2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to 1,2-dichloropropane. Its purpose is to present levels of significant exposure for 1,2-dichloropropane based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of 1,2-dichloropropane and (2) a depiction of significant exposure levels associated with various adverse health effects.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each exposure route and duration (for which data exist) 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies 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 on the tables and graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious effects." Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (minimal risk levels, MRLs) are of interest to health professionals and citizens alike.

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For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited. Because cancer effects could occur at lower exposure levels, the figures also show estimated excess risks, ranging from a risk of one in 10,000 to one in 10,000,000 ($10m^4$ to $10m^7$), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1980), uncertainties are associated with the techniques.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding lethal effects in humans following inhalation exposure to 1,2-dichloropropane.

The lethality after a single exposure by inhalation to 1,2-dichloropropane has been determined in rats and mice. Smyth et al. (1969) and Pozzani et al. (1959) reported LC50 values of 2000 ppm and 3029 ppm, respectively, after a single n-hour exposure in rats. Carpenter et al. (1949) determined that 2000 ppm resulted in the death of 2/6, 3/6 or 4/6 rats after a single 4-hour exposure to 1,2-dichloropropane; Heppel et al. (1946) reported the death of 3/12 rats after a single 7-hour exposure of 1600 ppm; Highman and Heppel (1946) reported the death of 6/24 rats several hours after one 7-hour exposure to 2200 ppm; and Nitschke and Johnson (1983) found no mortality in rats exposed to 1000 ppm 1,2-dichloropropane for 6 hours. Dow Chemical (1982) reported an LC_{50} value of 480 ppm in mice after a single 10-hour exposure to 1,2-dichloropropane. All mice (22-26 animals) died after a single exposure of four hours to 1000 ppm or 1500 ppm, while 3/10 mice died after a single two-hour exposure to 1500 ppm. Nitschke and Johnson (1983) reported the death of all mice within 24 hours of a 6-hour exposure to 1500 ppm 1,2-dichloropropane and, following a 6-hour exposure to 500 mm, mice became lethargic and 2/5 mice died within 3 days of exposure. The concentration of 480 ppm in air from the Dow Chemical (1982) study is presented in Table l-2.

Lethality was observed in rats, mice, guinea pigs and rabbits repeatedly exposed by inhalation to 1,2-dichloropropane for 14 days or less (acute exposure is defined as treatment for ≤14 calendar days). Exposures of 7 hours/day, 5 days/week for 2-10 exposures in the Heppel et al. (1946) study resulted in the deaths of 8/39 rats exposed to 1000 ppm; 3/18 rats and 3/18 guinea pigs exposed to 1500 ppm; and 8/20 rats, 11/16 guinea pigs and 2/4 rabbits exposed to 2200 ppm. Five consecutive days of -/-hour exposures

of 1600 ppm resulted in the death of 0/13 rats, 0/10 guinea pigs and l/2 rabbits (Heppel et al. 1946). Highman and Heppel (1946) reported the death of 7/20 guinea pigs after 2-3 exposures of 7 hours to 2200 ppm 1,2-dichloropropane. Heppel et al. (1948) observed no lethality in rats or guinea pigs following l-9, -7-hour exposures to 400 ppm 1,2-dichloropropane. Nitschke and Johnson (1983) reported no compound-related mortality in rats and rabbits intermittently exposed for 2 weeks to ≤1000 ppm or in mice exposed to ≤300 ppm 1,2-dichloropropane (6 hours/day, 4 to 5 days/week). The concentrations of 1000 ppm in air for rats and 1500 ppm in air for guinea pigs (Heppel et al. 1946) are presented in Table l-2.

The lethality of 1,2-dichloropropane inhaled repeatedly over an intermediate time period (intermediate exposure is defined as treatment for 15 to 364 calendar days) was reported for rats, mice, guinea pigs, rabbits and dogs. Exposures of 7 hours/day, 5 days/week for 11 to 128 exposures in the Heppel et al. (1946) study resulted in the death of 17/45 rats, 3/12 guinea pigs, 0/4 rabbits and 4/8 dogs exposed to 1000 ppm; and 4/18 rats, 2/18 guinea pigs and l/4 rabbits exposed to 1500 ppm. Heppel et al. (1948) observed no lethality in rats, dogs and guinea pigs exposed to 12-140, 7-hour exposures to 400 ppm 1,2-dichloropropane. Nitschke et al. (1988) reported no compound-related mortality in rats and mice intermittently exposed for 13 weeks to ≤150 ppm or in rabbits exposed to <1000 ppm 1,2-dichloropropane (6 hours/day, 5 days/week). Heppel et al. (1948) determined that 37 exposures of 4-7 hours at 400 ppm resulted in the death of 77/80 mice. The cause of death was not given, but some of the mice that died after receiving 14-28 exposures showed moderate to marked congestion and fatty degeneration of the liver, extensive centrolobular coagulation necrosis of the liver, and slight to moderate fatty degeneration of the kidney. The concentrations of 400 ppm in air for mice (Heppel et al. 1948) and 1000 ppm in air for rats, guinea pigs and dogs (Heppel et al. 1946) are presented in Table l-2.

No studies were found which determined the toxicity of 1,2-dichloropropane after inhalation for a chronic period of time (chronic exposure is defined as treatment for ≥365 calendar days).

The highest reliable NOAEL value and all reliable LOAEL values for lethal effects in each species and duration category are reported in Table 2-l and plotted in Figure 2-l. The Carpenter et al. (1949) study cannot be used as the basis for a LOAEL in rats since a small number of animals were evaluated (six), and it is not clear if controls were used. The data evaluating the lethal effects of 1,2-dichloropropane on rabbits in the Heppel et al. (1946) study and on rats and mice in the Nitschke and Johnson (1983) study cannot be used as a basis for NOAELs and LOAELs since so few animals were used (four rabbits, five mice, five rats).

TABLE 2-1. Levels of Significant Exposure to 1,2-Dichloropropane - Inhalation

Graph Key	Species	Duration/ Frequency Exposure		NOAEL[b] (ppm)	LOAEL[a] (Effect)		Reference
					Less Serious (ppm)	Serious (ppm)	
ACUTE EXPOSURE							
Lethality							
1	rat	7 hr				2200 (death)	Highman and Heppel 1946
2	rat	7 hr				1600 (death)	Heppel et al. 1946
3	rat	8 hr				2000 (LC_{50})	Smyth et al. 1969
4	rat	7 hr, 5 d/wk 3-9 exp		400			Heppel et al. 1948
5	rat	7 hr/day, 5 d/wk 6-10 exp				1000 (death)	Heppel et al. 1946
6	mouse	4 hr				1000 (death)	Heppel et al. 1946
7	mouse	6 hr				500 (2/5 died)	Nitschke and Johnson 1983
8	mouse	10 hr				480 (LC_{50})	Dow Chem. 1982
9	mouse	2 wk 4-5 d/wk 6 hr/d		300			Nitschke and Johnson 1983
10	gn pig	4 hr, 7 hr 2-3 exp				2200 (death)	Highman and Heppel 1946
11	gn pig	7 hr, 5 d/wk 6 exp				1500 (death)	Heppel et al. 1946
12	gn pig	7 hr 1-4 exp		400			Heppel et al. 1948
13	rabbit	2 wk 4-5 d/wk 6 hr/d		1000			Nitschke and Johnson 1983
14	rat	6 hr	Hepatic	1500			Nitschke and Johnson 1983
15			Renal	1500			

TABLE 2-1 (continued)

Graph Key	Species	Duration/ Frequency Exposure		NOAEL[b] (ppm)	LOAEL[a] (Effect)		Reference
					Less Serious (ppm)	Serious (ppm)	
Systemic							
16	rat	4 hr, 7 hr	Hepatic		2200 (increased fat)		Highman and Heppel 1946
17		1-5 exp	Renal		2200 (increased fat)		
18	rat	2 wk 4-5 d/wk	Resp		100[c] (nasal mucosa degeneration)		Nitschke and Johnson 1983
19		6 hr/d	Hemato	1000			
20	mouse	6 hr	Hepatic			500 (hemorrhagic necrosis)	Nitschke and Johnson 1983
21			Renal	1500			
22, 23	mouse	2 wk 4-5 d/wk	Resp	30	100 (nasal mucosa degeneration)		Nitschke and Johnson 1983
24		6 hr/d	Hemato	300			
25, 26			Hepatic	100	300 (vacuolization increased liver weight)		
27	gn pig	7 hr 1-8 exp	Ocular			2200 (conjuntivitis)	Heppel et al. 1946
28	gn pig	7 hr	Hepatic	400			Heppel et al. 1948
29		1-4 exp	Renal	400			
30	gn pig	4 hr, 7 hr	Hepatic		2200 (increased fat)		Highman and Heppel 1946
31		1-5 exp	Renal		2200 (increased fat)		
32, 33	rabbit	2 wk 4-5 d/wk	Resp	300	1000 (nasal mucosa degeneration)		Nitschke and Johnson 1983
34		6 hr/d	Hemato	1000			
35			Hepatic	1000			
36			Renal	1000			
Immunological							
37	rat	2 wk 4-5 d/wk 6 hr/d		1000			Nitschke and Johnson 1983

TABLE 2-1 (continued)

Graph Key	Species	Duration/ Frequency Exposure	NOAEL[b] (ppm)	LOAEL[a] (Effect)		Reference
				Less Serious (ppm)	Serious (ppm)	
Immunological						
38, 39	mouse	2 wk 4-5 d/wk 6 hr/d	100	300 (decreased weight of thymus, decreased lymphoid cells)		Nitschke and Johnson 1983
Neurological						
40, 41	rat	6 hr	500		1500 (anesthesia)	Nitschke and Johnson 1983
42	mouse	6 hr			500 (lethargy and death)	Nitschke and Johnson 1983
Reproductive						
43	rat	2 wk 4-5 d/wk 6 hr/d	1000			Nitschke and Johnson 1983
44	mouse	2 wk 4-5 d/wk 6 hr/d	300			Nitschke and Johnson 1983
45	rabbit	2 wk 4-5 d/wk 6 hr/d	1000			Nitschke and Johnson 1983
INTERMEDIATE EXPOSURE						
Lethality						
46	rat	7 hr/d 5 d/wk 12-59 exp			1000 (death)	Heppel et al. 1946
47	rat	7 hr, 5 d/wk 12-140 exp	400			Heppel et al. 1948
48	mouse	4-7 hr 15-37 exp			400 (death)	Heppel et al. 1948

TABLE 2-1 (continued)

Graph Key	Species	Duration/ Frequency Exposure		NOAEL[b] (ppm)	LOAEL[a] (Effect) Less Serious (ppm)	LOAEL[a] (Effect) Serious (ppm)	Reference
Lethality							
49	mouse	13 wk 5 d/wk 6 hr/d		150			Nitschke et al. 1988
50	gn pig	7 hr, 5 d/wk 134 exp		400			Heppel et al. 1948
51	gn pig	7 hr, 5 d/wk 22-126 exp				1000 (death)	Heppel et al. 1946
52	rabbit	13 wk 5 d/wk 6 hr/d		1000			Nitschke et al. 1988
53	dog	7 hr, 5 d/wk 27-96 exp				1000 (death)	Heppel et al. 1946
54	dog	7 hr, 5 d/wk 134 exp		400			Heppel et al. 1948
Systemic							
55	rat	13 wk 5 d/wk	Resp		15[d] (upper respiratory lesions)		Nitschke et al. 1988
56		6 hr/d	Cardio	150			
57			Gastro	150			
58			Hemato	150			
59			Musc/skel	150			
60			Derm/Oc	150			
61, 62			Body Weight	50	150 (decreased body weight gain)		
63	rat	7 hr/d	Hepatic	1000			Heppel et al. 1946
64		5 d/wk 12-59 exp	Renal	1000			

TABLE 2-1 (continued)

Graph Key	Species	Duration/ Frequency Exposure		NOAEL[b] (ppm)	LOAEL[a] (Effect) Less Serious (ppm)	LOAEL[a] (Effect) Serious (ppm)	Reference
Systemic							
65	mouse	13 wk	Resp	150			Nitschke et al. 1988
66		5 d/wk	Cardio	150			
67		6 hr/d	Gastro	150			
68			Hemato	150			
69			Musc/skel	150			
70			Hepatic	150			
71			Renal	150			
72			Derm/Oc	150			
73			Body Weight	150			
74	gn pig	7 hr	Hepatic	1500			Heppel et al. 1946
75		5 d/wk 11 exp	Renal	1500			
76	rabbit	13 wk 5 d/wk	Resp		1000 (olfactory degeneration)		Nitschke et al. 1988
77		6 hr/d	Cardio	1000			
78			Gastro	1000			
79			Hemato		150 (anemia)		
80			Musc/skel	1000			
81			Hepatic	1000			
82			Renal	1000			
83			Derm/Oc	1000			
84			Body Weight	1000			
85	dog	7 hr	Hepatic	400			Heppel et al. 1948
86		5 d/wk 134 exp	Renal	400			
Immunological							
87	rat	13 wk 5 d/wk 6 hr/d		150			Nitschke et al. 1988
88	mouse	13 wk 5 d/wk 6 hr/d		150			Nitschke et al. 1988

TABLE 2-1 (continued)

Graph Key	Species	Duration/ Frequency Exposure	NOAEL[b] (ppm)	LOAEL[a] (Effect)		Reference
				Less Serious (ppm)	Serious (ppm)	
Immunological						
89	rabbit	13 wk 5 d/wk 6 hr/d	1000			Nitschke et al. 1988
Neurological						
90	rat	13 wk 5 d/wk 6 hr/d	150			Nitschke et al. 1988
91	mouse	13 wk 5 d/wk 6 hr/d	150			Nitschke et al. 1988
92	rabbit	13 wk 5 d/wk 6 hr/d	1000			Nitschke et al. 1988
Reproductive						
93	rat	13 wk 5 d/wk 6 hr/d	150			Nitschke et al.1988
94	mouse	13 wk 5 d/wk 6 hr/d	150			Nitschke et al. 1888
95	rabbit	13 wk 5 d/wk 6 hr/d	1000			Nitschke et al. 1988

[a]LOAEL - Lowest Observed Adverse Effect Level
[b]NOAEL - No Observed Adverse Effect Level
[c]Used to derive acute inhalation MRL; dose adjusted for intermittent exposure, and divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans and 10 for human variability), resulting in an MRL of 50 ppb (0.050 ppm).
[d]Used to derive intermediate inhalation MRL; dose adjusted for intermittent exposure, and divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans and 10 for human variability), resulting in an MRL of 7 ppb (0.007 ppm).

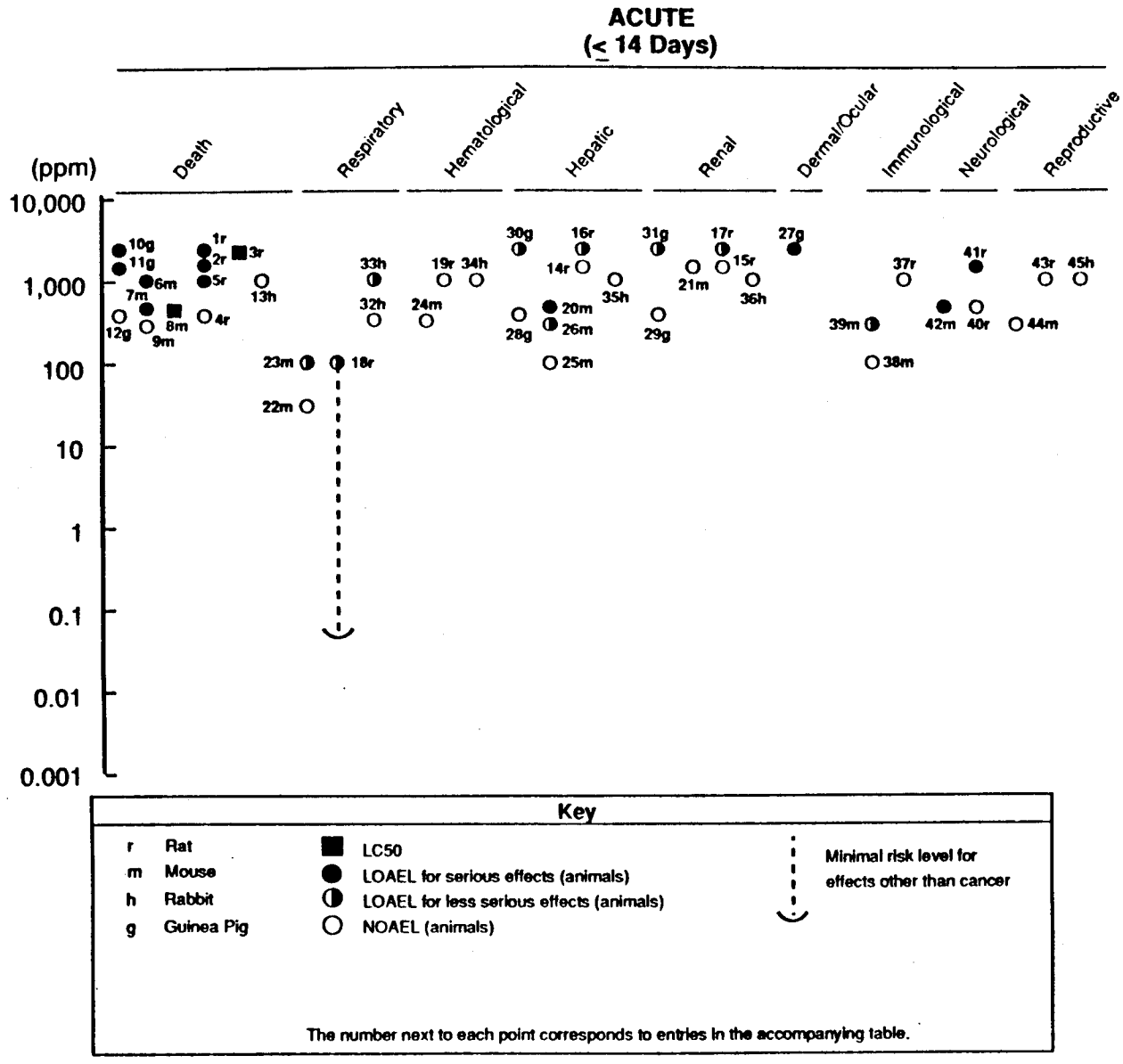

FIGURE 2-1. Levels of Significant Exposure to 1,2 - Dichloropropane - Inhalation

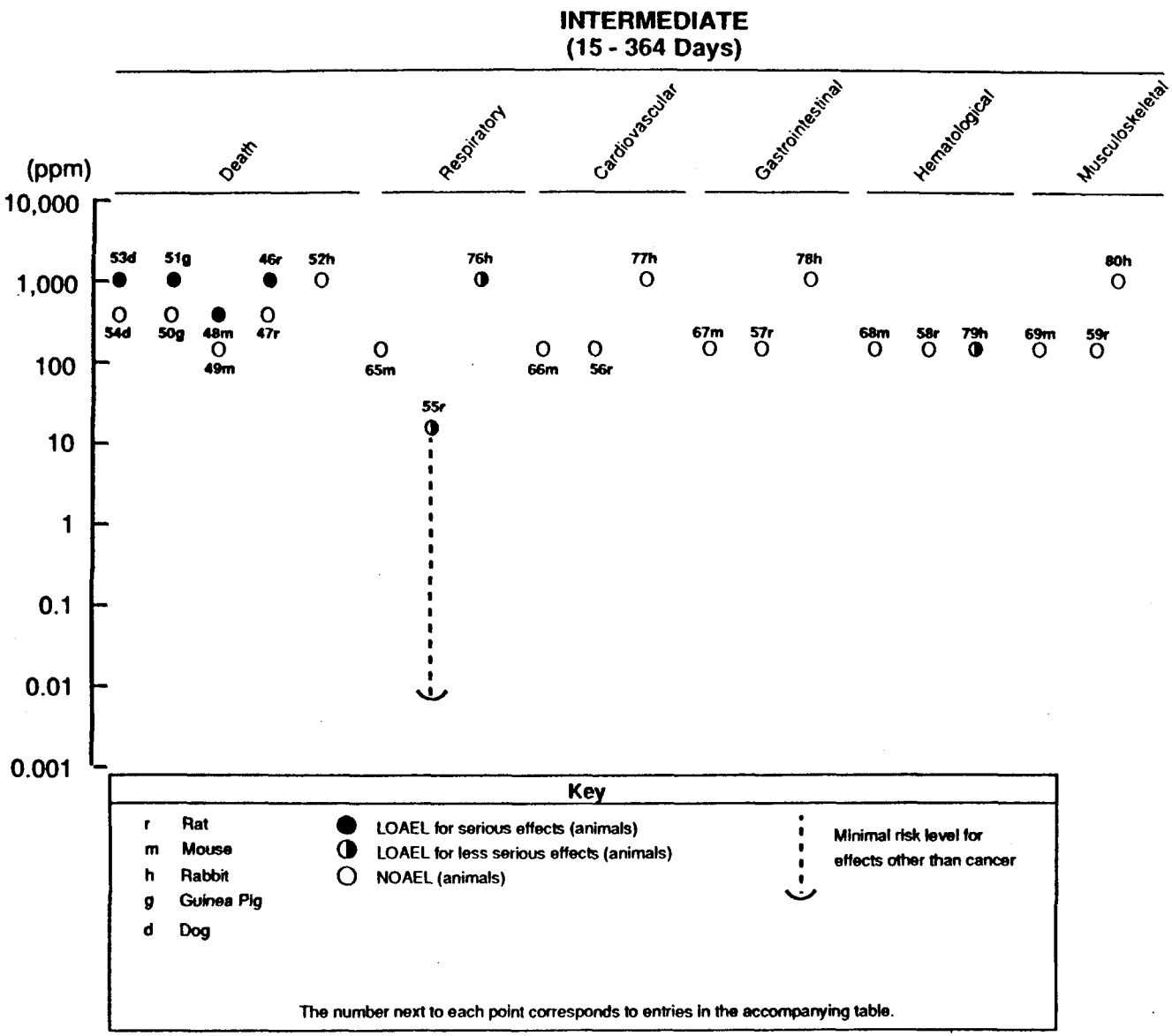

FIGURE 2-1. Levels of Significant Exposure to 1,2 - Dichloropropane - Inhalation (Continued)

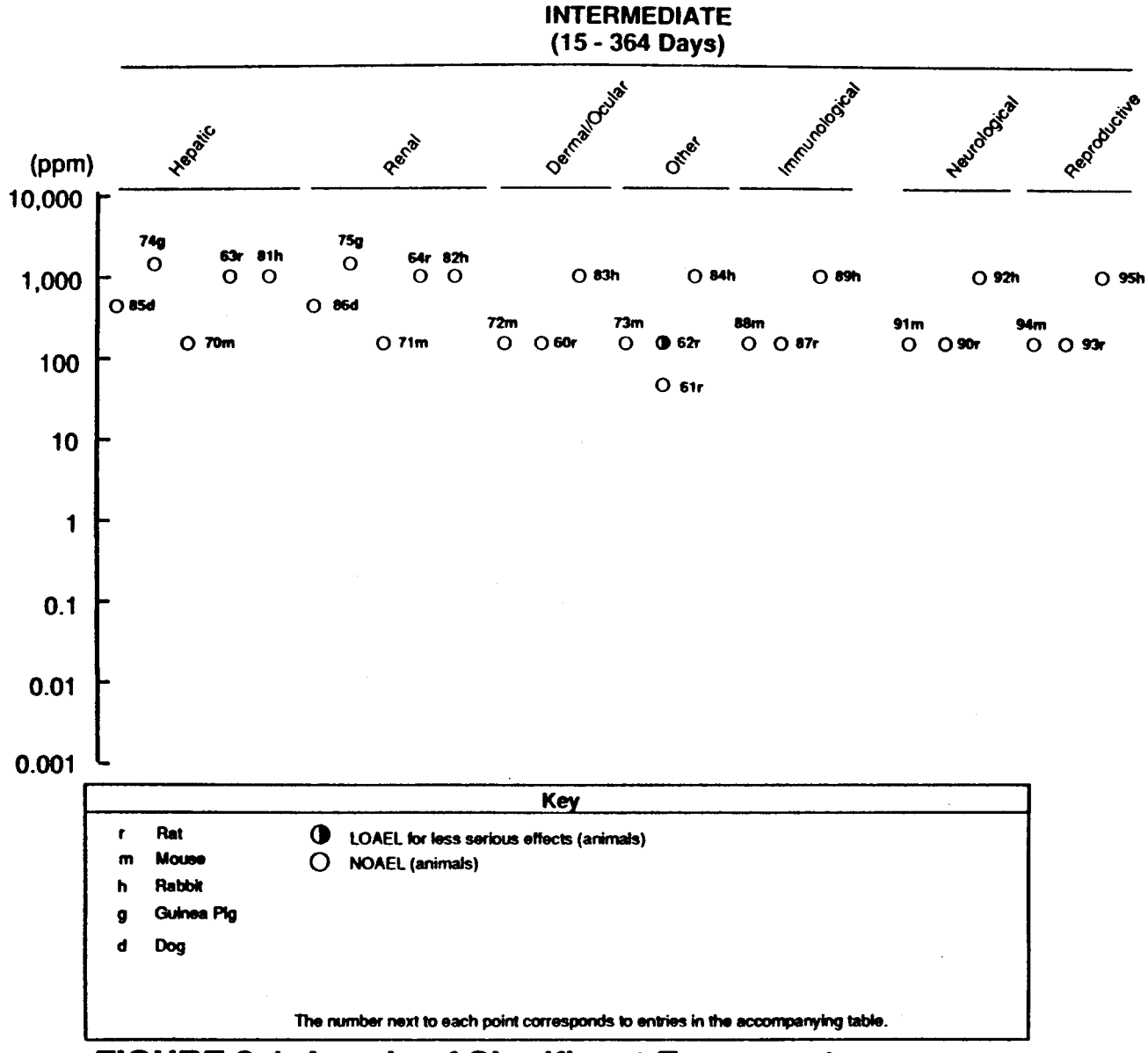

FIGURE 2-1. Levels of Significant Exposure to 1,2 - Dichloropropane - Inhalation (Continued)

2.2.1.2 Systemic Effects

Respiratory Effects. Rubin (1988) described the health effects in humans resulting from exposure to an accidental spill of 2000 gallons of 1,2-dichloropropane. The exposure resulted in chest discomfort, dyspnea, and a cough in some of the patients, indicating that 1,2-dichloropropane is a respiratory tract irritant. Air concentrations of 1,2-dichloropropane were not measured or estimated.

The effects of 1,2-dichloropropane on the respiratory systems of animals acutely exposed (1-14 days) were determined for rats, mice, and rabbits, Degeneration of the nasal mucosa was found in rats and mice exposed to ≥100 ppm and in rabbits exposed to 1000 ppm 1,2-dichloropropane for 2 weeks (6 hours/day, 4 to 5 days/week) (Nitschke and Johnson 1983). In the rats, the severity of the nasal mucosa degeneration was concentration related and the effects occurred at the lowest exposure level. In the mice, no adverse respiratory effects were found at an exposure level of 30 ppm and the effects found at 100 ppm were less severe than those found in the rat. In the rabbits, no adverse respiratory effects were found at an exposure level of 300 ppm. Therefore, rats appear to be the most sensitive species to the respiratory effects of 1,2-dichloropropane exposure. The concentrations of 100 ppm in air for rats and mice and of 1000 ppm in air for rabbits (Nitschke and Johnson 1983) are presented in Table l-2.

The effects of 1,2-dichloropropane on the respiratory systems of animals exposed for an intermediate time period (15-364 days) were determined for rats, mice and rabbits. Rabbits exposed to 1000 ppm and rats exposed to ≥50 ppm had slight degeneration of the olfactory epithelium; rats exposed to ≥15 ppm also had slight degeneration of the respiratory epithelium (Nitschke et al. 1988). No adverse effects on the respiratory system were found in rabbits exposed to ≤500 ppm or in mice exposed to ≤150 ppm (Nitschke et al. 1988). The concentration of 15 ppm in air (Nitschke et al. 1988) is presented in Table 1-2.

The highest reliable NOAEL value and all reliable LOAEL values for respiratory effects in each species and duration category are reported in Table 2-1 and plotted in Figure 2-1. Both the acute study of Nitschke and Johnson (1983) and the intermediate study of Nitschke et al. (1988) determined that rats are the most sensitive species to the respiratory effects of 1,2-dichloropropane. Therefore, the LOAEL of 100 ppm for respiratory effects in rats in the acute study (Nitschke and Johnson 1983) and the LOAEL of 15 ppm for respiratory effects in rats in the intermediate study (Nitschke et al. 1988) will be used as the basis for the acute and intermediate MRL, respectively. Based on the LOAEL of 100 ppm (Nitschke and Johnson 1983), an acute MRL of 50 ppb (0.05 ppm) was calculated and based on the LOAEL of 15 ppm (Nitschke et al. 1988), an intermediate MRL of 7 ppb (0.007 ppm) was calculated. These calculations are described in the footnote in Table 2-l.

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Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following inhalation exposure to 1,2-dichloropropane.

No adverse effects of 1,2-dichloropropane on the cardiovascular system were found following histological examination of the heart and aorta of rats and mice exposed to ≤150 ppm and of rabbits exposed to ≤1000 ppm, 6 hours/day, 5 days/week for 13 weeks (Nitschke et al. 1988). These NOAEL values for rats, mice and rabbits are reported on Table 2-l and plotted on Figure 2-1.

Heppel et al. (1946) observed fatty degeneration of the heart in dogs that were exposed to 1000 ppm 1,2-dichloropropane for 7 hours/day, 5 days/week for 27-128 exposures. This effect occurred only in animals that died (the dogs died after 27-96 exposures); therefore, it is inappropriate to consider this concentration a LOAEL for cardiovascular effects in dogs.

Gastrointestinal Effects. Pozzi et al. (1985) reported vomiting and abdominal pain in a young woman who had been sniffing a stain remover, consisting primarily (98%) of 1,2-dichloropropane, to alleviate nervousness, but no dose was determined. The woman sniffed the chemical four times in one night and the symptoms appeared the next morning. ,The woman recovered completely after 3 weeks of hospitalization.

No adverse effects of 1,2-dichloropropane on the gastrointestinal system were found following histological examination of the stomach, large intestine, and small intestine of rats and mice exposed to ≤150 ppm and of rabbits exposed to ≤1000 ppm, 6 hours/day, 5 days/week for 13 weeks (Nitschke et al. 1988). These NOAEL values for rats, mice, and rabbits are reported on Table 2-l and plotted on Figure 2-l.

Hematological Effects. Pozzi et al. (1985) discussed two case studies in which 1,2-dichloropropane, at unreported concentrations, was inhaled over a short period of time. One case involved the inhalation of 1,2-dichloropropane over the course of one evening, and the second case involved the inhalation over 6 hours while a woman was using a solvent containing 1,2-dichloropropane to. clean. Effects of exposure included epistaxis (nosebleed), hemolytic anemia and disseminated intravascular coagulation (DIC). Both patients recovered.

No hematological effects were observed in rats that were acutely exposed to 433 ppm 1,2-dichloropropane (Sidorenko et al. 1979).

Hematological effects as a result of exposure to 1,2-dichloropropane for intermediate durations have been evaluated in rabbits, mice, and rats. No hematological effects were observed in rats or mice exposed to ≤150 ppm (Nitschke et al. 1988). A dose-related increased severity of anemia

occurred in rabbits exposed to ≥150 ppm (Nitschke et al. 1988). The concentration of 150 ppm in air (Nitschke et al. 1988) is presented in Table 1-2.

The highest reliable NOAEL value and all reliable LOAEL values for hematological effects in each species and duration category are reported in Table 2-l and plotted in Figure 2-l. The Sidorenko et al. (1979) study cannot be considered a reliable study since the number of animals used was not reported.

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

No adverse effects of 1,2-dichloropropane on the musculoskeletal system were found following histological examination of the bone of rats and mice exposed to ≤150 ppm and of rabbits exposed to ≤1000 ppm, 6 hours/day, 5 days/week for 13 weeks (Nitschke et al. 1988). These NOAEL values for rats, mice, and rabbits are reported on Table 2-l and plotted on Figure 2-l.

Hepatic Effects. The liver is one of the main target organs for the toxic effects of 1,2-dichloropropane. Pozzi et al. (1985) discussed two human case studies where 1,2-dichloropropane was inhaled, leading to hepatic failure in one case and hepatic damage in the other. In the first case, a 55-year-old woman was already suffering from membrano-proliferative glomerulonephritis and undergoing home dialysis 3 times a week. The patient was hospitalized with abdominal pain after inhaling cleaning solution which contained 60% 1,2-dichloropropane for 6 hours; the remaining 40% of the solution was a mixture of acetone, isobutyl alcohol, and n-butyl acetate. Laboratory tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), prothrombin) showed severe hepatic failure but the woman recovered after a week of hospitalization. In the second case, a 20-year-old woman deliberately inhaled Trielina (98% 1,2-dichloropropane), over the course of one evening, as a means of sedation and was admitted to the hospital. Laboratory tests (AST, ALT, total bilirubin, prothrombin) showed acute liver damage. The woman recovered after 3 weeks of hospitalization. Concentrations were not reported for these chemical exposures so that a LOAEL cannot be determined.

Hepatic effects of acute inhalation exposure to 1,2-dichloropropane were evaluated in guinea pigs, mice, rabbits, and rats. Fatty degeneration of the liver occurred in guinea pigs and rats acutely exposed to 2200 ppm (Heppel et al. 1946; Highman and Heppel 1946); adverse effects were not observed in guinea pigs and rats acutely exposed to 400 ppm (Heppel et al. 1948) or in rats exposed to 1000 ppm (Heppel et al. 1946). Drew et al. (1978) found no alterations of serum levels of liver enzymes, which would indicate liver damage, in rats that were exposed to 1000 ppm for 4 hours. Nitschke and Johnson (1983) found no histopathologic effects on the liver in rats treated with a single 6-hour exposure of 1500 ppm 1,2-dichloropropane

or in rats and rabbits exposed to 1000 ppm for 2 weeks (6 hours/day, 4-5 days/week). In mice, extensive hemorrhagic necrosis was found in animals exposed for 6 hours to 500 ppm 1,2-dichloropropane. Following intermittent exposure to 300 ppm for 2 weeks (6 hours/day, 4-5 days/week), increased liver weight and hepatocellular hypertrophy were observed in mice (Nitschke and Johnson 1983).

The hepatic effects of the inhalation of 1,2-dichloropropane administered for intermediate time periods were studied in rats, mice, rabbits, guinea pigs, and dogs. Adverse effects on the liver were not observed in dogs, rats and guinea pigs exposed to 400 ppm (Heppel et al. 1948); in rats, guinea pigs, rabbits or dogs exposed to 1000 ppm; and in guinea pigs and rabbits exposed to 1500 ppm (Heppel et al. 1946). Nitschke et al. (1988) observed no histopathologic effects on the liver in rats or mice exposed to ≤150 ppm or in rabbits exposed to ≤1000 ppm 1,2-dichloropropane 6 hours/day, 5 days/week for 13 weeks.

The highest reliable NOAEL value and all reliable LOAEL values for hepatic effects in each species and duration category are reported in Table 2-l and plotted in Figure 2-l. The data regarding hepatic effects in rabbits in the Heppel et al. (1946) study are not reliable since a small number of animals (3-4) was used for evaluation.

Renal Effects. Pozzi et al. (1985) reported a case study of a 20-year-old female who deliberately inhaled an unknown amount of Trielina (98% 1,2-dichloropropane) over the course of one evening. Laboratory tests (serum creatine, blood urea nitrogen (BUN)) showed severe renal failure. Scant urine output (oliguria) and blood in the urine (hematuria) were also seen. Renal biopsy findings showed acute tubular necrosis. Other systems, such as the liver, were similarly effected. The woman recovered after 3 weeks of hospitalization.

Renal effects as a result of acute inhalation exposure to 1,2-dichloropropane were evaluated in rats, mice, and guinea pigs. Fatty degeneration of the kidney occurred in rats and guinea pigs acutely exposed to 2200 ppm (Highman and Heppel 1946); adverse effects were not observed in rats and guinea pigs acutely exposed to 400 ppm (Heppel et al. 1948) or in rats exposed to 1000 ppm (Heppel et al. 1946). The renal effects observed after acute exposure in rats and guinea pigs are similar to the effects seen in the liver (Highman and Heppel 1946). No adverse effects on the kidneys were found following histopathologic examination in rats and mice exposed for 6 hours to 1500 ppm 1,2-dichloropropane or in rats and rabbits exposed to 1000 ppm and in mice exposed to 300 ppm for 2 weeks (6 ,hours/day, 4-5 days/week) (Nitschke and Johnson 1983).

Renal effects for intermediate inhalation exposure to 1,2-dichloropropane were evaluated in rats, guinea pigs, rabbits, and dogs. Adverse effects on the kidney were not observed in dogs, guinea pigs and rats exposed to 400 ppm (Heppel et al. 1948), in guinea pigs, rats, rabbits

and dogs exposed to 1000 ppm, and in guinea pigs and rabbits exposed to 1500 ppm (Heppel et al. 1946). Nitschke et al. (1988) observed no histopathologic effects on the kidneys in rats and mice exposed to ≤150 ppm and in rabbits exposed to ≤1000 ppm 1,2-dichloropropane for 13 weeks (6 hours/day, 5 days/week).

The highest reliable NOAEL value and all reliable LOAEL values for renal effects in each species and duration category are reported in Table 2-l and plotted in Figure 2-1. The data regarding renal effects in rabbits in the Heppel et al. (1946) study are not reliable since a small number of animals (3-4) were used for evaluation.

Dermal/Ocular Effects. Periorbital and conjunctival hemorrhages were seen in a patient that was admitted to a hospital after exposure to vapors of 1,2-dichloropropane (Pozzi et al. 1985). It was not clear if the hemorrhages resulted from inhalation of 1,2-dichloropropane or from direct exposure of the eye to the 1,2-dichloropropane vapor. No concentration information was provided.

Severe conjunctivitis occurred in guinea pigs acutely exposed to 2200 ppm of 1,2-dichloropropane vapor (Heppel et al. 1946). This concentration of 1,2-dichloropropane also produced death; 5 exposures of 7 hours each resulted in the deaths of 11/16 of the animals. The paper did not clearly state at what point, during the 5 exposures, the conjunctivitis was first observed. This concentration represents a LOAEL for ocular effects and is reported in Table 2-l and plotted on Figure 2-l.

No adverse effects on the eye were found following gross and histopathologic examination of the eyes of rats and mice exposed to ≤150 ppm and in rabbits exposed to ≤1000 ppm 1,2-dichloropropane for 13 weeks (6 hours/day, 5 days/week) (Nitschke et al. 1988). These NOAEL values are reported in Table 2-l and plotted on Figure 2-l.

2.2.1.3 Immunological Effects

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

Histologic examination of the bone marrow and thymus revealed no adverse effects on the organs of the immune system in rats and rabbits exposed to 1000 ppm of 1,2-dichloropropane 6 hours/day, 4-5 days/week for 2 weeks (Nitschke and Johnson 1983). In mice exposed to 300 ppm 1,2-dichloropropane for 2 weeks (6 hours/day, 4-5 days/week), a decrease in the absolute and relative thymus weight and a decrease in cortical lymphoid cells were observed (Nitschke and Johnson 1983). Following 13 weeks of exposure to 1,2-dichloropropane (6 hours/day, 5 days/week), no histopathologic effects on the organs of the immune system (bone marrow, thymus) were found in rats (150 ppm), mice (150 ppm), or rabbits (1000 ppm)

(Nitschke et al. 1988). Parameters of immunological function, however, were not assessed in either study so that NOAELs or LOAELs cannot be defined.

2.2.1.4 Neurological Effects

Rubin (1988) described health effects in people who were exposed to unknown concentrations of 1,2-dichloropropane from a tank truck that leaked 2000 gallons of the chemical. Fatigue, possibly attributable to CNS depression, was among the symptoms observed in the exposed people.

Anesthesia was observed in rats during exposure to 1500 ppm 1,2-dichloropropane for 6 hours (Nitschke and Johnson 1983). The rats recovered within an hour after exposure, but remained lethargic. All mice exposed to 1500 ppm for 6 hours appeared anesthetized during exposure and died within 24 hours. Mice exposed to 500 ppm did not exhibit neurological effects during the exposure but became lethargic after the exposure period, and 2/5 of the animals died within 3 days.

No adverse effects on the nervous system were found following observation for overt signs of toxicity (tremors, convulsions, salivation, lacrimination, diarrhea, lethargy) or following histopathologic examination of the brain, spinal cord, and peripheral nerve of rats and mice exposed to $\leq$150 ppm and of rabbits exposed to $\leq$1000 ppm 1,2-dichloropropane 6 hours/day, 5 days/week for 13 weeks (Nitschke et al. 1988). No specialized staining methods were used for examination of the tissues of the nervous system.

Sidorenko et al. (1976) described the sequence of signs of intoxication in mice that were acutely exposed by inhalation to 1,2-dichloropropane. General agitation and decreased coordination of movements occurred initially, followed by sluggishness, amyotonia and sporadic clonic spasms, and subsequently by loss of righting reflex. The loss of the righting reflex occurred at the lowest concentration given, 1000 ppm. Sidorenko et al. (1979) evaluated the neurological effects in rats resulting from acute and intermediate duration exposure to 1,2-dichloropropane. A total threshold indicator (TTI) was used to assess the effects on the CNS, but the details of the TTI were not explained in the study. In addition, control data and numbers of treated rats and mice were not reported, Due to these inadequacies, it is inappropriate to identify LOAELs and NOAELs for neurological effects from these studies.

The highest reliable NOAEL value and all reliable LOAEL values for neurological effects in each species and duration category are reported in Table 2-l and plotted in Figure 2-l.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals following inhalation exposure to 1,2-dichloropropane.

2.2.1.6 Reproductive Effects

Pozzi et al. (1985) reported the case of a woman who was hospitalized with metrorrhagia (bleeding from the uterus between menstrual periods) after acute inhalation of 1,2-dichloropropane. The metrorrhagia was a transient effect. No information regarding concentration was given.

No histological changes in the testes of rats and rabbits exposed to 1000 ppm 1,2-dichloropropane and of mice exposed to 300 ppm 1,2-dichloropropane for 2 weeks (6 hours/day, 4 to 5 days/week) were observed (Nitschke and Johnson 1983).

No histological changes in the epididymis, prostate, or testes of males and in the oviduct, uterus, cervix, ovaries, or mammary glands of females were observed in rats and,mice exposed to ≤150 ppm and in rabbits exposed to ≤1000 ppm 1,2-dichloropropane for 13 weeks (6 hours/day, 5 days/week) (Nitschke et al. 1988).

The NOAEL values for each species and duration of exposure are reported on Table 2-l and plotted on Figure 2-l.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following inhalation exposure to 1,2-dichloropropane.

2.2.1.8 Cancer

No studies were located regarding carcinogenic effects in humans following inhalation exposure to 1,2-dichloropropane.

Heppel et al. (1948) examined the hepatocarcinogenic effects of 1,2-dichloropropane resulting from intermediate inhalation exposure. It was not clear if tissues other than the liver were examined. In the study, hepatomas were seen in 3 out of 80 mice exposed 37 times to 400 ppm for 4-7 hours. High mortality occurred throughout the study; only three mice survived all exposures plus a 7-month observation period. The hepatomas were observed in the three mice that survived. The morphology of the hepatomas was inadequately characterized and the incidence in controls was not reported, therefore, this study was not used as a basis for a Cancer Effect Level (CEL) in mice after intermediate inhalation exposure.

2.2.2 Oral Exposure

2.2.2.1 Death

There are several cases in the literature of lethality in humans resulting from ingestion of 1,2-dichloropropane. The most common method of

oral exposure was the accidental or intentional ingestion of 1,2-dichloropropane in the form of commercial solvents (Pozzi et al. 1985, Larcan et al. 1977, Perbellini et al. 1985, Zedda et al. (n.d.), Chiappino, and Secchi 1968). The quantity ingested cannot be determined accurately because of factors such as immediate vomiting after ingestion and unknown extent of absorption of 1,2-dichloropropane from the gastrointestinal tract. Typically, clinical signs of 1,2-dichloropropane overexposure in these incidences included primary effects on the CNS, liver, and kidney. Effects on the respiratory system, heart, and blood were also described. Specific causes of death included cardiac arrest and septic shock. No data on the lethal effects of 1,2-dichloropropane in humans resulting from repeated oral exposures, including chronic low-level exposure, were located.

The lethal effects of orally-administered 1,2-dichloropropane in animals have been reported by several investigators. Statistically determined oral LD_{50} values of 1942 mg/kg/day (Pozzani et al. 1959) and 2196 mg/kg/day (Smyth et al. 1969) have been determined for rats. An oral LD_{50} of approximately 2000 mg/kg/day in rats is reported in Table 2-2 and plotted in Figure 2-2.

Rats and mice were administered daily doses of 125-2000 mg/kg/day by gavage for 14 days (NTP 1986). All rats given 2000 mg/kg/day orally died but there was no mortality at ≤1000 mg/kg/day. In mice, increased mortality occurred at ≥500 mg/kg/day, but not at ≤250 mg/kg/day. No short-term studies of 1,2-dichloropropane administered in food were located; therefore, the dose level of 500 mg/kg/day in mice and 2000 mg/kg/day in rats, which were administered by gavage in corn oil (NTP 1986), were converted to an equivalent concentration of 3850 ppm in food for mice and 40,000 ppm in food for rats, for presentation in Table l-4.

Bruckner et al. (1989) reported no lethality in rats treated with up to 1000 mg/kg/day 1,2-dichloropropane by gavage in corn oil for 1, 5, or 10 consecutive days. In a 13-week study reported along with the acute study, 50% of the rats treated with 750 mg/kg/day (the highest dose) died within 10 days and the remaining animals in the treatment group were sacrificed. Also, 50% of the animals treated with 500 mg/kg/day died during the course of the 13-week study. The authors did not attempt to explain this apparent discrepancy in the lethal dose so that no NOAEL or LOAEL values for lethality will be defined.

In intermediate duration oral studies conducted by NTP (1986), rats and mice were administered doses in the range of 30-1000 mg/kg/day by gavage on 5 days/week for 13 weeks. Death was observed at the dose of 500 mg/kg/day but there was no mortality at ≤250 mg/kg/day for both rats and mice.

In chronic (103 weeks) gavage studies conducted by the NTP (1986), increased mortality occurred in female rats and female mice that were treated with 250 mg/kg/day (5 days/week). No increase in mortality occurred in rats or mice that were similarly treated with ≤125 mg/kg/day. No

TABLE 2-2. Levels of Significant Exposure to 1,2-Dichloropropane - Oral

Graph Key	Species	(Route)[c]	Duration/ Frequency Exposure		NOAEL[b] (mg/kg/day)	LOAEL[a] (Effect) Less Serious (mg/kg/day)	LOAEL[a] (Effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Lethality								
1, 2	rat	(G)	1/d, 14 d		1000		2000 (death)	NTP 1986
3	rat	(G)	one dose				2000 (LD_{50})	Pozzani et al. 1959 Smyth et al.1969
4, 5	mouse	(G)	1/d, 14 d		250		500 (death)	NTP 1986
Systemic								
6	rat	(G)	1, 5, 10 d	Resp	1000			Bruckner et al. 1989
7				Gastro	1000			
8, 9, 10				Hemato	100	250 (mild anemia)	500 (severe anemia)	
11, 12				Hepatic	100	250 (necrosis)		
13, 14				Renal	*500*	*1000 (increased BUN)*		
15, 16				Body Weight	100	250 (decreased body weight gain)		
17	mouse	(G)	14 d	Renal	2000			NTP 1986
18			5 d/wk	Body Weight	2000			
Neurological								
19, 20	rat	(G)	1, 5, 10 d			100[d] (slight CNS depression)	250 (definite CNS depression)	Bruckner et al. 1989
Reproductive								
21, 22	rat	(G)	1, 5, 10 d		250	500 (testicular degeneration)		Bruckner et al. 1989
INTERMEDIATE EXPOSURE								
Lethality								
23, 24	rat	(G)	5 d/wk 13 wk		250		500 (death)	NTP 1986

TABLE 2-2 (continued)

Graph Key	Species	(Route)[c]	Duration/ Frequency Exposure		NOAEL[b] (mg/kg/day)	LOAEL[a] (Effect) Less Serious (mg/kg/day)	LOAEL[a] (Effect) Serious (mg/kg/day)	Reference
25, 26	mouse	(G)	5 d/wk, 13 wk		250		500 (death)	NTP 1986
Systemic								
27, 28	rat	(G)	13 wk 5 d/wk	Hemato		100[e] (slight anemia)	250 (pronounced anemia)	Bruckner et al. 1989
29, 30				Hepatic	250	500 (hyperplosia vacuolization)		
31				Body Weight		100 (decreased body gain)		
32	rat	(G)	5 d/wk	Resp	1000			NTP 1986
33			13 wk	Gastro	1000			
34				Renal	1000			
35				Derm/Oc	1000			
36, 37				Body Weight	250	500 (decreased body weight gain)		
38	mouse	(G)	5 d/wk	Resp	500			NTP 1986
39			13 wk	Gastro	500			
40				Hemato	500			
41				Hepatic	500			
42				Renal	500			
43				Derm/Oc	500			
44				Body Weight	500			
Neurological								
45	rat	(G)	gestation day 6-21			125 (neurotoxic effects)		Kirk et al. 1989
46	rat	(G)	13 wk 5 d/wk				500 (pronounced depression)	Bruckner et al. 1989
Developmental								
47	rat	(G)	gestation day 6-21			125 (delayed ossification)		Kirk et al. 1989

TABLE 2-2 (continued)

Graph Key	Species	(Route)[c]	Duration/ Frequency Exposure		NOAEL[b] (mg/kg/day)	LOAEL[a] (Effect) Less Serious (mg/kg/day)	LOAEL[a] (Effect) Serious (mg/kg/day)	Reference
Reproductive								
48	rat	(G)	gestation day 6-21		125			Kirk et al. 1989
49, 50	rat	(G)	13 wk 5 d/wk		250	500 (testicular degeneration)		Bruckner et al. 1989
CHRONIC EXPOSURE								
Lethality								
51, 52	rat	(G)	5 d/wk 103 wk		125		250 (death)	NTP 1986
53, 54	mouse	(G)	5 d/wk 103 wk		125		250 (death)	NTP 1986
Systemic								
55	rat	(G)	5 d/wk	Resp	250			NTP 1986
56			103 wk	Cardio	250			
57				Gastro	250			
58, 59				Hepatic	125	250 (necrosis)		
60				Renal	250			
61				Derm/Oc	250			
62, 63				Body Weight	62	125 (decreased body weight gain)		
64	mouse	(G)	5 d/wk	Resp	250			NTP 1986
65			103 wk	Cardio	250			
66				Hepatic		125[f] (necrosis)		
67				Renal	250			
68				Derm/Oc	250			
69				Body Weight	250			

TABLE 2-2 (continued)

Graph Key	Species	(Route)[c]	Duration/ Frequency Exposure	NOAEL[b] (mg/kg/day)	LOAEL[a] (Effect)		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Carcinogenic							
70	rat	(G)	5 d/wk 103 wk			250 (mammary tumors)	NTP 1986
71	mouse	(G)	5 d/wk 103 wk			125 (hepatic tumors)	NTP 1986

[a]LOAEL - Lowest Observed Adverse Effect Level
[b]NOAEL - No Observed Adverse Effect Level
[c]Route - G - Gavage
[d]Used to derive acute oral MRL; dose divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), resulting in an MRL of 0.1 mg/kg/day.
[e]Used to derive intermediate oral MRL; dose adjusted for intermittent exposure and divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), resulting in an MRL of 0.07 mg/kg/day.
[f]Used to derive chronic oral MRL; dose adjusted for intermittent exposure and divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), resulting in an MRL of 0.09 mg/kg/day.

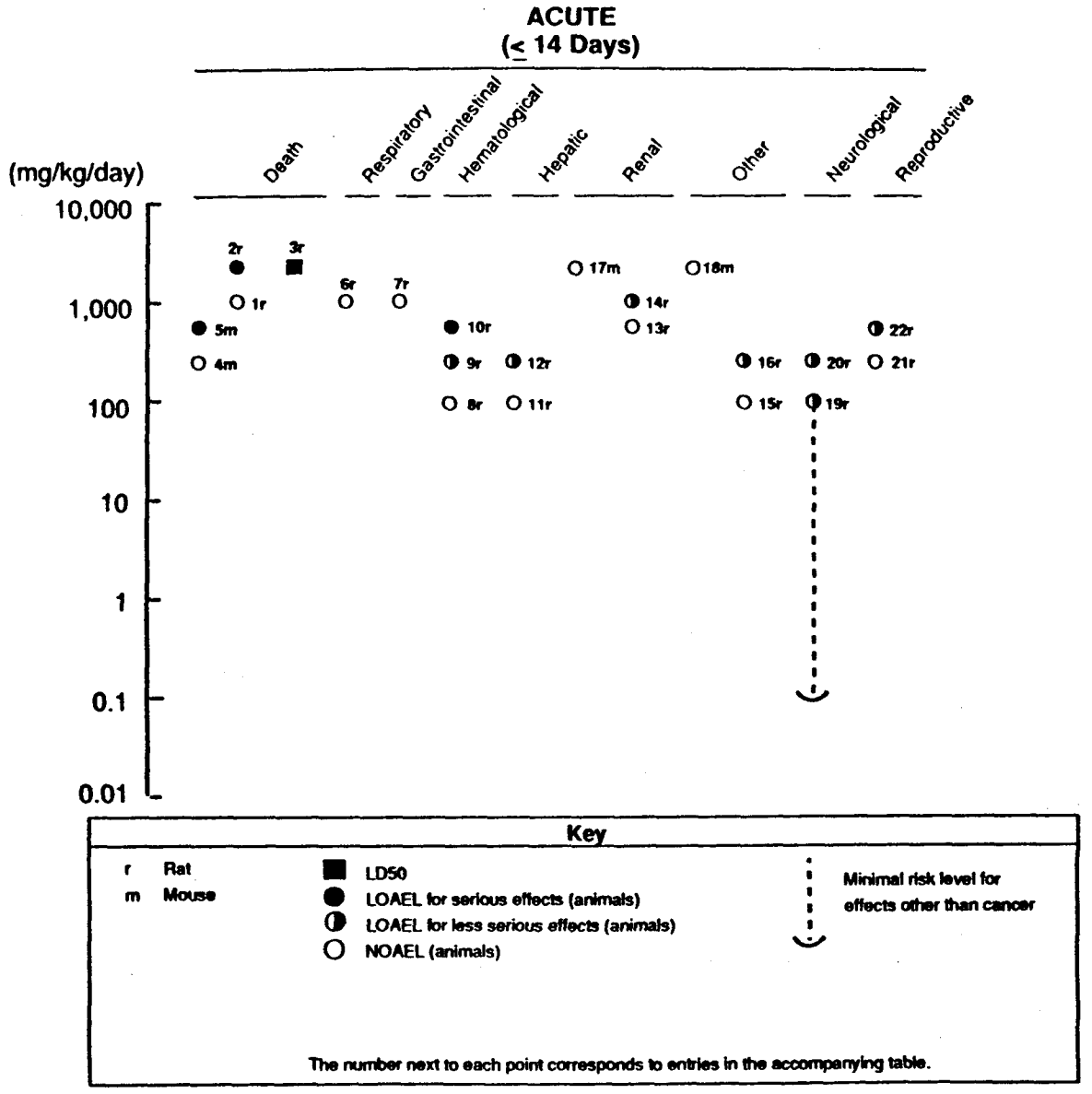


FIGURE 2-2. Levels of Significant Exposure to 1,2 - Dichloropropane - Oral

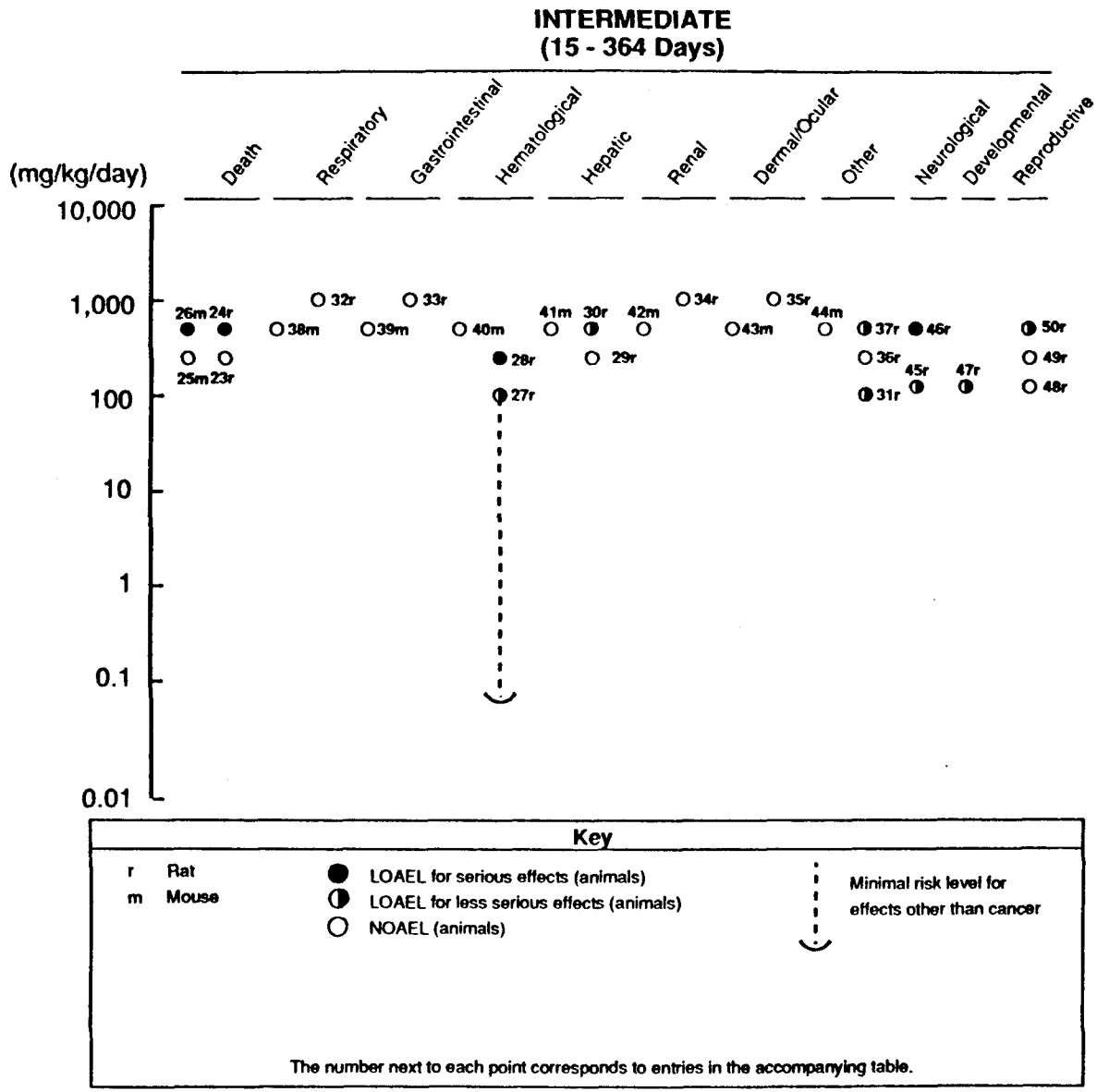


FIGURE 2-2. Levels of Significant Exposure to 1,2 - Dichloropropane - Oral (Continued)

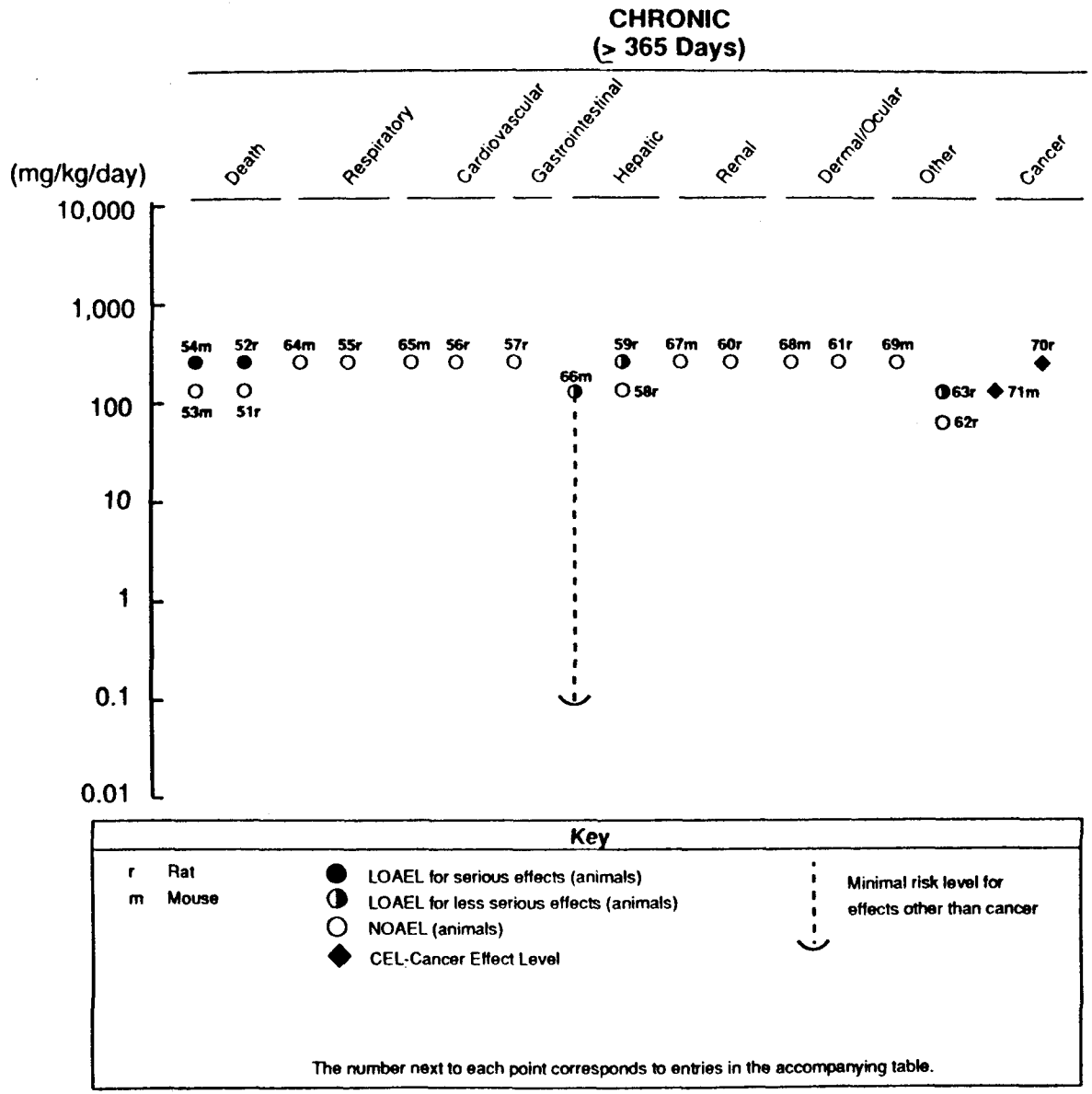


FIGURE 2-2. Levels of Significant Exposure to 1,2 - Dichloropropane - Oral (Continued)

long-term studies of 1,2-dichloropropane administered in food were located; therefore, the dose level of 250 mg/kg/day in mice and rats, which were administered by gavage in corn oil (NTP 1986), were converted to an equivalent concentration of 1900 ppm in food in mice and 5000 ppm in rats, for presentation in Table 1-4.

The highest reliable NOAEL value and all reliable LOAEL values for lethal effects in each species and duration category are reported in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

Respiratory Effects. No studies were located regarding respiratory effects in humans following oral exposure to 1,2-dichloropropane.

No histopathologic changes in the lungs were observed in rats treated by gavage in corn oil with up to 1000 mg/kg/day 1,2-dichloropropane for 1, 5, or 10 consecutive days, or with up to 500 mg/kg/day for 13 weeks (5 days/week) (Bruckner et al. 1989). In the gavage studies conducted by NTP (19861, no compound-related histopathological lesions were observed in lungs, bronchi, and trachea of F344/N rats treated with up to 1000 mg/kg/day of 1,2-dichloropropane for 13 weeks, B6C3Fl mice treated with up to 500 mg/kg/day for 13 weeks, or rats and mice treated with up to 250 mg/kg/day for 103 weeks.

The highest reliable NOAEL values for respiratory effects in each species and duration category are reported in Table 2-2 and plotted in Figure 2-2.

Cardiovascular Effects. Death resulting from cardiac failure occurred in two humans 30 and 36 hours after ingestion of single unknown doses of 1,2-dichloropropane (Larcan et al. 1977, Perbellini et al. 1985). A patient in the Perbellini et al. (1985) report showed ecchymoses (a purplish patch caused by extravasation of blood into the skin) on the cheeks, trunk and limbs, and epistaxis (nosebleed) after ingestion of an unknown dose of 1,2-dichloropropane.

Histological examination of the hearts of rats and mice that were treated with doses as high as 250 mg/kg/day (5 days/week) for 103 weeks revealed no compound-related lesions (NTP 1986). The dose of 250 mg/kg/day is reported in Table 2-2 and plotted in Figure 2-2 as a NOAEL for cardiovascular effects in rats and mice as a result of chronic oral exposure.

Gastrointestinal Effects. Chiappino and Secchi (1968) reported a case of acute overexposure by ingestion of 1,2-dichloropropane in which a 59-year-old man experienced an immediate burning sensation in the oropharynx, esophagus, and stomach, followed by vomiting for some time which became biliary vomiting. Nausea, vomiting, and intense anorexia subsided but

persisted over the next 4 days, and the patient ultimately recovered. Perbellini et al. (1985) reported reversible necrotic hemorrhagic lesions in the oral cavity of a man who ingested 1,2-dichloropropane. Thorel et al. (1986) observed reversible erosive esophagitis and esophageal varices in a man who ingested 1,2-dichloropropane in a suicide attempt. The exposures in the above cases were single, but doses were not reported.

Gross pathological lesions were not observed in the gastrointestinal tract of mice or rats that were treated by gavage with 1,2-dichloropropane doses as high as 2000 mg/kg/day for 2 weeks (NTP 1986). The fact that the rats and mice in this study were not examined histologically precludes the use of 2000 mg/kg/day as a NOAEL. Bruckner et al. (1989) observed no histological effects on the stomach in rats treated with 1000 mg/kg/day for 1, 5, or 10 consecutive days.

Rats that were treated with 1,2-dichloropropane doses as high as 1000 mg/kg/day (5 days/week) for 13 weeks and mice similarly treated with up to 500 mg/kg/day did not have histopathological alterations in the gastrointestinal tract (NTP 1986). Similarly, rats treated with up to 500 mg/kg/day for 13 weeks (5 days/week) showed no histopathologic changes in the stomach (Bruckner et al. 1989).

Rats that were treated with 1,2-dichloropropane doses as high as 250 mg/kg/day (5 days/week) for 103 weeks did not have histological alterations in the gastrointestinal tract (NTP 1986). In female mice that were treated by gavage with 1,2-dichloropropane doses of 125 or 250 mg/kg/day (5 days/week) for 103 weeks, increased incidences of acanthosis of the forestomach occurred. In male mice similarly treated, this effect was only observed in the high-dose group. Because it is uncertain whether the acanthosis is compound-related, a LOAEL or NOAEL for gastrointestinal effects as a result of chronic oral exposure to 1,2-dichloropropane cannot be determined for mice.

The highest reliable NOAEL value and all reliable LOAEL values for gastrointestinal effects in each species and duration category *are* reported in Table 2-2 and plotted in Figure 2-2.

Hematological Effects. Anemia, leukopenia and disseminated intravascular coagulation (DIC) occurred in humans after accidental ingestion of 1,2-dichloropropane (Pozzi et al. 1985; Perbellini et al. 1985). One of the patients recovered, one died 7 days after poisoning from septic shock, and one died 30 hours after poisoning from cardiac arrest. These overexposures resulted from a single deliberate ingestion of 1,2-dichloropropane, but doses were not reported.

A dose-related increase in the severity of anemia was found in rats treated with 250 mg/kg/day 1,2-dichloropropane by gavage in corn oil for 1, 5, or 10 consecutive days, and in rats treated with 100 mg/kg/day for 13 weeks (5 days/week) (Bruckner et al. 1989). No anemia was found in rats

treated with 100 mg/kg/day in the acute study. In the intermediate study, anemia was found at the lowest dose level so that a LOAEL of 100 mg/kg/day is defined. No short-term or long-term studies of 1,2-dichloropropane administered in food were located; therefore, the dose level of 250 mg/kg/day in the acute study and of 100 mg/kg/day in the intermediate study were converted to equivalent concentrations of 5000 and 2000 ppm in food, respectively, for presentation in Table l-4. The LOAEL of 100 mg/kg/day for rats in the intermediate study is the lowest effect level (LOAEL or NOAEL) found for any species following intermediate exposure. A LOAEL of 100 mg/kg/day for decreased body weight in rats was also found. Based on the LOAEL of 100 mg/kg/day, an intermediate oral MRL of 0.07 mg/kg/day was calculated as described in the footnote to Table 2-2. This MEL has been converted to an equivalent concentration in food (2.5 ppm) for presentation in Table l-3. The MRL can be compared with existing state and federal criteria levels (see Chapter 7) or to amounts of the chemical encountered in environmental or occupational situations (see Chapter 5).

No compound-related histopathological lesions were observed in the hematopoietic tissues of F344/N rats and B6C3F$_1$ mice treated for 5 days/week with 1,2-dichloropropane at doses of 30-1000 mg/kg/day for 13 weeks or 62-125 mg/kg/day for 103 weeks (NTP 1986). Since clinical hematological tests were not performed, the highest doses in these studies cannot be considered NOAELs for hematological effects.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals following oral exposure to 1,2-dichloropropane.

Hepatic Effects. Damage to the liver has been reported in people who deliberately drank 1,2-dichloropropane. Liver damage included centrolobular hepatic necrosis (Pozzi et al. 1985), centro- and mediolobular acute hepatic necrosis (Larcan et al. 1977), and acute icteric liver disease in which histological examination and electron microscopy showed diffuse, turbid degeneration in the liver cells, and evident ultrastructural changes in the mitochondria, the endoplasmic reticulum, and the Golgi apparatus (Chiappino and Secchi 1968). Perbellini et al. (1985) reported unspecified liver damage in a man orally overexposed. Thorel et al. (1986) found portal hypertension and histologically, dense, irregular portal fibrosis, which damaged the hepatic parenchyma in a man who ingested 1,2-dichloropropane in a suicide attempt. The aforementioned overexposures resulted from ingestion of a single large dose, but specific amounts were not reported.

In animal studies, the liver has been shown to be affected by acute, intermediate, and chronic oral exposure to 1,2-dichloropropane. Bruckner et al. (1989) reported adverse hepatic effects in rats treated orally for an acute and intermediate period of time. Liver necrosis, characterized by degenerative effects on the centrilobular hepatocytes and mild to moderate hepatitis, was observed in animals treated by gavage with ≥250 mg/kg/day

1,2-dichloropropane in corn oil for 1, 5, or 10 consecutive days. Similar effects (periportal vacuolization and fibroplasia) were found in animals treated with ≥500 mg/kg/day for 13 weeks (5 days/week). No adverse effects, on the rats were found at 100 mg/kg/day in the acute study and at 250 mg/kg/day in the intermediate study. No short-term studies of 1,2-dichloropropane administered in food were located; therefore, the dose level of 250 mg/kg/day in rats, which was administered by gavage in corn oil (Bruckner et al. 1989), was converted to an equivalent concentration of 5000 ppm in food in rats, for presentation in Table l-4. The NTP study (1986) found fatty changes, centrilobular necrosis, and congestion of the liver in rats given 1,2-dichloropropane orally at doses of 1000 mg/kg/day, but not ≤500 mg/kg/day for 13 weeks. Liver lesions were not observed in mice that were similarly treated with doses as high as 500 mg/kg/day (NTP 1986).

The NTP study (1986) found liver necrosis in female rats given 250 mg/kg/day 1,2-dichloropropane by gavage for 103 weeks, but not in females at ≤125 mg/kg/day or in males at any of the doses. The NTP study (1986) found necrosis of the liver in male mice, but not females, that were administered 125 or 250 mg/kg/day 1,2-dichloropropane by gavage for 103 weeks (5 days/week); lower doses were not tested. No long-term studies of 1,2-dichloropropane administered in food were located; therefore, the dose level of 125 mg/kg/day in mice and 250 mg/kg/day in rats, which were administered by gavage in corn oil (NTP 1986), were converted to an equivalent concentration of 960 ppm in food in mice and 5000 ppm in food in rats for presentation in Table l-4. The LOAEL of 125 mg/kg/day for hepatic effects in mice is the lowest LOAEL reported following chronic oral exposure to 1,2-dichloropropane (NTP 1986). A NOAEL of 62 mg/kg/day for effects on body weight in rats is reported (NTP 1986), but factors other than chemical toxicity may affect body weight; therefore, it will not be used as the basis for the MRL. Based on the LOAEL of 125 mg/kg/day, a chronic oral MRL of 0.09 mg/kg/day was calculated as described in the footnote to Table 2-2. The NTP study (1986) denoted that a significant dose-related increase in liver adenomas occurred in male mice treated with 250 mg/kg/day (P=0.017) and in female mice treated with the 125 and 250 mg/kg/day (P=0.102 at both doses) (see Section 2.2.2.8 on carcinogenic effects by oral exposure).

The highest reliable NOAEL value and all reliable LOAEL values for hepatic effects in each species and duration category are reported in Table 2-2 and plotted in Figure 2-2.

Renal Effects. Renal failure was observed in three patients after ingestion of 1,2-dichloropropane (Perbellini et al. 1985, Pozzi et al. 1985, Zedda et al. n.d.). Two of the patients died but renal failure did not appear to be the cause of death; one death was attributed to cardiac arrest and the other to septic shock. Dose information on 1,2-dichloropropane was not provided.

Gross pathologic examinations showed reddened renal medullae in almost all rats that were treated with 2000 mg/kg/day by gavage for 2 weeks, but not at 1000 mg/kg/day or lower doses (NTP 1986). This effect was also observed in mice that were similarly treated at doses of ≥125 mg/kg/day; lower doses were not tested, Histological examinations were not performed. NTP (1986) considered the reddened medullae to be a compound-related, but not an adverse effect. The reddened medullae may have been transient since no effects on the kidney, including the reddened renal medullae, were observed grossly or histologically in mice or rats in the 13-week study or in the 103-week study.

No adverse histopathologic effects on the kidneys were found in rats treated with ≤500 mg/kg/day 1,2-dichloropropane by gavage in corn oil following exposure for 1, 5, or 10 consecutive days or exposure for 13 weeks (5 days/week) (Bruckner et al. 1989). Increased BUN levels, however, were found in animals treated with 1000 mg/kg/day in the acute study.

No treatment-related histopathological kidney lesions were observed in rats or mice treated by gavage with 1,2-dichloropropane doses as high as 1000 mg/kg/day for rats and 500 mg/kg/day for mice in the 13 week study and as high as 250 mg/kg/day for both species in the 103 week study (NTP 1986).

The highest reliable NOAEL value and all reliable LOAEL values for renal effects in each species and duration category are reported in Table 2-2 and plotted in Figure 2-2. Since no histological examination of the kidney was done in the 2 week studies in rats and mice (NTP 1986), it would be inappropriate to consider this study as the basis for a NOAEL.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans following oral exposure to 1,2-dichloropropane. .

No treatment-related skin lesions were observed histologically in rats or mice treated with 1,2-dichloropropane by gavage for 13 or 103 weeks (NTP 1986). The highest doses (1000 mg/kg/day for rats, 500 mg/kg/day for mice in the 13-week study; 250 for both species in the 103-week study) are indicated in Table 2-2 and Figure 2-2 as NOAELs for dermal effects as a result of intermediate and chronic oral exposure to 1,2-dichloropropane.

Other Effects. Mean body weight gain was depressed by <10% in male rats treated with ≥500 mg/kg/day, but not ≤250 mg/kg/day, and in female rats treated with ≥1OOO mg/kg/day, but not ≤500 mg/kg/day, for 2 weeks; in male rats treated with ≥500 mg/kg/day, but not ≤250 mg/kg/day, and not in female rats treated with ≥500 mg/kg/day, for 13 weeks; and in male rats treated with ≥125 mg/kg/day, but not 62 mg/kg/day, and in female rats treated with ≤250 mg/kg/day, but not 125 mg/kg/day, for 103 weeks (NTP 1986). Body weight gain was not affected in mice similarly treated (≤2000 mg/kg/day for 2 weeks, ≤500 mg/kg/day for 13 weeks, ≤250 mg/kg/day for 103 weeks) in the NTP (1986) study, A significant dose-related decrease in body weight gain

was observed in rats treated with ≥100 mg/kg/day by gavage in corn oil for 13 weeks (5 days/week) (Bruckner et al. 1989). Since 100 mg/kg/day was the lowest dose tested, no NOAEL for body weight gain was defined. The LOAELs and NOAELs for the three durations are reported in Table 2-2 and plotted in Figure 2-2. No short- or long-term studies of 1,2-dichloropropane administered in food were located; therefore, the dose levels of 250 mg/kg/day (short-term) and 100 mg/kg/day (long-term) in rats, which were administered by gavage in corn oil (Bruckner et al. 1989), were converted to an equivalent concentration of 5000 ppm (short-term) and 2000 ppm (long-term) in food for presentation in Table l-4.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans following oral exposure to 1,2-dichloropropane.

Histological examination of organs and tissues of the immune system revealed no treatment-related effects in rats or mice treated by gavage with 1,2-dichloropropane on 5 days/week with doses ≥30 mg/kg/day for 13 weeks or ≥62 mg/kg/day for 103 weeks (NTP 1986). Reduced survival of the high-dose females in the 103-week study (see section 2.2.1) may have been due partly to infections of the reproductive system; of the animals that died during the study, 5/11 controls, 9/14 at 125 mg/kg/day, and 14/22 at 250 mg/kg/day had inflammation of the reproductive system. However, it is not known if 1,2-dichloropropane caused an increased susceptibility to infections. No specific immunological tests of rats and mice treated with 1,2-dichloropropane were performed in the NTP (1986) studies. Therefore, LOAELs and NOAELs for immunological effects cannot be determined.

2.2.2.4 Neurological Effects

Symptoms observed in patients lethally exposed to 1,2-dichloropropane include dizziness, headache, disorientation and coma (Larcan et al. 1977; Perbellini et al. 1985; Thorel et al. 1986). The overexposure resulted from a single ingestion, but no doses were determined.

Gorzinski and Johnson (1989) performed a neurotoxicological examination, including a Functional Observational Battery, on rats exposed daily to 1,2-dichloropropane by gavage in corn oil for 2 weeks. After the first dose, clinical signs (blinking, lacrimation, salivation and lethargy) were observed in the treated groups, but by the fifth dose, the treated animals were indistinguishable from the controls. Decreased locomotion in males and a trend towards decreased activity in females were found at ≥300 mg/kg/day. Histological examination of the brain was not done. Bruckner et al. (1989) found a dose-related increase in the severity of CNS depression in rats treated with 100 mg/kg/day 1,2-dichloropropane by gavage in corn oil for 1, 5, or 10 consecutive days. No histopathologic lesions were found in the brain. Therefore, a LOAEL of 100 mg/kg/day from the Bruckner et al. (1989) study and a LOAEL of 300 mg/kg/day from the Gorzinski and Johnson

(1989) study can be defined. No short-term studies -of 1,2-dichloropropane administered in the food were located; therefore, the dose level of 100 mg/kg/day in rats, which was administered by gavage in corn oil (Bruckner, et al. 1989), was converted to an equivalent concentration of 2000 ppm in food for presentation in Table l-4. Bruckner et al. (1989) also observed pronounced CNS depression in rats treated with 500 mg/kg/day by gavage for 13 weeks (5 days/week). The existence of CNS depression at the next lower dose (250 mg/kg/day) was not reported, but 250 mg/kg/day cannot be defined as a NOAEL for neurological effects following intermediate exposure since a LOAEL of 100 mg/kg/day was defined by Bruckner et al. (1989) in the acute study. The LOAEL of 100 mg/kg/day for rats is the lowest adverse effect level for any species following acute oral exposure. Based on this value, an acute oral MRL of 0.1 mg/kg/day was calculated, as described in the footnote in Table 2-2. This MRL has been converted to an equivalent concentration in food (3.6 ppm) for presentation in Table l-3. The MRL can be compared with existing state and federal criteria levels (see Chapter 7) or to amounts of the chemical encountered in environmental or occupational situations (see Chapter 5).

Kirk et al. (1989) performed an observational battery on pregnant female rats that were exposed by gavage to 1,2-dichloropropane during days 6-21 of gestation. The observational battery included observations in pupil size, respiration, movement, skin and hair coat, salivation, lacrimation, and urine and fecal staining. No adverse effects were found in dams exposed to ≤30 mg/kg/day, but at 125 mg/kg/day, decreased movement, muscle tone and extensor thrust reflex, and increased salivation and lacrimation were observed.

NTP (1986) found no treatment-related lesions histologically in the brains of rats and mice treated with doses ≥30 mg/kg/day for 13 weeks or ≥62 mg/kg/day for 103 weeks. Specific tests for neurological effects were not performed, however, precluding the determination of LOAELs and NOAELs from this study.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to 1,2-dichloropropane.

An increased incidence of delayed ossification of the bones of the skull was observed in the fetuses of dams treated with 125 mg/kg/day 1,2-dichloropropane by gavage in corn oil during gestation days 6-21 (Kirk et al. 1989). No adverse effects were found in the fetuses of dams treated with ≤30 mg/kg/day. The NOAEL of 30 mg/kg/day and the LOAEL of 125 mg/kg/day are reported on Table 2-2 and plotted on Figure 2-2. No long-term (≥14 days) studies of 1,2-dichloropropane administered in food were located; therefore, the dose level of 125 mg/kg/day in rats, which was administered by gavage in corn oil (Bruckner et al. 1989), was converted to an equivalent concentration of 2500 ppm in food for presentation in Table l-4.

2.2.2.6 Reproductive Effects

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

Kirk et al. (1989) administered 1,2-dichloropropane by gavage to pregnant rats during gestation days 6-21. No dose-related effects on the number of pregnancies, the number of implantation sites, the number of resorptions, the gravid uterine weight, or the number of fetuses were found at the highest dose level (125 mg/kg/day).

Testicular degeneration was found in rats treated with 500 mg/kg/day by gavage in corn oil for 1, 5, or 10 consecutive days or for 13 weeks (5 days/week) (Bruckner et al. 1989). The degeneration included reduced sperm production, increased numbers of degenerate sperm and reduced numbers of sperm in the epididymis. These effects were not found at dose levels of ≤250 mg/kg/day. No short-term studies of 1,2-dichloropropane administered in food were located; therefore, the dose level of 500 mg/kg/day in rats, which was administered by gavage in corn oil, was converted to an equivalent concentration of 10,000 ppm in food for presentation in Table l-4.

Increased incidences of suppurative infection of the ovary, uterus, or other organs were found in the female mice treated by gavage with doses of 125 and 250 mg/kg/day for 103 weeks (NTP 1986), but it is not known if these infections were related to 1,2-dichloropropane treatment since controls were also infected. Histological examination of the reproductive organs of the male rats and mice in the 103-week study, and of the higher dosed animals in the 13-week study, revealed no compound-related lesions.

The NOAEL of 125 mg/kg/day (Kirk et al. 1989) for effects on the female reproductive system following intermediate exposure and the NOAEL of 250 mg/kg/day and the LOAEL of 500 mg/kg/day for effects on the male reproductive system following intermediate exposure are reported in Table 2-2 and plotted in Figure 2-2. Since no tests of reproductive function were performed in the NTP (1986) study, it is not appropriate to regard the levels that produced no histopathological lesions as NOAELs.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following oral exposure to 1,2-dichloropropane.

In a dominant-lethal study, male rats were continuously exposed to 1,2-dichloropropane in the drinking water for at least 10 weeks prior to breeding and for 1 week after breeding (Hanley et al. 1989). Two days after exposure was ended, the males were bred with untreated females. No effects on mating performance or fertility in the males, or on the number of

implantations, resorptions, and litter sizes were observed at the highest dose (162 mg/kg/day).

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to 1,2-dichloropropane.

A marginal but statistically significant increased incidence of adenocarcinomas of the mammary gland was observed in female rats given 250 mg/kg/day 1,2-dichloropropane by gavage for 103 weeks (NTP 1986). NTP (1986) considered this to be equivocal evidence for carcinogenicity. 1,2-Dichloropropane was not found to be carcinogenic in other tissues in the females or in any tissues in similarly treated (62 and 125 mg/kg/day) male rats. The 250 mg/kg/day dose is indicated as a Cancer Effect Level (CEL) in rats in Table 2-2 and is plotted in Figure 2-2.

A dose-related increase in liver adenomas for both male and female mice was observed when treated with 125 or 250 mg/kg/day 1,2-dichloropropane by gavage for 103 weeks (NTP 1986). The incidences were significantly greater than control incidences in high-dose male (34% in treated vs. 14% in control) and in low- and high-dose female groups (10% in both treated groups vs. 2% in control). The incidences of hepatocellular carcinoma were increased in the dosed animals although the increase was not significant. NTP (1986) concluded that there was some evidence for carcinogenicity in male and female mice based on the increased incidences of hepatocellular neoplasms, primarily adenomas. The dose of 125 mg/kg/day is presented as a Cancer Effect Level (CEL) in mice in Table 2-2 and is plotted in Figure 2-2. EPA (1987a) classified 1,2-dichloropropane in Group B2 (i.e., a probable human carcinogen), and derived a q_1^* of 6.8×10^{-2} $(mg/kg/day)^{-1}$ from the data in male mice. This q_1^* corresponds to upper bound individual lifetime cancer risks at 10^{-4} to 10^{-7} risk levels of 1.5×10^{-3} to 1.5×10^{-6} mg/kg/day. The EPA plans to recalculate the q_1^* taking into consideration the life table adjustments; therefore, the cancer risk levels are not plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding lethal effects in humans following dermal exposure to 1,2-dichloropropane.

A dermal LD_{50} of 8.75 mL/kg was calculated for rabbits (Smyth et al. 1969). The treatment site was covered with an impervious plastic film for 24 hours following application and the animals were observed for 14 days. The LOAEL of 8.75 mL/kg is reported in Table 2-3.

TABLE 2-3. Levels of Significant Exposure to 1,2-Dichloropropane - Dermal[a]

	Species	Exposure Frequency/ Duration		NOAEL[b]	LOAEL[c] (Effect) Less Serious	LOAEL[c] (Effect) Serious	Reference
ACUTE EXPOSURE							
Death							
	rabbit	24 h				8.75 mL/kg (LD_{50})	Smyth et al. 1969
	rabbit	one dose		3.16 g/kg			Exxon 1982a
Systemic							
	rabbit	one dose	Derm/Oc		3.16 g/kg (erythema)		Exxon 1982a

[a]These levels are not displayed graphically because none of the studies used doses expressed in units of $mg/cm^2/day$.
[b]NOAEL - No Observed Adverse Effect Level
[c]LOAEL - Lowest Observed Adverse Effect Level

2.2.3.2 Systemic Effects

Grzywa and Rudzki (1981) reported 2 cases of dermatitis resulting from dermal exposure to aerosols containing 1,2-dichloropropane [7.4-12.7% 2-dichloropropane, with the remainder consisting of methysilicone oils (3.6-8.5%) and freons 11 and 12 in a 1:l proportion (83.6-84.1%)] in the workplace. In one case, a woman with no family history of allergy was dermally exposed to 1,2-dichloropropane by repeated spraying it during the course of her work. Dermatitis appeared on her right hand after several months of work and recurred several times during 6 years of employment. After stopping work, there was no improvement in her condition; and new areas of dermatitis appeared on her left hand and right foot. Patch tests showed a strongly positive reaction to Siliform AR-1 (an aerosol containing 1,2-dichloropropane) and to 1,2-dichloropropane. Twenty-one other workers who were similarly exposed in her workplace did not develop dermatitis. In the second case, a woman with no family history of allergy was dermally exposed to 1,2-dichloropropane in a similar manner; after 4 years of work, dermatitis appeared on the dorsa of her feet and continued for at least 10 years. The dermatitis was exacerbated in the summer and occasionally appeared on her neck. After 13 years of work, the woman developed hand dermatitis, which receded after she changed her work and was no longer exposed to 1,2-dichloropropane. Patch tests showed a positive response to 1,2-dichloropropane and a negative response to Siliform AR-l. Skin changes were seen in two of 39 other persons exposed in her workplace, but these cases were not documented. No dose information was available for either of the above cases.

No studies were located regarding any other systemic effects in humans following dermal exposure to 1,2-dichloropropane.

No studies were located regarding hepatic, renal, musculoskeletal, or cardiovascular system effects in animals following dermal exposure to 1,2-dichloropropane.

No respiratory, gastrointestinal, or hematological effects were observed upon gross examination of rabbits treated dermally with a single dose of 3.16 g/kg 1,2-dichloropropane (Exxon 1982a). Erythema was observed in rabbits treated in the same experiment. The treatment site was occluded for 24 hours following application, and the animals were examined 14 days following treatment. Since tissues of the respiratory, gastrointestinal and hematological systems were only grossly examined, it would be inappropriate to consider the dose of 3.16 g/kg a reliable NOAEL for these effects. The dose of 3.16 g/kg, however, can be considered a LOAEL for dermal effects in rabbits since erythema was observed upon gross examination (see Table 2-3).

Ocular irritation (redness, iridial irritation, cornea1 ulceration) was seen when an unspecified amount of 1,2-dichloropropane was instilled in the conjunctival sac of rabbits (Exxon 1982b). The 1,2-dichloropropane was

placed in the eye, the upper and lower lids were held together for one second to prevent loss of material, and the animals were observed from 1 hour to 14 days after administration. Since no dose information was available for this study, it would be inappropriate to consider it the basis for a LOAEL.

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

2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

No studies were located regarding reproductive effects in humans following dermal exposure to 1,2-dichloropropane.

No effects on the ovaries were observed upon gross examination of rabbits dermally treated with a single dose of 3.16 g/kg 1,2-dichloropropane (Exxon 1982a). The treatment site was occluded for 24 hours following application and the animals were examined 14 days following treatment. Since the ovaries were only grossly examined, the dose of 3.16 g/kg cannot be considered a NOAEL for reproductive effects.

2.2.3.7 Genotoxic Effects

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

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals following dermal exposure to 1,2-dichloropropane.

2.3 RELEVANCE TO PUBLIC HEALTH

Death. The few deaths observed in humans as a result of deliberate ingestion of 1,2-dichloropropane were apparently due to toxic effects on the central nervous system, liver, and kidney (Pozzi et al. 1985; Larcan et al. 1977; Zedda et al. (n.d.); Perbellini et al. 1985). The ultimate cause of death has been reported to be cardiac arrest and septic shock. No deaths have been reported resulting from inhalation or dermal exposure to 1,2-dichloropropane. All of the documented human overexposures resulted from ingestion or inhalation of 1,2-dichloropropane in the form of a cleaning solvent. Since the use of 1,2-dichloropropane as a consumer cleaning solvent has been curtailed, documented overexposures may be rare in the

future. Information on human lethality resulting from repeated exposures to 1,2-dichloropropane has not been reported.

Doses causing death in animals have been reported for acute and intermediate inhalation exposures, for acute, intermediate, and chronic oral exposure, and for acute dermal exposure. In general, mice were more sensitive to the lethal effects of acute oral exposure to 1,2-dichloropropane than are other laboratory animals. This difference in sensitivity was not found following acute inhalation exposure. During intermediate or chronic oral or inhalation exposure, mice and rats were equally sensitive (NTP 1986; Nitschke et al. 1988). The reason for this difference in sensitivity is not known; and it is not clear if humans are more or less sensitive to 1,2-dichloropropane in relation to other animals, since dose information is not available for the cases of human overexposure. Conventionally, it is assumed that humans are as sensitive as the most sensitive species tested when assessing the risk of 1,2-dichloropropane lethally to humans. The concentrations associated with death in animals are much higher than would be found in the environment, in occupational settings, or in water or soil surrounding waste sites; therefore, it is unlikely that humans would die from noncancer effects after brief or prolonged exposure to 1,2-dichloropropane in air, food, water, or soil. 1,2-Dichloropropane has been rated a B2 carcinogen, however, so prolonged exposure could result in death from cancer.

Systemic Effects. Systemic effects of 1,2-dichloropropane include respiratory effects due to irritation of the respiratory tract, hematological effects, and hepatic and renal alterations manifested primarily as fatty degeneration.

Respiratory effects, including chest discomfort, dyspnea and cough, were reported in humans as a consequence of inhalation exposure to 1,2-dichloropropane (Rubin 1988); respiratory effects have not been observed in humans following oral or dermal exposure. Similarly, respiratory effects in animals were seen only as a result of inhalation exposure. Following inhalation exposure, rats appeared to be more sensitive to the effects of 1,2-dichloropropane on the nasal tissues than mice (Nitschke et al. 1988). This sensitivity was observed following both acute and intermediate exposure (Nitschke and Johnson 1983; Nitschke et al. 1988).

Cardiac failure was the cause of death for 2 patients who ingested a single dose of 1,2-dichloropropane (Larcan et al. 1977; Perbellini et al. 1985). It is likely, however, that the cardiac failure in humans is a result of toxicity to the CNS. Oral studies in animals did not show cardiovascular effects resulting from 1,2-dichloropropane, but this may be a consequence of the limited scope of pathological examination in the high dose acute studies. Human inhalation studies did not report adverse effects on the cardiovascular system. Animal inhalation studies by Heppel et al. (1946), however, reported some fatty degeneration of the heart, but this effect was only seen in the animals that died. Similar effects,

however, were not observed in more recent studies by Nitschke and coworkers (Nitschke and Johnson 1983; Nitschke et al. 1988).

Adverse gastrointestinal effects were seen in humans after deliberate inhalation and ingestion of 1,2-dichloropropane (Pozzi et al. 1985; Chiappino and Secchi 1968; Perbellini et al. 1985). These effects included nausea, vomiting and gastrointestinal tract lesions. Nausea and vomiting are general effects that could very well be due to CNS toxicity.; therefore, it is difficult to determine if these effects are secondary to the gastrointestinal irritation/corrosion or CNS toxicity. Acanthosis of the forestomach was seen in mice in a chronic oral study done by NTP (1986), but no effects on the gastrointestinal system were seen in any inhalation studies. The acanthosis may be a consequence of repeated ingestion of an irritant which is consistent with the gastrointestinal effects of 1,2-dichloropropane on humans. It was not clear that the acanthosis was specifically due to 1,2-dichloropropane.

Disseminated intravascular coagulation (DIC) and hemolytic anemia were found in humans as a result of overexposure to 1,2-dichloropropane (Perbellini et al. 1985; Pozzi et al. 1985). This finding, somewhat unusual in cases of solvent exposure, was reported in a total of five patients between the two studies regardless of route of exposure (inhalation or ingestion). Perbellini et al. (1985) suggested that hemolysis resulting from 1,2-dichloropropane may trigger DIC, but the mechanism has yet to be proven. In animal studies, a dose-related increase in the severity of anemia was found in rabbits exposed to 1,2-dichloropropane by inhalation (≥150 ppm, 6 hours/day, 5 days/week, 13 weeks) (Nitschke et al. 1988) and in rats treated orally with 1,2-dichloropropane (≥250 mg/kg/day for up to 10 consecutive days and at ≥100 mg/kg/day, 5 days/week for 13 weeks) (Bruckner et al. 1989). These results are consistent with the anemia observed in humans as a result of both inhalation and ingestion of 1,2-dichloropropane.

One of the principal target organs, in both animals and humans, for the toxicity of 1,2-dichloropropane is the liver. The major effects in both animals and humans resulting from both inhalation and oral exposure are fatty degeneration and necrosis. The hepatic effects of 1,2-dichloropropane on humans result from unknown, but apparently high, doses either ingested in a single bolus dose or inhaled over a short period of time.

Secchi and Alessio (1968, 1971) reported increases in hepatic enzymes found in human serum as an indicator of hepatic damage resulting from ingestion of 1,2-dichloropropane (mixture of 70% 1,2-dichloropropane and 30% trichloroethylene). Cytoplasmic liver enzymes found in the serum indicated less severe damage to hepatocytes, while mitochondrial and lysosomal liver enzymes found in the serum indicated severe hepatic damage, usually associated with death (3/6 subjects died). Compound-related damage to mitochondrial structures results in the depression of metabolic processes related to the production of energy, and damage to the lysosomes results in the release of hydrolytic enzymes into the cell which is responsible for

fatal cellular necrosis. In this study, histological examination of the liver of the patients positively correlated with the serum-enzymological findings.

Bonashevskaya et al. (1976) discussed a proposed mechanism of action of 1,2-dichloropropane on the rat liver based on work done on chlorinated aromatic compounds. The centrolobular region of the liver was reported as the focus for detoxification of lipophilic substances, while the peripheral region of the liver manages the elimination of toxins with the bile. The toxic effects of 1,2-dichloropropane are generally localized in the centrolobular region of the liver. The 1,2-dichloropropane penetrates the plasma membranes in the centrolobular region and is metabolically transformed because of the activity of microsomal enzymes. This system of microsomal enzymes is also described by Van Dyke and Wineman (1971) (see section 2.3.1.3 on Metabolism). The activation of the enzyme system results in hyperplasia of the endoplasmic reticulum, resulting in the loss of ribosomes. The loss of the ribosomes results in a decrease in protein synthesis and, therefore, an inhibition of lipoprotein formation. Consequently, lipid inclusions appear in the cytoplasm of the cells, resulting in fatty degeneration of the liver. This mechanism has been proposed in the literature but has yet to be completely proven, and the relevance of the mechanism to humans remains unknown.

Renal failure has occurred in people exposed to 1,2-dichloropropane orally and by inhalation (Pozzi et al, 1985; Zedda et al. (n.d.); Perbellini et al. 1985). Fatty degeneration of the kidney was seen in animals exposed by inhalation to 1,2-dichloropropane (Highman and Heppel 1948). Reddened renal medullae were found in animals treated by gavage for 2 weeks, but was not found in animals treated for longer time periods (NTP 1986). The reddened medullae may be transient lesions that disappear after initial exposure to 1,2-dichloropropane. The animal inhalation and oral studies suggest that kidney toxicity may be a consequence of single and repeated exposure to 1,2-dichloropropane.

Dermal/ocular effects of 1,2-dichloropropane have occurred in humans; these include periorbital and conjunctival hemorrhages following vapor exposure (Pozzi et al. 1985) and dermatitis after dermal exposure (Grzywa and Rudzki 1981). Conjunctivitis was seen in guinea pigs exposed to 1,2-dichloropropane vapor (Heppel et al. 1946), but no dermal/ocular effects were seen as a result of oral exposure. These local irritative effects of 1,2-dichloropropane are consistent with the gastrointestinal tract data; the chemical appears to be a local irritant by all routes, as might be expected.

The reported systemic effects of 1,2-dichloropropane in humans have resulted from inhalation or ingestion of 1,2-dichloropropane in the form of a cleaning solvent, or from dermal contact with aerosols in the workplace. Since 1,2-dichloropropane is no longer available as a consumer solvent, and its use as an industrial solvent involves closed systems, the potential for human exposure is minimal. The concentrations associated with systemic

effects in animals are much higher than those found in the environment, in occupational settings, or in water or soil surrounding waste sites, so it is not likely that harmful, noncancer effects would result from brief or prolonged human exposure to 1,2-dichloropropane in air, food, water, or soil. 1,2-Dichloropropane has been rated a B2 carcinogen, however, so prolonged exposure may result in cancer.

Immunological Effects. Sensitization has occurred in humans dermally exposed to 1,2-dichloropropane in the workplace (Grzywa and Rudzki 1981) (see Section 2.2.3.2). Immunological effects in humans have not been observed as a result of oral or inhalation exposure. An in vitro study on the toxicity of 1,2-dichloropropane on human lymphocytes was conducted by Perocco et al. (1983). The cellular parameters studied included tritiated thymidine uptake and viability in cells grown with or without the S-9 rat liver metabolizing system. The S-9 liver system is included to provide mammalian liver enzymes that may be necessary to metabolize the compound being tested into a more or less toxic chemical, simulating events in vivo. No cytotoxic action against human lymphocytes was seen as a result of exposure to 1,2-dichloropropane. Dermal exposure in humans may result in immunological effects, but it is inappropriate to draw any conclusions regarding other routes of exposure due to the limited data. In mice, a decrease in the absolute and relative thymus weight and a decrease in cortical lymphoid cells were found in animals exposed by inhalation to 300 ppm 1,2-dichloropropane (6 hours/day, 5 days/week, 2 weeks) (Nitschke and Johnson 1983). Except for the acutely exposed mice described above (Nitschke and Johnson 1983), no changes in the immunological organs or tissues were observed in animals exposed by inhalation (acute or intermediate exposure periods) or treated orally (intermediate and chronic exposure periods). Tests of immunological function were not performed following any route of exposure in animals.

Neurological Effects. The CNS is a principal target for 1,2-dichloropropane toxicity. Dizziness, disorientation, and coma are some of the effects on the central nervous system which have occurred in humans after overexposure by ingestion (Larcan et al. 1977; Perbellini et al. 1985; Thorel et al. 1986). The dose-response relationship for this effect cannot be characterized due to lack of quantitative dose information. Reported neurological effects resulting from inhalation exposure were less pronounced than the effects resulting from oral exposure, probably due to different exposure levels. Since only two case studies of inhalation overexposure are available (Pozzi et al. 1985; Rubin 1988) and since CNS effects as a result of oral overexposure to high levels are severe, it is reasonable to assume that inhalation exposures (at concentrations that would result in the same internal dose as in the oral studies), may produce CNS effects of similar severity to those found in the oral studies. The mechanism of action on the CNS has not been determined, but Perbellini et al. (1985) found a high concentration of 1,2-dichloropropane in the brain of a woman who died following ingestion of 1,2-dichloropropane. In animal studies, neurological effects (lethargy, CNS depression, decreased activity) were found following

acute inhalation exposure (Nitschke and Johnson 1983) and following acute and intermediate oral exposure (Gorzinski and Johnson 1989; Bruckner et al. 1989). These observations are consistent with the effects found in humans following both inhalation and ingestion of 1,2-dichloropropane.

Since 1,2-dichloropropane is no longer available as a consumer solvent, it is unlikely that other modes of human exposure (air, food, or water) would result in harmful central nervous system effects.

Genotoxic Effects. No studies were located regarding genotoxic effects in humans or animals following inhalation or dermal exposure to 1,2-dichloropropane. In an oral dominant-lethal study in mice, no effects were found on mating performance or fertility in the males, or on the number of implantations, resorptions, and litter sizes (Hanley et al. 1989). Results of in vitro genetic testing of 1,2-dichloropropane are presented in Table 2-4. A number of investigators found that 1,2-dichloropropane is mutagenic for various strains of Salmonella, when tested with or without S-9 exogenous metabolic activation preparation. Carere and Morpurgo (1981) and Principe et al. (1981) found that 1,2-dichloropropane was mutagenic for Aspergillus but not Streptomyces when tested without an exogenous metabolic activation system. 1,2-Dichloropropane was mutagenic in mouse lymphoma cells when tested with exogenous activation (Tennant et al. 1987) and in Drosophila (exposed by inhalation and ingestion) (Woodruff et al. 1985). Chromosomal aberrations were induced in Chinese hamster ovary cells under both activated and non-activated conditions, but not in Aspergillus (Crebelli et al. 1984). Since 1,2-dichloropropane is mutagenic in bacteria, mouse lymphoma cells and Drosophila, and clastogenic in Chinese hamster cells, it is appropriate to predict that 1,2-dichloropropane poses a genotoxic threat to humans.

Cancer. Chronic oral exposure to 1,2-dichloropropane produced significantly increased incidences of hepatocellular neoplasms in male and female mice and mammary gland adenocarcinomas in female rats (NTP 1986). Male mice of the strain used (B6C3Fl) in the NTP (1986) study are known to have a high incidence of benign liver tumors. The normally high rate of these tumors can be enhanced by various stimuli including stress, irritants, carcinogenic chemicals and promoters. As discussed by NTP (1986), promoters seem to enhance the incidence of liver tumors only in animals that have a high spontaneous rate. Carcinogenic chemicals, however, have increased the incidence of both benign and malignant liver tumors in mice, regardless of whether a certain strain has a high incidence of spontaneous tumors. NTP (1986) discussed the possibility that 1,2-dichloropropane was a tumor promotor but could not come to a conclusion.

NTP (1986) regarded the increased incidences of mammary gland adenocarcinoma in female rats as equivocal evidence of carcinogenicity. That the increase was associated with 1,2-dichloropropane exposure is strengthened by the following facts: these are relatively rare tumors in the strain of rat used; the incidence was 25% in the high-dose females that

TABLE 2-4. Genotoxicity of 1,2-Dichloropropane

Endpoint	Species	Activation	Result	Reference
Gene mutation	Salmonella	+	+	Haworth et al. 1983
		-	+	Principe et al. 1981 Zeiger 1987 Carere et al. 1981 Tennant et al. 1987 Stolzenberg et al. 1980; NTP 1986
	Streptomyces	NT	-	Carere et al. 1981; Principe et al. 1981
	Aspergillus	NT	+	Carere et al. 1981; Principe et al. 1981
	Drosophila	NA	+	Woodruff et al. 1985
	Mouse lymphoma cells	+	+	Tennant et al. 1987
		-	-	
Chromosomal aberrations	Aspergillus	NT	-	Crebelli et al. 1984
	Chinese hamster ovary cells	+	+	von der Hude et al. 1987; Galloway et al. 1987; Tennant et al. 1987; NTP 1986
		-	+	
Dominant lethal	Rat	NA	-	Hanley et al. 1989

NT = Not tested
NA = Not applicable

survived until the end of the study; and the lower body weight of the high-dose females would be expected to decrease the spontaneous rate, rather than enhance it. However, the toxicity of the high dose may have affected the homeostasis of the female rats; the incidence of mammary fibroadenomas was decreased in the high-dose females relative to controls, and the adenocarcinomas were morphologically similar to tumors classified by some pathologists as highly cellular fibroadenomas.

The EPA (1987b) has classified 1,2-dichloropropane as a B2 carcinogen (probable human carginogen) based on the NTP (1986) study, which concluded that 1,2-dichloropropane is reasonably anticipated to be a human carcinogen.

2.4 LEVELS IN HUMAN TISSUES AND FLUIDS ASSOCIATED WITH HEALTH EFFECTS

No studies were located that associated human tissue levels with human health effects or with environmental levels of 1,2-dichloropropane.

Perbellini et al. (1985) described a case of oral overexposure to 1,2-dichloropropane where the subject died from cardiac arrest 30 hours after ingestion. Symptoms of the overexposure included; initial agitation, bradycardia, hypertension and anuria, followed by hypoxemia, shock, DIC and cardiac arrest. Approximately 28 hours after ingestion, 7614 µg/L of 1,2-dichloropropane was found in the subject's blood and, after 29 hours, the concentration found was 6900 µg/L. At autopsy, the concentration of 1,2-dichloropropane was determined in several tissues; brain tissue contained 18,005 µg/L, cerebellar tissue contained 39,890 µg/L and adipose tissue contained 531,840 µg/L.

2.5 LEVELS IN THE ENVIRONMENT ASSOCIATED WITH LEVELS IN HUMAN TISSUES AND/OR HEATH EFFECTS

Rubin (1988) described health effects as a result of an accidental spill of 2000 gallons of 1,2-dichloropropane in 1981. The complaints from those exposed included chest discomfort, dyspnea, and a cough, suggesting that 1,2-dichloropropane is a respiratory tract irritant. The concentration of 1,2-dichloropropane in the air was not determined, so the health effects cannot be correlated level.

Amoore and Hautala (1983) odor thresholds of 214 industrial chemicals, including 1,2-dichloropropane, and compared these values with the Threshold Limit Values (TLV) recommended by the ACGIH. The air odor threshold of 1,2-dichloropropane is 0.25 ppm. The study reported that 50-90% of distracted persons would perceive the odor of 1,2-dichloropropane at the TLV of 75 ppm. The experiment was done with distracted persons, and not persons focused on detecting an odor, in order to better simulate the work environment. It is likely that unacclimated people would smell 1,2-dichloropropane before experiencing significant exposure.

Ghittori et al. (1987) evaluated the Biological Equivalent Exposure Limit (BEEL) for nine solvents, including 1,2-dichloropropane. BEEL refers to the concentration of a substance in a biological compartment when the environmental exposure level through the lungs equals the Threshold Limit Value (TLV). Ghittori et al. (1987) used urinary concentration of 1,2-dichloropropane as a biological indicator and correlated it with the TLV. A linear relationship between breathing zone concentration and urinary concentration was obtained. This relationship is displayed graphically in Figure 2-3.

Cramer et al. (1988) introduced a method for the detection of volatile compounds, including 1,2-dichloropropane, at parts per trillion (ppt) levels in whole blood (see Table 6-l). This method was validated using blood samples from a small population. Based on the method validation data, this method appears reliable and, in the future, may be routinely used to detect organic chemicals in human whole blood.

Wallace et al. (1982) monitored 1,2-dichloropropane and other volatile organic compounds in the breathing-air zone, in drinking water and in exhaled breath at a petrochemical area in Texas and in a non-industrial area in North Carolina. In this study, it was determined that inhalation was the main route of exposure to volatile organic compounds. No 1,2-dichloropropane, however, was found in the ambient air or in expired breath at either test site.

2.6 TOXICOKINETICS

2.6.1 Absorption

2.6.1.1 Inhalation Exposure

No studies were located regarding the rate and extent of absorption of 1,2-dichloropropane following inhalation exposure of humans. During the first 24 hours after a 6-hour exposure of rats to ^{14}C-1,2-dichloropropane (5, 50, or 100 ppm), 71-88% of the recovered dose was found in the excreta, with 55-65% of the recovered dose found in the urine and 16-23% of the recovered dose found in expired air as $^{14}CO_2$ (Timchalk et al. 1989). These data suggested that 1,2-dichloropropane was absorbed through the lungs. The data indicated that 1,2-dichloropropane was rapidly absorbed according to a zero-order input, but that absorption was not linear with respect to the concentration of 1,2-dichloropropane. The authors assumed that 60% of the inspired concentration of ^{14}C-1,2-dichloropropane was absorbed, but the basis for this assumption was not reported (Timchalk et al. 1989). Sato and Nakajima (1979) measured the blood/air partition coefficient of 10.7 for 1,2-dichloropropane indicating that 1,2-dichloropropane is readily absorbed from the lungs.

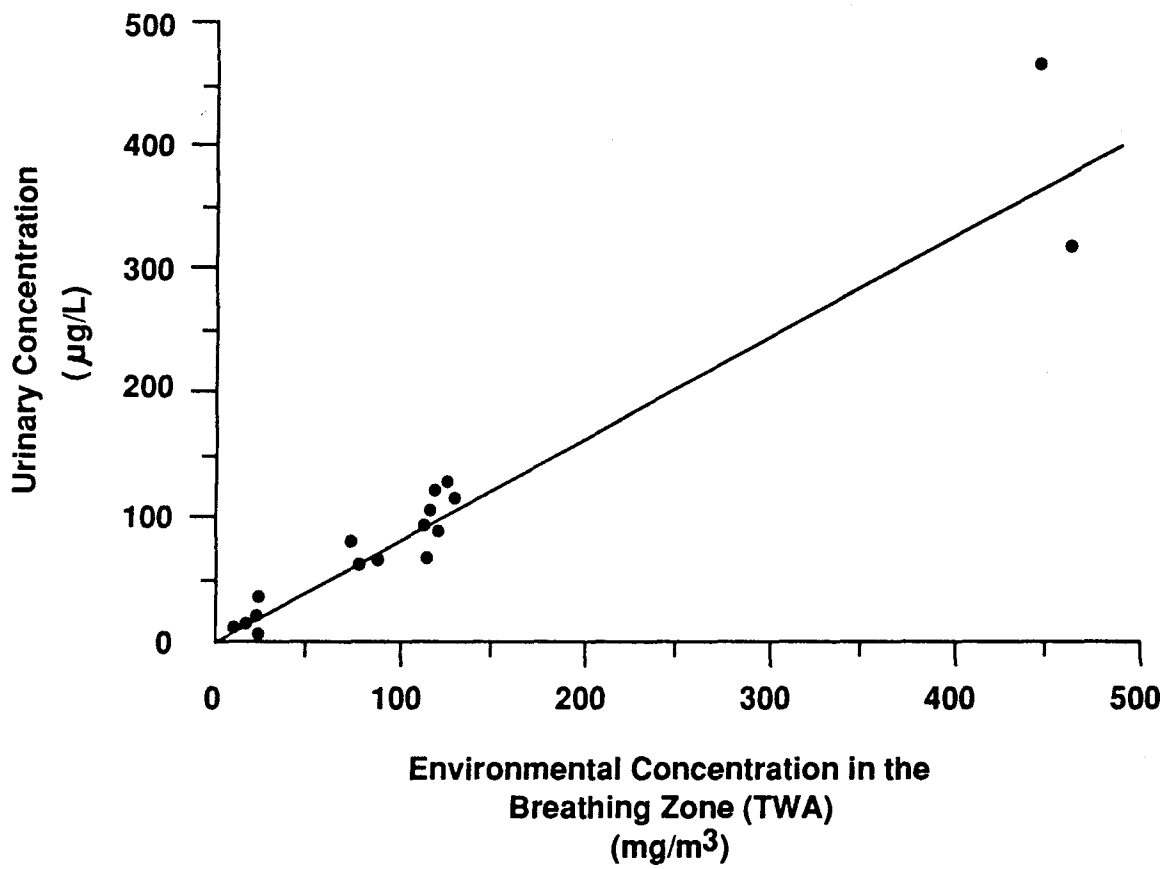


FIGURE 2-3. Relationship Between Breathing Zone Concentration of 1,2-Dichloropropane and Urinary Concentration

Source: Ghittori et al. 1987

2.6.1.2 Oral Exposure

No studies were located regarding the rate and extent of absorption of 1,2-dichloropropane following oral exposure of humans. Studies in rats by Hutson et al. (1971) and Timchalk et al. (1989), which found that an average of 74-95% of the ^{14}C-labeled 1,2-dichloropropane dose was excreted in the urine or in expired air within 24 hours of dosing, suggest that 1,2-dichloropropane is readily and extensively absorbed from the gastrointestinal tract. This is supported by the fact that only 0.5% of the administered dose remained in the gut 4 days after administration (Hutson et al. 1971).

2.6.1.3 Dermal Exposure

No studies were located regarding the rate and extent of absorption of 1,2-dichloropropane following dermal exposure of humans or animals. That 1,2-dichloropropane is absorbed by the skin can be inferred from the lethality observed in rabbits following dermal exposure (see section 2.2.3.1 on Death following dermal exposure).

2.6.2 Distribution

2.6.2.1 Inhalation Exposure

After rats were exposed for 6 hours to 5, 50, or 100 ppm ^{14}C-labeled 1,2-dichloropropane, the radioactivity was well distributed among the major tissues, with the highest concentration in the liver, kidney, lung, and blood (Timchalk et al. 1989).

2.6.2.2 Oral Exposure

Perbellini et al. (1985) described a case of a lethal overdose from a single ingestion of 1,2-dichloropropane. Death occurred 30 hours after ingestion. At autopsy, 18,005 µg/L 1,2-dichloropropane was found in the brain tissue, 39,890 µg/L was found in the cerebellar tissue, and 531,840 µg/L was found in adipose tissue.

Timchalk et al. (1989) observed that 48 hours after administration of ^{14}C-labeled 1,2-dichloropropane, the radioactivity was well distributed among the major tissues, with liver having the highest concentration. The distribution of radioactivity in the tissues of rats was similar following inhalation and oral exposure to 1,2-dichloropropane in the Timchalk et al. (1989) study, with the exception of high levels of radioactivity found in the lungs only after inhalation exposure. In a study by Hutson et al 1971), rats were administered one dose of 4.0 mg kg 1,2-dichloro(l-^{14}C)propane. Approximately 1.5% and 3.5% of the ^{14}C dose were found in the skin and carcass, respectively, after 96 hours.

2.6.2.3 Dermal Exposure

No studies were located regarding the distribution of 1,2-dichloropropane following dermal exposure.

2.6.3 Metabolism

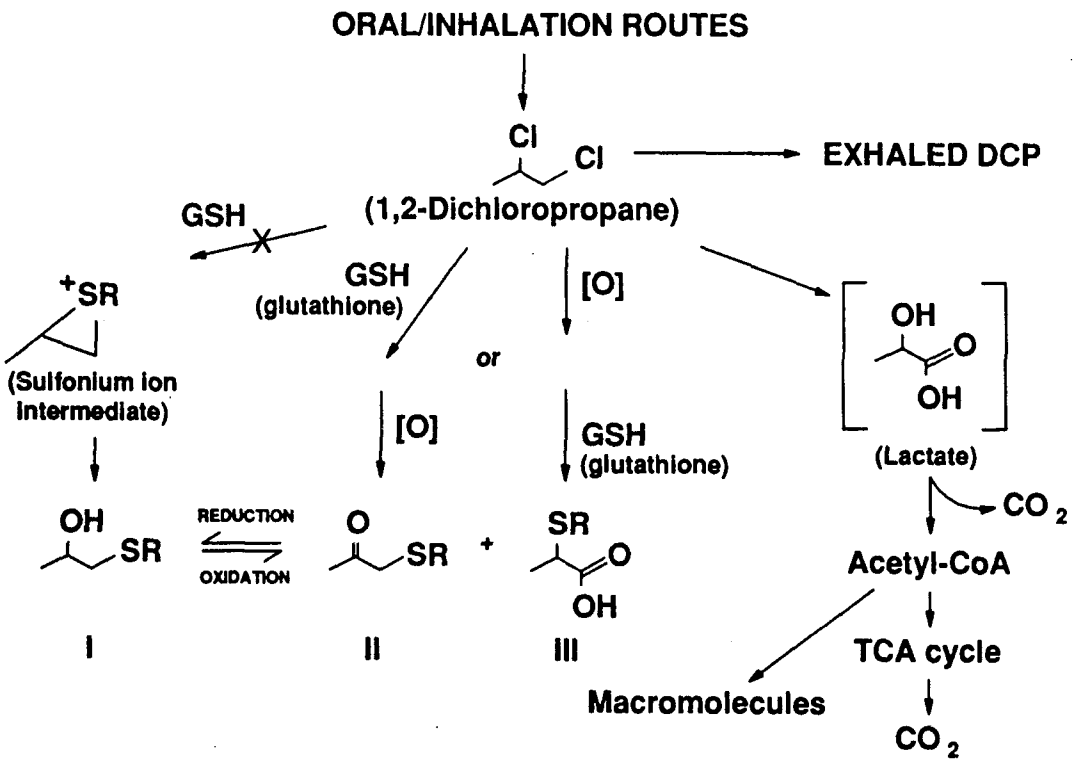
No studies were located regarding the metabolism of 1,2-dichloropropane following dermal exposure in humans or in animals.

Hutson et al. (1971) administered 4.8 mg/kg 1,2-dichloro(l-^{14}C)propane orally to rats and 42.4% of the given dose was measured in the expired air after 96 hours. Of the 42.4%, 19.3% was expired as (^{14}C)C0$_2$, indicating that extensive metabolism of 1,2-dichloropropane had occurred.

Jones and Gibson (1980) administered one dose of 100 mg/kg/day intraperitoneally to rats and measured the amount of 1,2-dichloropropane in the expired air, They found 5% of the administered dose after 0-3 hours, and 5% of the dose after 9-18 hours, indicating that the 1,2-dichloropropane is transported in the blood and expired by the lungs.

Timchalk et al. (1989) described the time course of 1,2-dichloropropane in the blood as a one-compartment open pharmacokinetic model, with zero-order input and first-order elimination. In rats exposed to 50 or 100 ppm 1,2-dichloropropane vapors for 6 hours, the peak blood concentrations were 17- to 19- and 68- to 84-fold higher, respectively, than the peak blood concentration of the 5 ppm group. This dose-dependent non-linearity of blood clearance suggests that metabolism and/or elimination of 1,2-dichloropropane becomes saturated with increasing concentrations (Timchalk et al. 1989).

The major urinary metabolites in rats treated by gavage or exposed to 1,2-dichloropropane vapors are N-acetyl-S-(2-hydroxypropyl)-L-cysteine, N-acetyl-S-(2-oxopropyl)-L-cysteine, and N-acetyl-S-(l-carboxyethyl)-Lcysteine. These metabolites accounted for approximately 84% of the urinary metabolites excreted (Timchalk et al. 1989) (see Figure 2-4). Data indicate that the three N-acetyl cystein conjugates result from 1,2-dichloropropane undergoing oxidation, either before or after conjugation with gluathione. The data also indicate that 1,2-dichloropropane may conjugate with lactate, forming CO_2 and Acetyl Co-A. Acetyl Co-A may then enter the TCA cycle and generate more CO_2 or may be utilized in various biosynthetic pathways. In another study, 25-35% of an oral dose of 20 mg/kg/day 1,2-dichloropropane administered for 4 days was excreted as N-acetyl-S-(2-hydroxypropyl)-cysteine. β-Chloroactate and N-acetyl-S-(2,3-dihydroxypropyl)-cysteine were also detected in the urine (Jones and Gibson 1980). Similar urinary metabolites (mercapturic acids) were detected following intraperitoneal administration of 1,2-dichloropropane (Trevisan et al. 1988).



I = N-acetyl-S-(2-hydroxypropyl)-L-Cysteine
II = N-acetyl-S-(2-oxopropyl)-L-Cysteine
III = N-acetyl-S-(1-carboxyethyl)-L-Cysteine

Figure 2-4. Proposed Metabolic Scheme for 1,2-Dichloropropane in the Rat (R = N-acetylcysteine).

Repeated exposure of rats to 1 mg kg/day 1,2-dichloropropane via gavage for 7 days following a single dose of ^{14}C-labeled compound resulted in enhanced oxidative metabolism (increased CO_2 formation) and reduced radioactivity excreted in the urine compared to rats receiving only the single-labeled dose (Timchalk et al. 1989).

Van Dyke and Wineman (1971) determined that 5.8% of (^{36}Cl)1,2-dichloropropane was enzymatically dechlorinated in vitro by an enzyme system found in hepatic microsomes. This system required NADPH and oxygen and was inducible by phenobarbital and benzpyrene, but not by methylcholanthrene. The optimum pH of the system was 8.2.

2.6.4 Excretion

2.6.4.1 Inhalation Exposure

In rats exposed to 5, 50, or 100 ppm of ^{14}C-labeled 1,2-dichloropropane vapors for 6 hours, the principal routes of elimination were the urine and expired air; 55-65% of the recovered does was excreted in the urine, expired CO_2 accounted for 16-23% of the recovered dose, and 1.7, 2.1-3.4, and 6.3-6.7% of the recovered dose was expired as organic volatiles in the 5, 50, and 100 ppm groups, respectively. The majority of the administered dose was excreted within the first 24 hours after exposure (Timchalk et al. 1989).

2.6.4.2 Oral Exposure

In a study by Hutson et al. (1971), rats were administered one dose of 4.0 mg/kg 1,2-dichloro(1 -^{14}C)propane by gavage. In the first 24 hours, 80-90% of the ^{14}C dose was excreted in the urine, feces, and expired air. After 24 hours, males had excreted 48.5% of the dose in the urine and 5.0% of the dose in the feces. Females had excreted 51.9% of the dose in the urine and 3.8% of the dose in the feces in the same time period. Therefore, the percentage of radioactivity in expired air after 24 hours ranged from 24.3-36.5% of the dose in both sexes. Similar results were observed in rats administered 1 or 100 mg/kg of ^{14}C-labeled 1,2-dichloropropane (Timchalk et al. 1989). In a separate experiment, 42.4% of the administered ^{14}C dose of 4.8 mg/kg 1,2-dichloro(l-^{14}C)propane was detected in the expired air after 96 hours (Hutson et al. 1971).

In rats exposed to 1 mg/kg of ^{14}C-labeled 1,2-dichloropropane, 31-36% of the dose was expired as CO_2 and 0.14-1.13% as volatile organics. In animals treated with 100 mg/kg, 23-27% of the label was expired as CO_2 and 10-16% as volatile organics. The differences between the two groups were statistically significant. In the 100 mg/kg groups, 82% of the exhaled volatile organics were identified as 1,2-dichloropropane (Timchalk et al. 1989).

Trevisan et al. (1988) administered 1,2-dichloropropane intraperitoneally to rats and determined that it is excreted in the urine in

the form of mercapturic acids, N-acetyl-S-(2-hydroxypropyl)cysteine and N-acetyl-S-(2,3-dihydroxypropyl)cysteine. A non-linear, dose-dependent excretion was observed with the maximum excretion seen 9 hours after injection.

2.6.4.3 Dermal Exposure

No studies were located regarding the excretion of 1,2-dichloropropane following dermal exposure.

2.7 INTERACTIONS WITH OTHER CHEMICALS

A common soil fumigant known as D-D consists of 1,2-dichloropropane (27.1%), 1,3-dichloropropene (53%), related compounds and 1% epichlorohydrin. Nater and Gooskens (1976) reported three incidences of exposure to D-D which resulted in dermatosis. Patch testing suggested the existence of a contact allergic sensitivity to D-D in one of the patients. Patch tests with components of D-D suggest that the cause of the contact allergy is with the dichloropropene component.

Shell Oil Co. (1982) studied the toxic effects of 1,2-dichloropropane (light ends) which is a mixture of 65% 1,2-dichloropropane and various other dichloropropane/dichloropropenes. The oral LD_{50} in rats was 487 mg/kg (95% confidence limits, 387-613 mg/kg), which was found in fairly good agreement with the LD_{50} value of 604 mg/kg, calculated on the basis of the additive effects of the major components of the mixture, indicating that potentiation of toxicity was not occurring. The 24-hour percutaneous LD_{50} in rats was greater than 2340 mg/kg (the maximum dose volume that could be applied). The Draize skin irritancy test showed necrosis of female rabbit skin with a less severe effect seen in males. In both sexes, skin reactions persisted at 21 days after dosing. The mixture was mildly irritating to rabbit eyes with a severe initial pain reaction. The mixture was a strong sensitizer in guinea pigs (19/20 positive after 24 hours, 16/20 after 48 hours).

Shell Oil Co. (1983) studied the genotoxic effects of a mixture of dichloropropanes and dichloropropenes in which 1,2-dichloropropane was the major component (65%). Compound-related effects were observed with several strains of Salmonella that contained base substitution mutations, and with Saccharomyces. Similar effects were found with 1,3-dichloropropene (25% of mixture), indicating that the mutagenic response may have been due to 1,3-dichloropropene. The mixture did not mutate rat liver cells (RL4) in vitro.

Parker et al. (1982) exposed CD-1 mice and F344 rats to mixtures of D-D [1,3-dichloropropene (52%)/1.2-dichloropropane (29%)] at concentrations of 0, 5, 15 or 50 ppm, 6 hours/day, 5 days/week for 6 or 12 weeks. Exposure-related effects in the animals exposed to 50 ppm D-D included increased mean liver/body weight ratios in male rats, increased mean kidney/body weight ratios in female rats and slight to moderate diffuse hepatic enlargement in

male mice after 12 weeks of exposure. No exposure-related effects were found at the lower exposure levels.

Linnett et al. (1988) studied the effects of subchronic inhalation of D-D (1,3-dichloropropene (53.7%)/1,2-dichloropropane(25.6%)) on reproduction in male and female rats. Exposures up to 90 ppm for 10 weeks had no effects on the libido, fertility, or morphology of the reproductive tracts of male or female rats.

In animals, the joint toxicity of 1,2-dichloropropane was assessed with a variety of different compounds since environmental or occupational exposures to chemicals usually occur in combination with other chemicals. Pozzani et al. (1959) determined that 1,2-dichloropropane has an additive toxic effect (LD_{50} assessed) when given orally or by inhalation to rats with 1,1,2-trichloroethane, and when given with both ethylene dichloride and perchloroethylene. Drew et al. (1978) reported that inhalation of 1,2-dichloropropane in combination with trichloropropane by rats did not result in a greater-than-additive toxic effect (serum enzymes assessed: SGOT, SGPT, G-6-phosphatase, ornithine carbamyl transferase). Tsulaya et al. (1979) and Sidorenko et al. (1976, 1979) determined that inhalation of 1,2-dichloropropane has an additive effect in rats and mice when given in combination with 1,2,3-trichloropropane and perchloroethylene (effects on lung, liver and nervous system assessed).

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No populations with unusual or increased susceptibility to the health effects of 1,2-dichloropropane could be identified based on the available literature.

2.9 ADEQUACY OF THE DATABASE

Section 104 (i) (5) of CERCLA, 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-dichloropropane is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

2.9.1 Existing Information on the Health Effects of 1,2-Dichloropropane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2-dichloropropane are summarized in Figure 2-5.

Data regarding the toxic effects of 1,2-dichloropropane on humans result solely from case reports of people exposed by inhalation, ingestion or skin exposure. The case reports contain information regarding the lethal and systemic effects of acute inhalation and oral exposure to the agent. These reports indicate that 1,2-dichloropropane primarily affected the central nervous system, liver, and kidneys, but respiratory and hematopoietic system alterations were also observed. Chronic dermal exposure to 1,2-dichloropropane in aerosol form in the workplace resulted in dermatitis.

There are data regarding the lethality and toxic effects of 1,2-dichloropropane in animals exposed by inhalation for acute and intermediate time periods. The central nervous system, respiratory system, liver, and kidney are the major target organs of 1,2-dichloropropane toxicity. Hematological effects are also reported. A limited study on the carcinogenicity of 1,2-dichloropropane in mice after inhalation exposure has been done and has suggested that 1,2-dichloropropane was carcinogenic (see Section 2.2.1.8), but the study is unreliable (high mortality occurred in the exposed group; tumor incidence in controls was not reported; morphology of the hepatomas was inadequately characterized) so no conclusions may be drawn.

Data are available regarding the lethality and toxic effects of 1,2-dichloropropane in animals orally exposed for acute, intermediate and chronic time periods. These data show that the liver is the main target organ for the toxic effects of 1,2-dichloropropane; effects on the hematological and nervous systems were also observed. An increase in the incidence of a developmental effect in rats (delayed ossification of the bones of the skull) was also observed. The carcinogenicity in rats and mice after chronic oral exposure to 1,2-dichloropropane was assessed and carcinogenic potential was found in both species: there was equivocal evidence in female rats (chemically related marginal increase in adenocarcinomas of the mammary gland), no evidence in male rats (no chemically related increases in neoplasms), and some evidence in male and female mice (chemically increased incidence of hepatocellular neoplasms).

Application of 1,2-dichloropropane to the skin or eye of rabbits produced irritation. Application to the skin of rabbits has also produced death.

No genotoxic effects were found in a dominant-lethal study in rats.

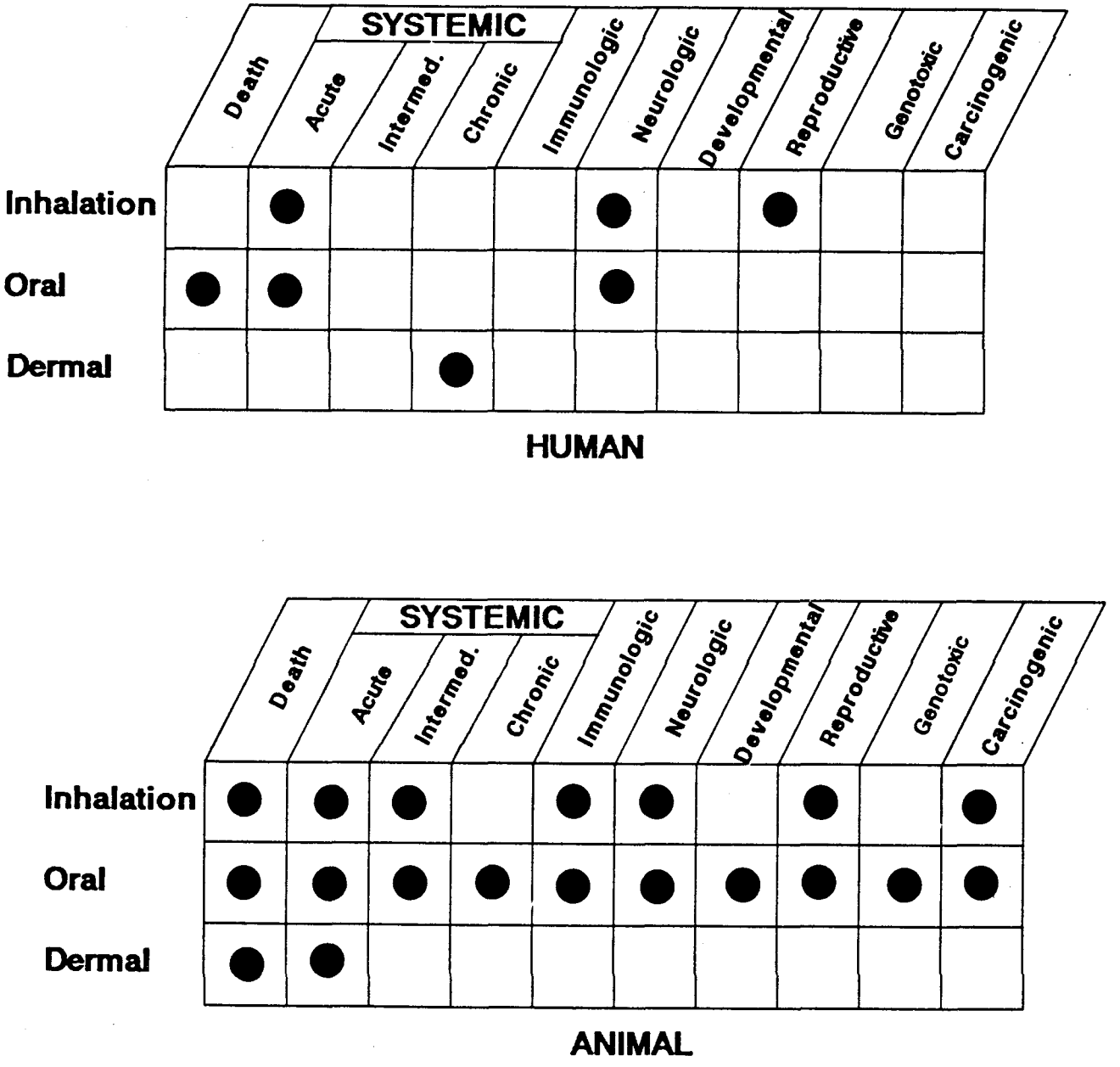


FIGURE 2-5. Existing Information on Health Effects of 1,2-Dichloropropane

Genotoxicity data in bacteria, fungus, Drosophila and mammalian cell lines was evaluated. The preponderance of data indicate that 1,2-dichloropropane ,is mutagenic in these systems.

2.9.2 Data Needs

Single Dose Exposure. Information regarding single inhalation and oral exposure of various animal species to 1,2-dichloropropane provides information on lethal effect levels. The limited data available on the non-lethal effects of a single dose of 1,2-dichloropropane show effects on the liver and kidney. More studies that use non-lethal doses and examine tissues histologically might provide information on dose-response relationships and mechanisms of lethality and toxicity. Single dose dermal and ocular studies in rabbits have shown that 1,2-dichloropropane is a skin and eye irritant. Additional observations in other species of animals dermally exposed to 1,2-dichloropropane would help to more fully characterize the irritative effects of this chemical.

Repeated Dose Exposure. Available repeated exposure inhalation and oral studies of 1,2-dichloropropane provide information on the lethal and non-lethal effects in various species of animals. The major target organs for the effects of 1,2-dichloropropane are the central nervous system, liver and kidney, and effects on the respiratory, hematological systems and body weight were also seen. Repeated dose dermal studies with animals are not available but would provide information on the possible systemic effects of 1,2-dichloropropane. Since occupational dermal exposure has resulted in dermatitis in humans, repeated dermal dose studies in animals might also provide information on allergic responses as well as local irritation.

Chronic Exposure and Carcinogenicity. Well-conducted chronic oral gavage studies provide information on the systemic and carcinogenic effects of 1,2-dichloropropane in rats and mice. Chronic inhalation, oral drinking water, and dermal animal studies are not available but could provide information on similarity of systemic effects across routes and dose-response data that may be useful for human health risk evaluation. These studies may also help categorize the carcinogenic potential of 1,2-dichloropropane in humans.

Genotoxicity. The available genotoxicity studies conducted with bacteria, fungus, and mammalian cell lines indicate that 1,2-dichloropropane is genotoxic in some systems. A dominant-lethal study in rats resulted in no genotoxic effects, but further in vivo studies with mammals will help fully characterize the genotoxic potential of 1,2-dichloropropane, with regard to potential for heritable mutations, chromosomal damage, and chromosomal aberrations. Cell transformation studies may also be useful to augment carcinogenesis bioassays.

Reproductive Toxicity. Histological examination of the reproductive organs of female rats and mice exposed orally to 1,2-dichloropropane for subchronic or chronic durations, showed inflammation of the uterus and ovary and hyperplasia of the mammary gland. It was not found conclusively that these effects were compound-related; this uncertainty and the fact that limited human data (metrorrhagia) suggest an adverse effect on the reproductive system suggests that additional studies examining the effects of 1,2-dichloropropane on the female reproductive organs are desirable. Male and female reproductive organs in rodents were also histologically examined after subchronic and chronic oral exposure but no compound-related lesions were found. A 2-generation oral reproduction study is now in progress, and the results of these studies will provide further information regarding any reproductive effects of 1,2-dichloropropane in animals, which then may be related to possible reproductive effects in humans. Studies examining the reproductive effects of 1,2 dichloropropane following inhalation and dermal exposure of animals would also be helpful in assessing the potential effects in humans.

Developmental Toxicity. Toxic effects in rats (delayed ossification of the bones of the skull) have been found following oral exposure to 1,2-dichloropropane. Further studies using a greater range of doses and studies testing other relevant routes of exposure would provide information on possible fetotoxic and teratogenic effects in animals that might be relevant to humans.

Immunotoxicity. Subchronic and chronic oral studies in rats and mice have found no adverse effects after histological examination of organs and tissues of the immunological system, but a battery of immunotoxicity tests have not been performed. A decrease in thymus weight and a decrease in cortical lymphoid cells were found in mice following acute inhalation exposure to 1,2-dichloropropane, but no tests of immunological function were performed. These studies in animals by relevant environmental routes would provide a better assessment of immunotoxic effects than histological examination of organs and tissues. Two case studies suggested that 1,2-dichloropropane may sensitize humans. Testing in animals to determine the dose and time of exposure needed to sensitize animals would be helpful in determining levels of 1,2-dichloropropane leading to sensitization in , humans.

Neurotoxicity. Signs of central nervous system toxicity have been seen in humans after both inhalation and oral exposure. Signs of central nervous system toxicity were found in animals acutely exposed to 1,2-dichloropropane by inhalation and in animals treated orally with 1,2-dichloropropane (acute and subchronic exposures). Functional Observational Batteries have been performed on rats acutely exposed to 1,2-dichloropropane and neurological effects (decrease in activity) were found at ≥300 mg/kg/day. A battery of tests by other relevant routes of exposure and the assessment of neuropathology using specialized fixation methods would provide further

information on the neurotoxicity in animals, which may relate to possible neurotoxic effects in humans.

Epidemiological and Human Dosimetry Studies. In humans, 1,2-dichloropropane primarily affects the central nervous system, liver and kidney. This information comes from case studies where patients either inhaled or ingested 1,2-dichloropropane, accidentally or as a suicide attempt. The only occupational exposure was reported in a Polish study in which two women out of sixty that were dermally exposed to liquid 1,2-dichloropropane developed allergic dermatitis. The most likely routes of exposure for the United States general population are through inhalation of contaminated ambient air or consumption of contaminated drinking water. As discussed in Chapter 5, the use of 1,2-dichloropropane as a consumer solvent and as a soil fumigant has been discontinued. 1,2-Dichloropropane is now used as a commercial solvent, but only in closed systems. Therefore, exposure to the general population via inhalation should be much lower than in the past. The most likely exposure to humans is the consumption of contaminated drinking water resulting from the use of 1,2-dicholopropane soil fumigant in agricultural areas. Elimination of 1,2-dichloropropane from the groundwater is slow so that contamination may remain for a long and indeterminate period of time. The monitoring of urine and blood levels of 1,2-dichloropropane in populations exposed to contaminated drinking water or air (such as those living near industries using 1,2-dichloropropane as a solvent, those living near hazardous waste sites, or those people occupationally exposed) and the correlation of these levels with health effects, may provide a basis for further epidemiological studies.

Biomarkers of Disease. Secchi and Alessio (1968, 1971) reported differences in hepatic enzymes found in human serum as an indicator of hepatic damage resulting from ingestion of 1,2-dichloropropane. It was found that cytoplasmic liver enzymes found in the serum indicated less severe damage to hepatocytes, while mitochondrial and lysosomal liver enzymes found in the serum indicated severe liver damage, which usually results in death. Further epidemiological studies may validate these indices and correlate other parameters with a particular disease state resulting from exposure to 1,2-dichloropropane.

Disease Registries. At present, the only toxicological effects of 1,2-dichloropropane reported in humans are acute effects resulting from ingestion or inhalation of cleaning solvents containing 1,2-dichloropropane. If epidemiological studies identify particular diseases associated with 1,2-dichloropropane exposure, it may be possible to determine the number of people affected and the factors associated with identifying the disease in certain populations, such as exposure to 1,2-dichloropropane in the ambient air or in the drinking water near hazardous waste sites.

Bioavailability from Environmental Media. Detection of exposure to 1,2-dichloropropane through urinalysis, blood analysis, and odor thresholds have been studied (Amoore and Hautala 1983, Ghittori et al. 1987, Cramer et

al. 1988). Epidemiology studies that correlate levels of 1,2-dichloropropane in the environment with levels in human tissues, blood or urine and with specific health effects would be useful. While no data on the uptake of 1,2-dichloropropane in other tissue or bodily fluids are available, a pilot study demonstrated that similar low molecular weight chlorinated alkanes are found in human milk (Pellizzarri et al. 1982). The source of these pollutants was probably ambient air. The major source of human exposure to 1,2-dichloropropane could be from contaminated well water, and an animal study (Hutson et al. 1971) indicates that it is readily adsorbed from the GI tract. An analysis of body fluids of those people whose drinking water contains 1,2-dichloropropane or who have come into contact (orally or dermally) with soil contaminated with 1,2-dichloropropane, may allow a determination of the existence of exposure and bioavailability of the chemical.

Food Chain Bioaccumulation. 1,2-Dichloropropane has not been reported in food or biota nor were any studies located in which the uptake of this chemical in plants or animals was investigated. The bioaccumulation potential for a chemical is most conveniently studied by measuring the bioconcentration factor (BCF) or the concentration of a chemical in fish divided by the concentration in water from which the chemical is taken up. Lacking any data on such studies for 1,2-dichloropropane, the bioaccumulation can be estimated from its partitioning behavior between octanol and water which, in turn, can be estimated from structure-activity relationships. Accordingly, the BCF of 1,2-dichloropropane estimated from its K,, is 18 (Lyman et al. 1982, Eqn 5-2), indicating that there is a very low potential for bioaccumulation in the food chain.

Absorption, Distribution, Metabolism, Excretion. The only in vivo toxicokinetic data of 1,2-dichloropropane are the inhalation metabolism and the excretion study of Timchalk et al. (1989), oral metabolism and excretion studies of Hutson et al. (1971) and Timchalk et al. (1989), the oral metabolism study of Jones and Gibson (1980), and the intraperitoneal excretion study of Trevisan et al. (1988). These studies indicate that inhaled 1,2-dichloropropane and orally administered 1,2-dichloropropane are readily and extensively absorbed by the gastrointestinal tract, is primarily metabolized to N-acetyl-S-(2-hydroxypropyl)cysteine, and is rapidly excreted in the urine, feces and expired air. Studies in animals of the rate and extent of absorption and distribution following exposure to all three routes, and metabolism and excretion following dermal exposure would provide more complete characterization the pharmacokinetics of 1,2-dichloropropane, Ghittori et al. (1987) and Cramer et al. (1988) reported methods for detection of 1,2-dichloropropane in urine and blood. These methods may provide means of monitoring human exposure and of extrapolating results from animal studies,

Comparative Toxicokinetics. No studies were found that evaluated differences in toxicokinetics between species. Toxicokinetic differences may explain the increased sensitivity of mice to the toxic effects of 1,2-

dichloropropane in comparison to other species. Ethical considerations limit the amount of information that can be obtained in humans, but analysis of the urine of people with known exposure to the parent compound or its metabolites could provide knowledge of the metabolic 'pathways in humans. Qualitative and quantitative comparison of human metabolites with those of animals could help identify the most appropriate species to serve as a model for predicting toxic effects in humans and studying the mechanisms of action.

2.9.3 On-going Studies

The EPA (1987d) issued a final rule requiring the manufacturers and processors of 1,2-dichloropropane to conduct health effects studies. All of the required studies have been incorporated into this profile, except for a 2-generation oral study, which has yet to be completed.