/or 1,2-dichloroethane; and (3) developing cell turnover and carcinogenesis models and integrating them with PBPK/PD models to characterize cancer risks associated with exposure to arsenic, vinyl chloride, and/or 1,2-dichloroethane. These goals will be accomplished using a medium-term angiosarcoma bioassay to investigate the effects of each of the chemicals, alone and in combination, in inducing hepatic angiosarcoma. Data gathered from these experiments will be used to develop models to determine cancer risks and safe drinking-water levels of these chemicals.