2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of HCCPD. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

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

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

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 199Oe), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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

2. HEALTH EFFECTS

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding lethality in humans after inhalation exposure to HCCPD.

Short-term inhalation of HCCPD at concentrations that ranged from 0.3 to 66 ppm was lethal to rats, mice, guinea pigs, and rabbits (Rand et al. 1982a; Treon et al. 1955). Duration of exposure and compound concentration affected lethality. With a 15minute exposure to 11.6 ppm HCCPD, 3 of 4 rats, 4 of 5 mice, 2 guinea pigs, and 1 of 3 rabbits survived, but with a 3-hour exposure to 10.0 ppm, all animals died. Males appeared to be more susceptible to HCCPD than females. The LC_{50} (lethal concentration, 50% kill) for male rats exposed to HCCPD for 4 hours was 1.6 ppm, while that for females was 3.5 ppm (Rand et al. 1982a).

Exposures lasting from 30 minutes to 4 hours at concentrations of 17.9-66 ppm were uniformly lethal to rats, mice, guinea pigs, and rabbits (Treon et al. 1955). The number of animals exposed was small (2-5), and a broad range of durations and doses was used. The small group size and variability in individual animal susceptibility must be considered when interpreting the data. With 15minute exposures to a concentration of 18 ppm, 4 rats, 3 of 5 mice, 2 guinea pigs, and none of 3 rabbits survived, but at a concentration of 17.4 ppm for the same period of time, 2 of 3 rats, none of 4 mice, neither of 2 guinea pigs, and 1 of 3 rabbits survived. With 2-week exposures to 0.5 ppm HCCPD, all male rats but only 2 of 10 female rats died (Rand et al. 1982a). When exposures were reduced to 5 days, 3 of 5 males and no females died.

In a 13-week study, all mice exposed to 2 ppm HCCPD for 5 days a week, 6 hours a day died during the first week, while rats exposed to the same concentration survived for up to 3 weeks (NTP 1994). Only 1 of 20 rats survived a 4-week exposure to 1 ppm, while 2 of 20 mice survived up to 5 weeks. Even with the 1 ppm exposure, most animals died during the first or second week. A lower concentration of 0.4 ppm caused the death of 5 of 10 male mice and 2 of 10 female mice during the first and second weeks of exposure. At the lowest concentration tested (0.04 ppm), 2 of 10 male mice and 1 of 10 female mice died. There were no deaths among rats exposed to concentrations of 0.04-0.4 ppm.

2. HEALTH EFFECTS

With an intermediate-duration exposure (6 weeks, 5 days a week, 7 hours a day) to 0.3 ppm, all of 4 rats, all of 5 mice, and 4 of 6 rabbits died, while 2 guinea pigs survived (Treon et al. 1955). The exact time of death for individual animals was not specified. Following 30 weeks of exposure (5 days a week, 7 hours a day) to 0.13 ppm HCCPD, 4 of 5 mice died, but all of 4 rats, 2 guinea pigs, and 3 rabbits survived.

Of the species evaluated, guinea pigs appeared to be the most resistant to compound toxicity, especially during intermediate-duration exposures. When the fatalities were plotted by concentration and duration of exposure for each species, it was possible to draw a single straight line to separate the conditions that were uniformly lethal from those that were not lethal for rats, mice, and rabbits (Treon et al. 1955). Thus, rats, mice, and rabbits exhibited a linear dose/duration response to the toxic and fatal effects of HCCPD. With guinea pigs there were two lines that separated the lethal from the nonlethal conditions. The line for durations of 4 hours or more and concentrations of 3 ppm or less had a lower slope than that for durations of 4 hours or less and concentrations of 3 ppm or more. The authors interpreted this to mean that the guinea pigs adapted to the low level, longer-term exposures to HCCPD. In general, mice appear to be more susceptible to HCCPD toxicity than rats (NTP 1994; Treon et al. 1955).

Survival of male and female rats and male mice chronically exposed to 0.01-0.2 ppm HCCPD was similar to that for controls. Survival was diminished in female mice exposed to 0.2 ppm, but not at lower concentrations (NTP 1994). Ovarian inflammation resulting from infection appeared to be the cause of premature deaths in females. The authors suggest that this may be due to an adverse effect of HCCPD on immune function.

The HCCPD available commercially has a minimum purity of 97%. The purity of the material used by Treon et al. (1955) was 89.5%; thus, it is possible that impurities contributed to the toxicity of HCCPD in this study, especially at the high-exposure concentrations. Impurity concentrations in one 97.4% pure sample of HCCPD included 0.15% tetrachloroethylene, 0.5 1% hexachloro- 1,3-butadiene, 1.73% octachlorocyclopentene, and 0.48% hexachloro-3-cyclopentene-l-one (Abdo et al, 1984). A 98% pure sample contained 0.4% hexachlorobutadiene and 1.5% hexachloro-3-cyclopentene-l-one (NTP 1994). Other impurities that have been reported in HCCPD include hexachlorobenzene, PCBs, and mirex (EPA 1991a; HSDB 1998; WHO 1991). For one report (Treon et al. 1955), all exposure concentrations were adjusted to reflect exposure to HCCPD rather than to the mixture. The purity of the material used by Rand

et al. (1982a) was 97.7% and that used by NTP (1994) was 98% pure; the exposure concentrations were not adjusted to account for compound purity.

LC_{50} values and all reliable LOAEL values for lethality in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l. These values indicate that HCCPD is highly toxic to animals when exposures occur through inhalation of vapors.

2.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal, endocrine, or body weight effects in humans after inhalation exposure to HCCPD. Data are available pertaining to respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, dermal, or ocular effects. Data are available for all systems in animal studies. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

Respiratory Effects. The available data on respiratory effects of HCCPD in humans are limited to reports of waste water treatment plant workers and clean-up crew members exposed to HCCPD after an industrial release of this material into the sewage system (Kominsky et al. 1980; Morse et al. 1979).

One report of this incident focused on the employees at the waste water treatment plant who were exposed for a period of 3-15 days (Morse et al. 1979). Accidental discharge of HCCPD into a municipal sewer line at a treatment plant exposed sewage workers (125 males, 68 females; average age of 35 years). Seventyfive percent of the workers noticed unusual odors for up to 4 weeks, but particularly during the last 3 days prior to plant closing. An odiferous substance coated bar screens and grit collectors in the primary treatment area. Airborne concentrations were unknown at time of exposure, but 4 days after the plant closed, concentrations ranged from 0.27 to 0.97 ppm in screen and grit chambers. Although large amounts of contamination were found in waste water, exact amounts of contamination were not specified.

The other report considered the adverse health effects reported by the clean-up crew workers who were exposed during the 2-month clean-up period as well as by the waste water treatment workers (154 males, 23 females) (Kominsky et al. 1980). Sewage system contamination of HCCPD dispersed in fuel oil and mixed with sewage created a sticky conglomerate requiring close worker contact with contaminated sewage

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	1-2 wk 5 d/wk 6 hr/d				0.5 M (3/5 deaths for 1 wk, 10/10 deaths for 2 wk exposure) 0.5 F (2/10 deaths for 2 wk exposure)	Rand et al. 1982a
2	Rat (Sprague-Dawley)	4 hr				1.6 M (LC50) 3.5 F (LC50)	Rand et al. 1982a
3	Rat	2.5-3.6 hr				2.8 (2/4 animals died)	Treon et al. 1955
4	Rat	5 d 7 hr/d				0.9 (4/4 animals died)	Treon et al. 1955
5	Rat	0.25 hr				11.6 (1/4 animals died)	Treon et al. 1955
6	Mouse	5 d 7 hr/d				0.9 (4/5 animals died)	Treon et al. 1955
7	Mouse	0.25 hr				11.6 (1/5 animals died)	Treon et al. 1955
8	Mouse	2.5-3.6 hr				1.25 (1/5 animals died)	Treon et al. 1955
9	Rabbit	0.25 hr				11.6 (2/3 animals died)	Treon et al. 1955
10	Rabbit	2.5-3.6 hr				1.25 (2/3 rabbits died)	Treon et al. 1955

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
11	Rabbit	5 wk 5 d/wk 7 hr/d					0.3	(4/6 rabbits died)	Treon et al. 1955
12	Gn pig	2.5-3.6 hr					6.4	(1/2 animals died)	Treon et al. 1955
13	Gn pig	5 d 7 hr/d					1.4	(1/2 animals died)	Treon et al. 1955
	Systemic								
14	Rat (Sprague-Dawley)	1-2 wk 5 d/wk 6 hr/d	Resp	0.11	0.5	(lung weight increased 13-14%; bronchial and olfactory epithelial changes)			Rand et al. 1982a
			Cardio	0.5					
			Hemato	0.11	0.5	(WBC reduced; red blood cell, packed cell volume, and hemoglobin increased)			
			Hepatic	0.5					
			Renal	0.5					
			Bd Wt	0.11 M 0.5 F	0.5 M	(~10% reduced body weight)			

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL			Reference
					Less serious (ppm)	Serious (ppm)		
15	Rat	2.5-3.6 hr	Resp			1.25	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			1.25	(diffuse degeneration of the heart)	
			Hepatic			1.25	(diffuse degeneration of the liver)	
			Renal			1.25	(diffuse degeneration of the kidney)	
			Endocr			1.25	(diffuse degeneration of the adrenals)	
16	Rat	0.25 hr	Resp			11.6	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			11.6	(diffuse degeneration of the heart)	
			Hepatic			11.6	(diffuse degeneration of the liver)	
			Renal			11.6	(diffuse degeneration of the kidneys)	
			Endocr			11.6	(diffuse degeneration of the adrenals)	
17	Rat	4 hr	Resp			65.9	(respiratory distress, hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			65.9	(diffuse degeneration of the heart)	
			Hepatic			65.9	(diffuse degeneration of the liver)	
			Renal			65.9	(diffuse degeneration of the kidneys)	
			Endocr			65.9	(diffuse degeneration of the adrenals)	

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference
18	Rat	5 d 7 hr/d	Resp			0.3	(increased respiration; hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			0.3	(diffuse degeneration of the heart)	
			Hepatic			0.3	(diffuse degeneration of the liver)	
			Renal			0.3	(diffuse degeneration of the kidneys)	
			Endocr			0.3	(diffuse degeneration of the adrenal glands)	
19	Mouse	0.25 hr	Resp			11.6	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			11.6	(diffuse degeneration of the heart)	
			Hepatic			11.6	(diffuse degeneration of the liver)	
			Renal			11.6	(diffuse degeneration of the kidney)	
			Endocr			11.6	(diffuse degeneration of the adrenals)	
20	Rabbit	2.5-3.6 hr	Resp			1.25	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			1.25	(diffuse degeneration of the heart)	
			Hepatic			1.25	(diffuse degeneration of the liver)	
			Renal			1.25	(diffuse degeneration of the kidneys)	
			Endocr			1.25	(diffuse degeneration of the adrenals)	

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference
21	Rabbit	0.25 hr	Resp			11.6	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			11.6	(diffuse degeneration of the heart)	
			Hepatic			11.6	(diffuse degeneration of the liver)	
			Renal			11.6	(diffuse degeneration of the kidneys)	
			Endocr			11.6	(diffuse degeneration of the adrenals)	
22	Rabbit	7 hr	Resp			1.3	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			1.3	(diffuse degeneration of the heart)	
			Hepatic			1.3	(diffuse degeneration of the liver)	
			Renal			1.3	(diffuse degeneration of the kidneys)	
			Endocr			1.3	(diffuse degeneration of the adrenals)	
23	Gn pig	2.5-3.6 hr	Resp			1.25	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			1.25	(diffuse degeneration of the heart)	
			Hepatic			1.25	(diffuse degeneration of the kidney)	
			Renal			1.25	(diffuse degeneration of the kidneys)	
			Endocr			1.25	(diffuse degeneration of the adrenal glands)	

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference
24	Gn pig	0.25 hr	Resp			11.6	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			11.6	(diffuse degeneration of the heart)	
			Hepatic			11.6	(diffuse degeneration of the liver)	
			Renal			11.6	(diffuse degeneration of the kidneys)	
			Endocr			11.6	(diffuse degeneration of the adrenals)	
25	Gn pig	4 hr	Resp			65.9	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			65.9	(diffuse degeneration of the heart)	
			Hepatic			65.9	(diffuse degeneration of the liver)	
			Renal			65.9	(diffuse degeneration of the kidneys)	
			Endocr			65.9	(diffuse degeneration of the adrenals)	
Neurological								
26	Rat	1-2 wk 5 d/wk 6 hr/d		0.5				Rand et al. 1982a
27	Rat	0.25 hr				11.6	(diffuse degeneration of the brain)	Treon et al. 1955
28	Mouse	7 hr				1.3	(diffuse degeneration of the brain)	Treon et al. 1955

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference
29	Mouse	5 d 7 hr/d				0.3	(diffuse degeneration of the brain)	Treon et al. 1955
30	Mouse	0.25 hr				11.6	(diffuse degeneration of the brain)	Treon et al. 1955
31	Rabbit	0.25 hr				11.6	(diffuse degeneration of the brain)	Treon et al. 1955
32	Gn pig	0.25 hr				11.6	(diffuse degeneration of the brain)	Treon et al. 1955
INTERMEDIATE EXPOSURE								
Death								
33	Rat (Fischer- 344)	2-4 wk 5 d/wk 6 hr/d				1	(10/10 males and 10/10 females died)	NTP 1994
34	Rat	4 wk 5 d/wk 7 hr/d				0.3	(4/4 animals died)	Treon et al. 1955
35	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d				0.04	(20% [2/10] mortality in males, 10% [1/10] mortality in females)	NTP 1994
36	Mouse	30 wk 5 d/wk 7 hr/d				0.13	(4/5 died)	Treon et al. 1955

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
37	Gn pig	4 wk 5 d/wk 7 hr/d					0.3	(5/5 animals died)	Treon et al. 1955
	Systemic								
38	Human	10 wk	Resp	7.1			19.2	(mucous membrane irritation, sinus congestion, dyspnea, chest discomfort in 1 individual)	Kominsky et al. 1980
			Gastro	7.1	19.2	(nausea in 1 individual)			
			Hemato	19.2					
			Hepatic			(elevated values for 4 liver enzymes in some workers)			
			Dermal		0.04	(skin irritation in 4 individuals)			
			Ocular		0.04	(eye irritation in 4 individuals)			
39	Monkey	13 wk 5 d/wk 6 hr/d	Resp	0.2					Rand et al. 1982a
			Cardio	0.2					
			Gastro	0.2					
			Hemato	0.2					
			Hepatic	0.2					
			Renal	0.2					
			Bd Wt	0.2					
40	Monkey	14 wk 5 d/wk 6 hr/d	Resp	0.2					Rand et al. 1982b

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Less serious	LOAEL Serious (ppm)	Reference
41	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Hemato	0.04	0.4	(increased mean and packred cell volume; and red blood cell increased hemoglobin; decreased reticulocytes)		NTP 1994
			Hepatic	0.04	2	(increased aspartate aminotransferase)		
			Renal	0.04	0.4	(decreased urinary creatinine and volume)		
42	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Resp	0.15	0.4	(inflammation and necrosis of the bronchi and bronchioles; increased lung weight in males)		NTP 1994
			Cardio	2				
			Gastro	2				
			Hemato	0.15	0.4	(increased hemoglobin and hematocrit)		
			Musc/skel	2				
			Hepatic	2				
			Renal	2				
			Endocr	2		(absence of effects on adrenal, thyroid parathyroid, and pituitary glands)		
			Bd Wt		0.04	(decreased weight gain - 11%)		

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
43	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d	Resp	0.2					Rand et al. 1982a
			Cardio	0.2					
			Gastro	0.2					
			Hemato		0.01	(increased hemoglobin, red blood cell count, mean corpuscular hemoglobin concentration in males)			
			Hepatic	0.2					
			Renal	0.2					
44	Rat (Sprague-Dawley)	14 wk 5 d/wk 6 hr/d	Resp	0.2[b]					Rand et al. 1982b
45	Rat	30 wk 5 d/wk 7 hr/d	Resp				0.13	(pneumonia)	Treon et al. 1955
			Cardio	0.13					
			Hepatic		0.13	(slight degenerative changes)			
			Renal			(slight degenerative changes)			
			Bd Wt	0.13					

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference
46	Rat	6 wk 5 d/wk 7 hr/d	Resp			0.3	(pulmonary edema and hyperemia)	Treon et al. 1955
			Cardio			0.3	(degenerative changes in the heart)	
			Hepatic			0.3	(degenerative changes in the liver)	
			Renal			0.3	(degenerative changes in the kidneys)	
			Endocr			0.3	(degenerative changes in the adrenal gland)	
47	Mouse (B6C3F1)	33 wk 5 d/wk 6 hr/d	Resp		0.2 M		(pigmentation of the nose, trachea, and lungs)	NTP 1994
			Bd Wt	0.2 M				
48	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d	Resp	0.15	0.4		(metaplasia of larynx or trachea; focal supprative inflammation of the nose)	NTP 1994
			Cardio	0.4				
			Gastro	0.4				
			Hemato	0.4				
			Musc/skel	0.4				
			Hepatic	0.4				
			Renal	0.4				
			Bd Wt	0.04	0.15		(decreased mean final body weight gain in males - 16%)	
49	Mouse (B6C3F1)	26 wk 5 d/wk 6 hr/d	Resp		0.5 M		(pigmentation of the epithelium of the nose, trachea, and lung)	NTP 1994
			Bd Wt	0.5 M				

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
50	Mouse (B6C3F1)	42 wk 5 d/wk 6 hr/d	Resp		0.5 M	(pigmentation of the epithelium of the nose, trachea, and lungs)			NTP 1994
			Bd Wt		0.5 M	(decreased body weight gain during exposure when compared to controls; recovery during the post- exposure period)			
51	Mouse	30 wk 5 d/wk 7 hr/d	Resp				0.13	(pulmonary edema and bronchitis)	Treon et al. 1955
			Hepatic		0.13	(slight degenerative changes)			
			Renal		0.13	(slight degenerative changes)			
			Bd Wt	0.13					
52	Rabbit	6 wk 5 d/wk 7 hr/d	Resp				0.3	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio				0.3	(diffuse degeneration of the heart)	
			Hepatic				0.3	(diffuse degeneration of the liver)	
			Renal				0.3	(diffuse degeneration of the kidneys)	
			Endocr				0.3	(diffuse degeneration of the adrenals)	

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
53	Rabbit	30 wk 5 d/wk 7 hr/d	Resp	0.13					Treon et al. 1955
			Cardio	0.13					
			Hepatic		0.13	(slight degenerative changes)			
			Renal		0.13	(slight degenerative changes)			
			Bd Wt	0.13					
54	Gn pig	6 wk 5 d/wk 7 hr/d	Resp				0.3	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio				0.3	(degenerative changes in the heart)	
			Hepatic				0.3	(degenerative changes in the liver)	
			Renal				0.3	(degenerative changes in the kidneys)	
			Endocr				0.3	(degenerative changes in the adrenals)	
55	Gn pig	30 wk 5 d/wk 7 hr/d	Resp				0.13	(pneumonia)	Treon et al. 1955
			Cardio	0.13					
			Hepatic		0.13	(slight degenerative change)			
			Renal		0.13	(slight degenerative change)			
			Bd Wt	0.13					

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
56	Gn pig	6 wk 5 d/wk 7 hr/d	Resp				0.3	(pulmonary edema and hyperemia)	Treon et al. 1955
			Cardio				0.3	(diffuse degeneration of the heart)	
			Hepatic				0.3	(diffuse degeneration of the liver)	
			Renal				0.3	(diffuse degeneration of the kidneys)	
			Endocr				0.3	(diffuse degeneration of the adrenals)	
	Neurological								
57	Human	10 wk		7.1	19.2	(fatigue in one individual)			Kominsky et al. 1980
58	Monkey	13 wk 5 d/wk 6 hr/d		0.2					Rand et al. 1982a
59	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		0.15	0.4	(listless)			NTP 1994
60	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d		0.2					Rand et al. 1982a
61	Rat	30 wk 5 d/wk 7 hr/d		0.13					Treon et al. 1955

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
62	Rat	6 wk 5 d/wk 7 hr/d					0.3	(degenerative changes in the brain)	Treon et al. 1955
63	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		0.15	0.4	(listless)			NTP 1994
64	Mouse	30 wk 5 d/wk 7 hr/d					0.13	(degenerative changes in the brain)	Treon et al. 1955
65	Rabbit	30 wk 5 d/wk 7 hr/d		0.13					Treon et al. 1955
66	Rabbit	6 wk 5 d/wk 7 hr/d					0.3	(diffuse degenerative changes in the brain)	Treon et al. 1955
67	Gn pig	6 wk 5 d/wk 7 hr/d					0.3	(diffuse degeneration of the brain)	Treon et al. 1955
68	Gn pig	6 wk 5 d/wk 7 hr/d					0.3	(degenerative changes in the brain)	Treon et al. 1955
69	Gn pig	30 wk 5 d/wk 7 hr/d		0.13					Treon et al. 1955

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
CHRONIC EXPOSURE							
Death							
70	Mouse (B6C3F1)	103-104 wk 5 d/wk 6 hr/d				0.2 (death in 57% of females)	NTP 1994
Systemic							
71	Rat (Fischer- 344)	103-104 wk 5 d/wk 6 hr/d	Resp		0.01[c] (pigmentation of mucosa of the nose and lung)		NTP 1994
			Cardio	0.2			
			Gastro	0.2			
			Musc/skel	0.2			
			Hepatic	0.2			
			Renal	0.2			
			Endocr	0.2			
			Bd Wt	0.2			
72	Mouse (B6C3F1)	66 wk 5 d/wk 6 hr/d	Resp		0.2 M (pigmentation of the epithelium of the nose, trachea, and lung)		NTP 1994
			Bd Wt	0.2 M			
73	Mouse (B6C3F1)	103-104 wk 5 d/wk 6 hr/d	Resp		0.01 (pigmentation of mucosa of nose and trachea)		NTP 1994
			Cardio	0.2			
			Gastro	0.2			
			Musc/skel	0.2			
			Hepatic	0.2			
			Renal	0.2			
			Endocr	0.2			
			Bd Wt	0.2			

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	Neurological						
74	Mouse (B6C3F1)	103-104 wk 5 d/wk 6 hr/d		0.2			NTP 1994
	Reproductive						
75	Mouse (B6C3F1)	103-104 wk 5 d/wk 6 hr/d		0.01	0.05	(supprative inflammation of the ovaries)	NTP 1994

[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.01 ppm based on a $NOAEL_{HEC}$ of 0.39 ppm; concentration divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration inhalation MRL of 0.02 ppb (0.0002 ppm) based on a $LOAEL_{HEC}$ of 0.02 ppm; concentration divided by an uncertainty factor of 90 (3 for a minimally adverse LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

Cardio = cardiovascular; d = day(s); F = female; Gastro = gastrointestinal; Gn Pig = guinea pig; HEC = human equivalency concentration; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; WBC = white blood cells; wk = week(s)

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

Acute (≤14 days)

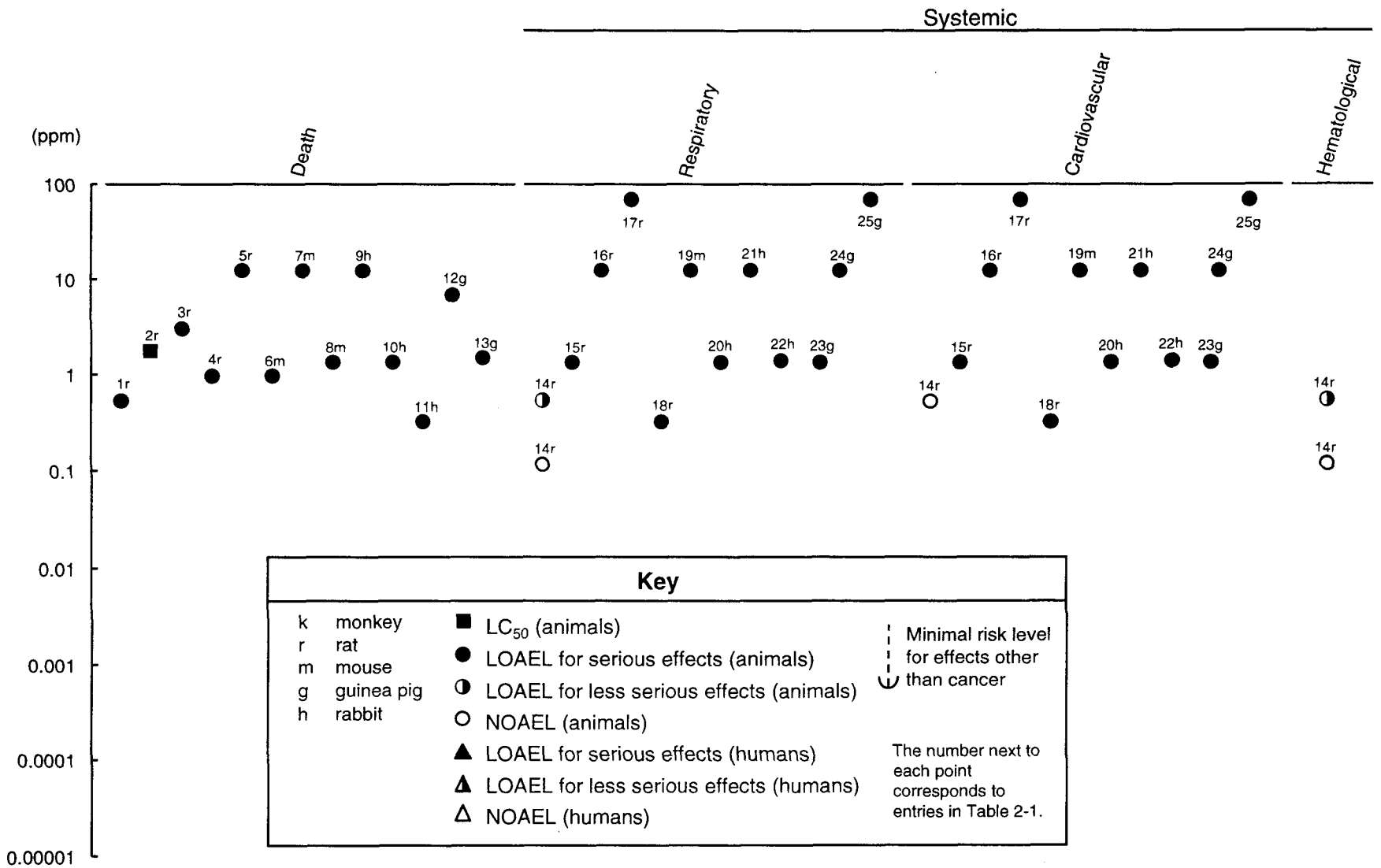


Figure 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (cont.)

Acute (≤14 days)

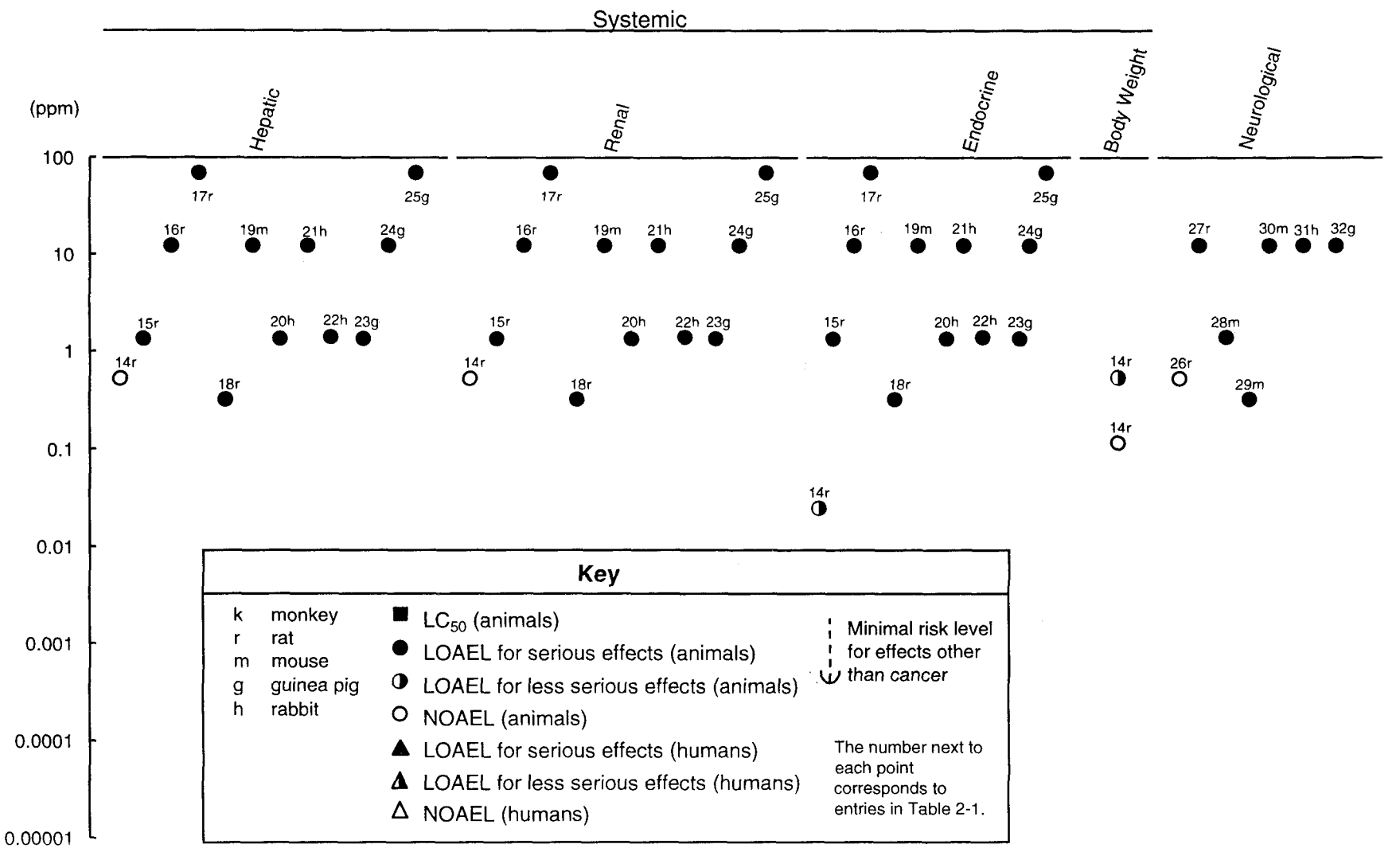


Figure 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (cont.)

Intermediate (15-364 days)

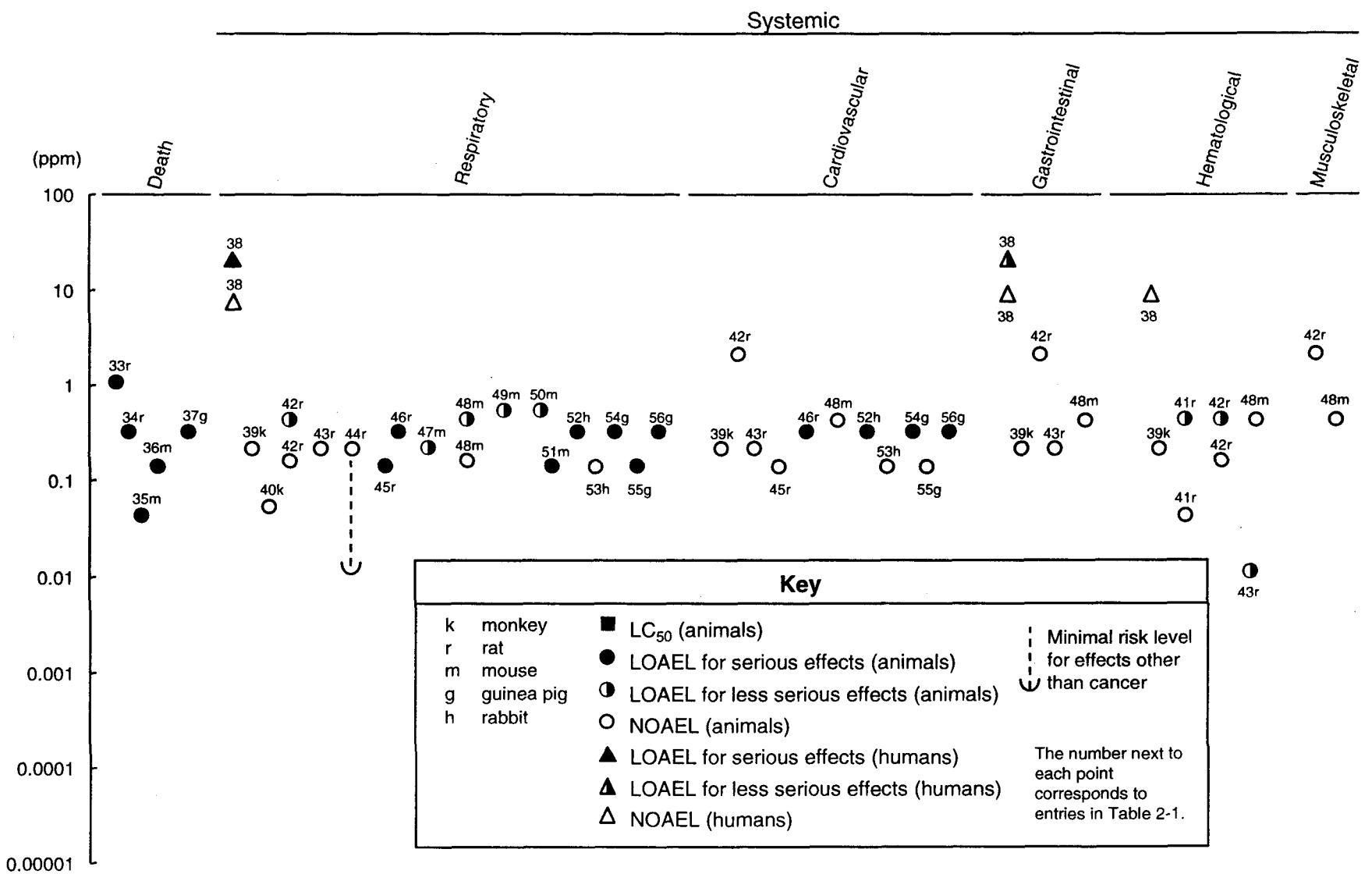


Figure 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (cont.)

Intermediate (15-364 days)

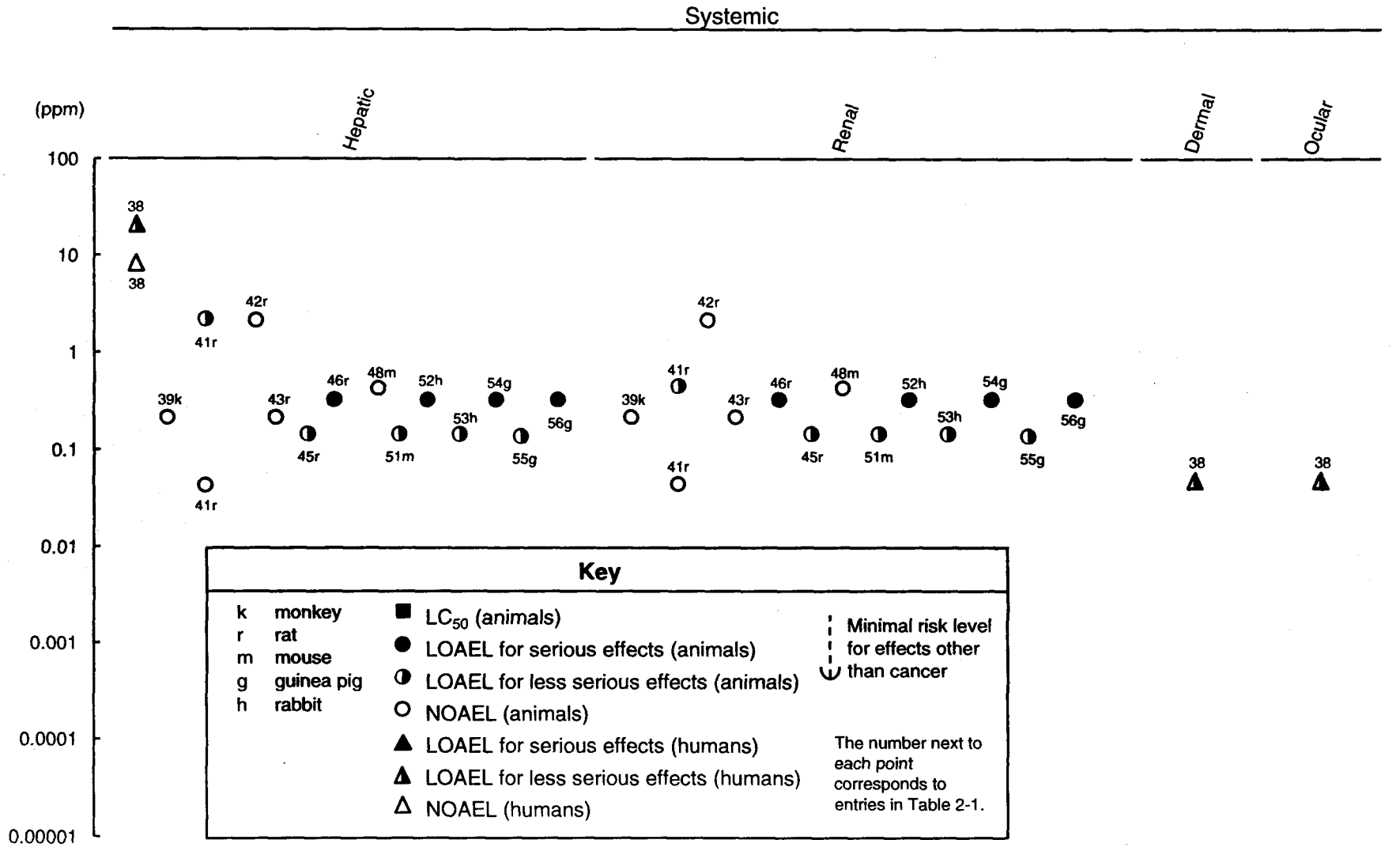


Figure 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (cont.)

Intermediate (15-364 days)

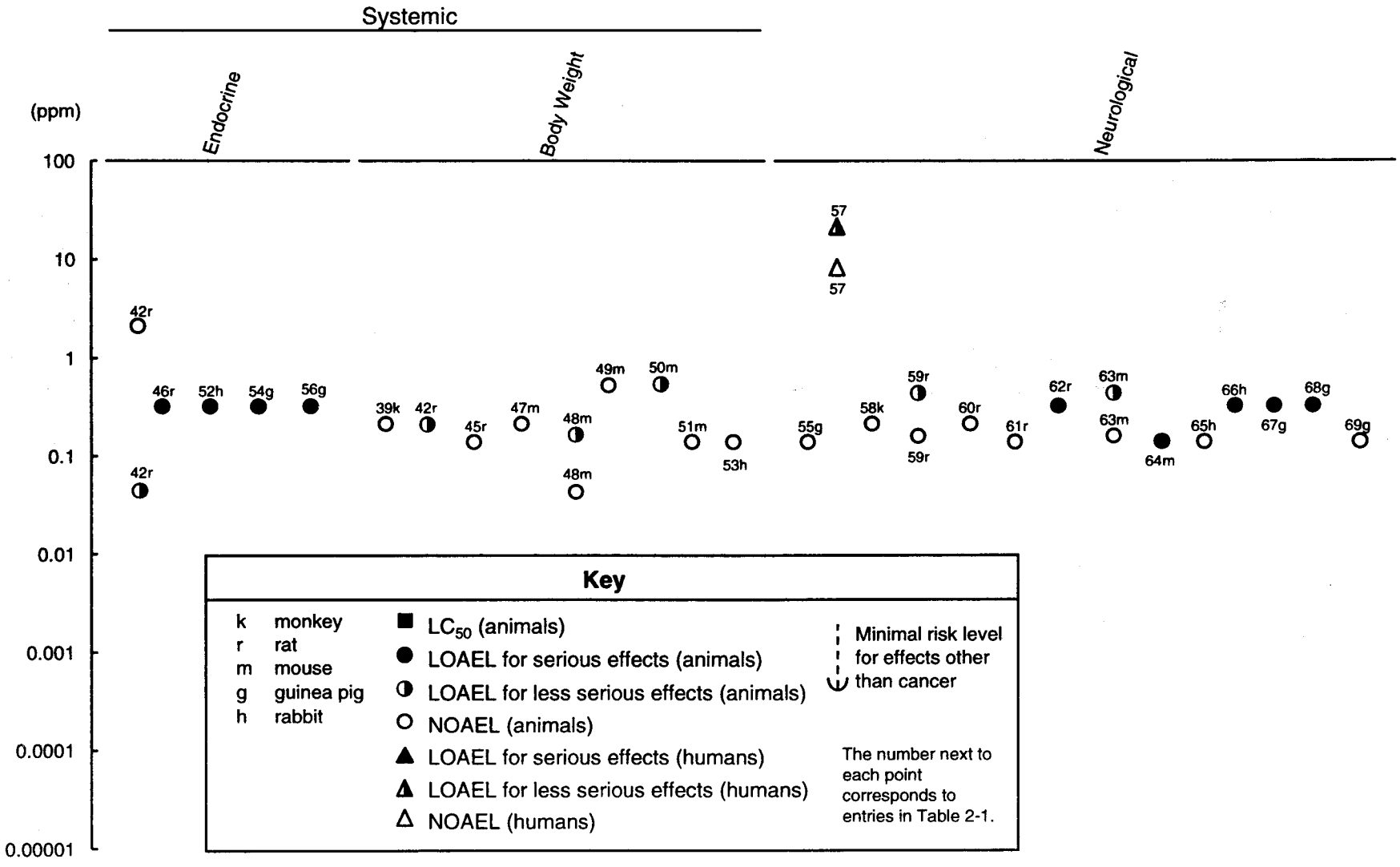
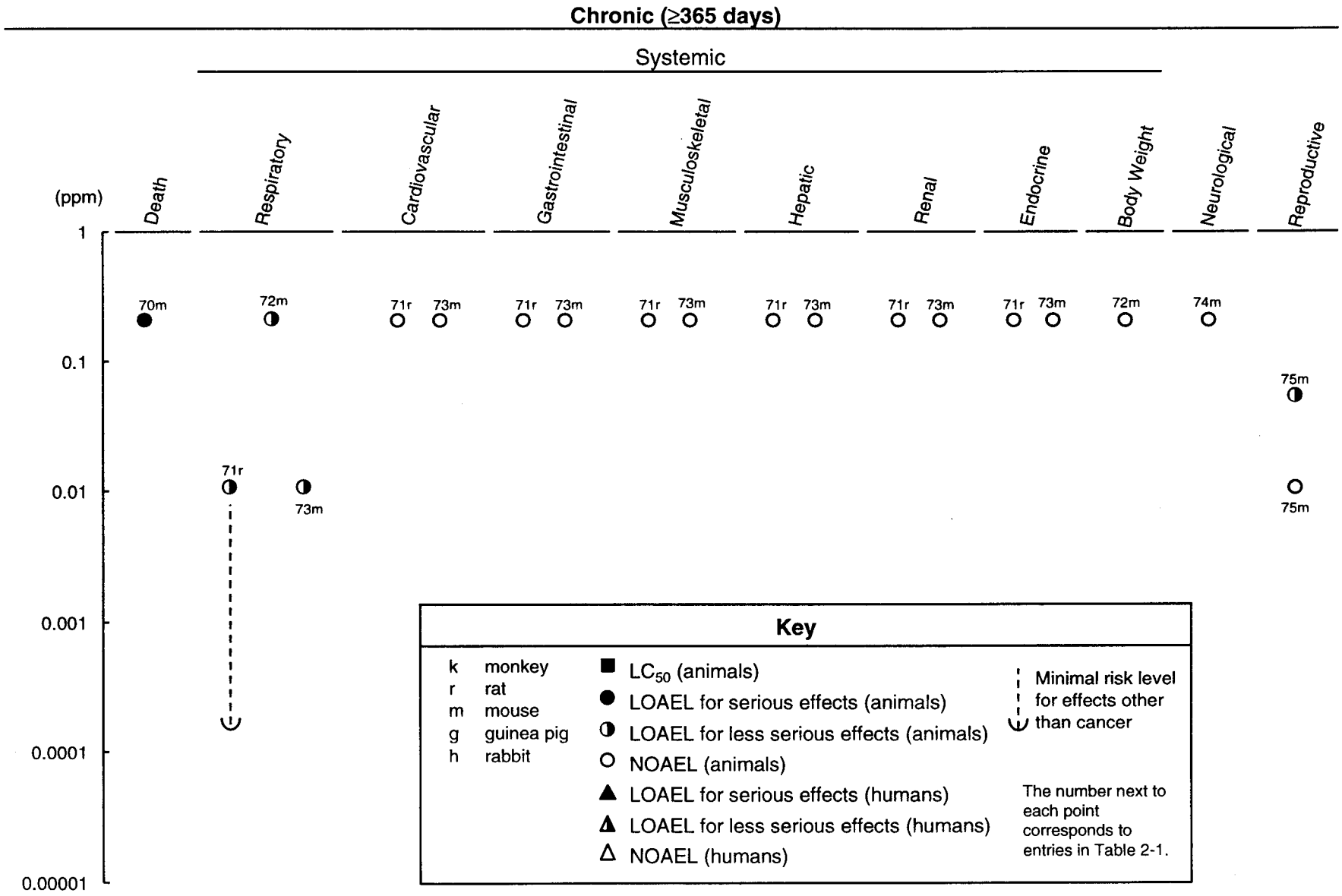


Figure 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (cont.)



during scraping, shoveling, and high pressure water cleaning operations in Louisville, Kentucky (Kominsky et al. 1980). Epidemiological evidence suggests that material entered as early as March 14, 1977, when there were concurrent above-background level increases in detection of an objectionable odor and in symptoms. On March 26, 1977, four employees used steam to attempt to remove an odiferous, highly viscous and sticky substance from the bar screens and gut collection systems. Although airborne concentration at the time of exposure was unknown, HCCPD concentrations in screen and grid chambers ranged from 0.270 to 0.97 ppm on April 2, 1977 (4 days after plant closing). This initial attempt at removal produced a blue haze, which permeated the primary treatment area and caused about 20 workers to seek medical attention. On the next day, following a heavy rain, operating personnel observed a blue haze hovering over grit collection channels and noted an objectionable odor throughout the primary treatment area. The plant was closed on March 29, 1977 (15 days after an odor had been first noticed), when analysis showed waste water to be contaminated with HCCPD at an unspecified level. Workers' symptoms were determined by physical examination, blood and urine analyses, and by a review of medical records for employees seen by the plant physician from about April 15 to May 15, 1977; one questionnaire was administered to 145 employees on April 1-2, 1977, by the Center for Disease Control (CDC), and a second questionnaire was administered to 177 employees by the National Institute for Occupational Safety and Health (NIOSH).

Maximum atmospheric concentrations for the treatment plant workers were unknown, but were most likely greater than 0.97 ppm. This was the maximum concentration measured 4 days after compound identification (Morse et al. 1979). Small amounts of octachlorocyclopentene and other chlorinated cyclohydrocarbons were also contaminants of the waste water. Cleanup crew members were equipped with personal protective equipment and had minimum or no direct exposure to HCCPD. The maximum concentration recorded during cleanup was 19.2 ppm. Two cleanup crew members were exposed to the HCCPD for at least one brief period without protective gear. Seven other workers were exposed for brief periods with half-face respirators (Kominsky et al. 1980).

Symptoms of tracheobronchial irritation were reported by the treatment plant workers early in the exposure paradigm. These symptoms were recounted by 39 of 145 employees who responded to a questionnaire shortly after the exposure incident and in 16 or 177 employees who responded to a follow-up questionnaire 6 weeks later. Chest X-rays of 28 exposed workers were normal. Tests of pulmonary function were normal in a subset of 22 workers from this group (Kominsky et al. 1980). The date of testing was not specified. Minor respiratory complaints included sore throats, coughs, chest discomfort, and difficulty in

breathing. Because all the workers knew that exposure to a noxious substance had occurred, it is possible that some symptoms were psychosomatic. One cleanup crew worker also reported respiratory difficulty when exposed for a few seconds to 19.2 ppm HCCPD without protective equipment (Kominsky et al. 1980). Chest discomfort persisted for several days in this individual.

Headaches were reported by 45% of 145 individuals after exposure to HCCPD at a waste water treatment plant for 3-15 days. Six weeks later, 18% of 177 questionnaire respondents were still experiencing headaches (Morse et al. 1979). These headaches may have been secondary to sinus irritation and congestion.

Animals exposed to HCCPD vapors exhibited labored breathing and gasping during acute (≤ 1 hour) exposures at concentrations greater than 41.6 ppm (Treon et al. 1955). All animals exposed to these concentrations of HCCPD died as a result of the exposure. Lung tissues, when examined, displayed inflammation, hemorrhagic lesions, edema, and necrosis of the bronchi. In some cases the walls of the alveoli became coated with a hyaline or fibroid membrane. Where lung injury was severe, there was a proliferation of fibrous tissue into the bronchi and alveoli (Treon et al. 1955). Hyperemia and edema of the lungs were seen in all the rats, mice, rabbits, and guinea pigs acutely exposed to HCCPD at concentrations of 0.3-66 ppm. These effects were more severe in those animals that died from exposure than those that did not.

Exposures to 0.5 ppm (6 hours a day, 5 days a week) for l-2 weeks resulted in inflammation, hyperplasia, and epithelial erosion in the lungs, but recovery was apparent 2 weeks after exposure ceased in those animals that survived treatment (Rand et al. 1982a). Similar lesions were present in the lungs, bronchi, larynx, and nasal passages of rats and mice exposed to 1 and 2 ppm HCCPD for < l-5 weeks (their survival time) (NTP 1994). During exposure, the rats displayed respiratory distress with mouth breathing and increased respiratory rate. Some rats, particularly males, had lesions of the lungs with 13-week exposures to 0.4 ppm HCCPD. Absolute and relative lung weights were increased in females and significantly increased in males. Squamous metaplasia of the larynx and trachea was found in mice exposed to concentrations of 0.15 and 0.4 ppm (NTP 1994). Lesions were not present in the lungs of rats exposed to 0.15 ppm HCCPD or mice exposed to 0.4 ppm. Exposure to a concentration of 0.13 ppm for 30 weeks (6 hours a day, 5 days a week) caused pulmonary edema in mice and was associated with pneumonia in some rats and guinea pigs (Treon et al. 1955). Comparable effects were not seen in rabbits (Treon et al. 1955).

2. HEALTH EFFECTS

Pulmonary function tests performed on 6 monkeys after 7 and 13 weeks of exposure to concentrations of 0.01-0.2 ppm HCCPD showed all parameters remained within the normal range (Rand et al. 1982a). However, monkeys are more resistant to pulmonary irritants than rats (Rand et al. 1982b), most likely due to the differences in airway diameters; therefore, the lack of an HCCPD effect on lung function in this species is not surprising.

Even under exposure conditions where no overt lung damage was apparent (Rand et al. 1982a), changes were present in rat Clara cells when they were examined by electron microscopy (Rand et al. 1982b). Exposure to 0.01-0.2 ppm HCCPD for 14 weeks (6 hours a day, 5 days a week) caused a significant doserelated incidence of rod-shaped, electron-lucent inclusions in the Clara cells. One monkey exposed to 0.2 ppm displayed comparable cell inclusions under parallel exposure conditions (Rand et al. 1982b). There is no evidence that these minor changes in cell structure may have caused impaired oxygen transport across the lung epithelium (see Section 2.2.1.2).

Chronic exposure of rats and mice to 0.01-0.2 ppm HCCPD for 2 years (6 hours/day, 5 days/week) caused the accumulation of a granular yellow-brown pigment in the lung, nasal, and tracheal epithelium (NTP 1994). The pigmentation appeared in the noses of 80% of the male and female rats exposed to 0.01 ppm for 15 months and 80% of those exposed for 2 years. The severity and incidence of the lesions increased with dose. Pigmentation of the lungs was present in 98-100% of the male and female rats exposed to 0.2 ppm for 2 years. The lungs of no male rats were affected at the 0.01 ppm concentration and only 2 of 50 were affected at the 0.05 ppm concentration. However, 50% of the female rats had pigmentation of the lungs with exposure to 0.01 ppm, and 86% with exposure to 0.05 ppm. The situation was very similar in mice. A concentration of 0.01 ppm caused nasal pigmentation in 80% or more of the animals and exposure to 0.2 ppm caused lung pigmentation in a higher percentage of the animals.

In order to examine the progression and permanence of pigmentation, NTP (1994) conducted stop exposure studies in male mice. These studies were designed to measure the relative effects of dose and duration on the pigment formation. In these studies, a concentration of 0.2 ppm (6 hours/day, 5 days/week) was used for 26 or 42 weeks. The animals were allowed to complete their lifespan without additional exposures. Pigmentation of the respiratory tract (nose, trachea, and/or lungs) was seen in all animals and did not disappear when exposure ceased. A comparison of the data for different durations and different exposure

concentrations showed that both concentration and duration of exposure had an effect on the amount of pigmentation.

The human and animal data indicate that the linings of the respiratory passages and the lungs are very susceptible to damage from low concentrations of HCCPD following inhalation exposure. The irritating effects of HCCPD on the lungs and nasal passages were evidenced by mouth breathing and shallow, labored respiration. Inflammation of the tissues was followed by necrosis, exfoliation, and hemorrhage. Tissue repair was often fibrous in appearance. Long-term exposure to very low levels of HCCPD (0.01 ppm, 6 hours/day, 5 days/week) produced granular yellow-brown pigmentation of the epithelium of the nose, trachea, larynx, and lungs. In animals, the inflammation of the trachea and lungs did not appear to occur unless the product of the concentration and duration was greater than 20 or 21 ppm-weeks (NTP 1994).

Cardiovascular Effects. Elevated lactic dehydrogenase (LDH) levels were detected in blood samples from 11 of 41 workers examined after a 3-15-day exposure to HCCPD at a waste water treatment plant, but not in blood samples evaluated 3 weeks later (Morse et al. 1979). LDH values were elevated in only one of 97 members of the cleanup crew, but aspartate amino-transferase (AST) values were elevated in 12 cleanup crew members and seemed to be related to the HCCPD exposure (Kominsky et al. 1980). Elevated LDH and AST values can be indicative of damage to the heart muscle as well as the liver. Therefore, without some evidence of impaired cardiac function, it is not possible to conclude that there was damage to the heart based on enzyme levels alone.

In animals acutely exposed to HCCPD (0.3-66 ppm) for varying periods of time (15 minutes to 2 weeks of intermittent exposure), diffuse degenerative changes were noted in the heart (Treon et al. 1955). These degenerative changes may have been the result of autolysis in deceased animals. In another study, there were no effects on rat heart weights or tissue histopathology with exposures to 0.022-0.5 ppm (6 hours a day, 5 days a week) after either 1 or 2 weeks, and there were no changes in the levels of serum AST (Rand et al. 1982a).

Intermediate-duration (13-week) exposure of female rats and mice of both sexes to 0.01-0.4 ppm HCCPD had no effect on heart tissues, heart weight, or serum LDH and AST values (NTP 1994; Rand et al. 1982a). Relative heart weights were increased in male rats with exposure to 0.4 ppm but not with the

lower concentrations tested. Diffuse degenerative changes in the heart were seen in rats, mice, guinea pigs, and rabbits exposed to 0.3 ppm HCCPD for 6 weeks or 0.13 ppm for 30 weeks (Treon et al. 1955).

There were no effects on the histopathology of the heart tissues of rats or mice in the NTP (1994) bioassay for HCCPD where doses of 0.01-0.2 ppm were evaluated. Thus, there is no clear evidence that HCCPD has an adverse effect on the cardiovascular system with any duration of exposure or dose level.

Gastrointestinal Effects. Waste water treatment plant workers exposed to HCCPD for 3-15 days due to a large industrial release complained of nausea (22%) and abdominal cramps (Kominsky et al. 1980; Morse et al. 1979). One member of the cleanup crew who was exposed to 19.2 ppm for several seconds without protective equipment experienced nausea several minutes after the exposure (Kominsky et al. 1980).

No microscopic changes were seen in the stomach, esophagus, or intestines of rats, mice, or monkeys exposed to 0.01-0.4 ppm HCCPD for 13 weeks (6 hours a day, 5 days a week) (NTP 1994; Rand et al. 1982a), or in chronic-duration studies of rats and mice using exposure concentrations of 0.01-0.2 ppm (NTP 1994). The gastrointestinal tract is apparently not vulnerable to damage from exposure to HCCPD inhaled vapors.

Hematological Effects. No changes in blood counts were observed in workers exposed to HCCPD at a waste water treatment plant after an industrial discharge of the material into the sewage system (Kominsky et al. 1980).

Significant increases in hemoglobin, red blood cell count, and packed cell volume resulted from acuteduration exposures of rats to 0.5 ppm HCCPD for one or 2 weeks (Rand et al. 1982a). Intermediate-duration (13-week) exposure of males to 0.01 ppm and 0.2 ppm and exposure of females to 0.05 and 0.2 ppm HCCPD resulted in increased hemoglobin and hematocrit values (Rand et al. 1982a). These minor variances in hematological parameters were believed to be a consequence of hemorrhagic lesions in the lungs and not a direct influence of HCCPD on hematopoiesis or red cell turnover.

In rats exposed to 0.4 ppm HCCPD, 6 hours/day, 5 days/week for 13 weeks, there was also a statistically significant increase in packed cell volume, hemoglobin, and erythrocytes, but these values were not increased in all groups of animals evaluated (NTP 1994). Absolute and relative lung weights showed a

statistically significant increase in males, but not females, and lung effects were more severe in males than in females. Thus, it may be that the hematological effects in males reflect a compensatory response to lung damage as was suggested by Rand et al. (1982a), even though NTP scientists judged that the effects were not compound-related. Mean cell hemoglobin concentration was the only hematological parameter affected in male and female mice (NTP 1994).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to HCCPD.

There were no observed effects in mice or rats on bone or bone marrow histopathology with either 13-week or 2-year studies (NTP 1994). The intermediate-duration studies used doses of 0.04-0.4 ppm HCCPD and the chronic-duration studies used doses of 0.01-0.2 ppm.

Hepatic Effects. Elevated LDH levels were detected in blood samples from 11 of 41 workers examined shortly after exposure to HCCPD at a waste water treatment plant, but not in blood samples evaluated 3 weeks later (Morse et al. 1979). Exposure occurred over a 3-15-day period as a result of an industrial discharge of HCCPD. LDH values were elevated in only one of 97 members of the cleanup crew, but AST values were elevated in 12; alkaline phosphatase (AP) in 5; and bilirubin in one (Kominsky et al. 1980). For eight of the cleanup crew members, these biochemical parameters were abnormal on more than one occasion and, in some cases, were temporarily related to exposure conditions.

Relative to a group of 35 controls, 73 male operators employed for an average of 8.2 years (range 0.5-23 years) in a plant producing chlorinated hydrocarbons, including HCCPD, showed no evidence of hepatotoxicity (Boogaard et al. 1993). The tests included measurement of alanine and aspartate aminotransferases, alkaline phosphatase, total bilirubin, γ-glutamyltranspeptidase, lactate dehydrogenase, and total bile acids.

In animals, mild to moderate hepatic tissue degeneration was a common manifestation of acute-duration inhalation exposures to 0.3-66 ppm for 15 minutes to 2 weeks, and to intermediate-duration exposures to 0.3 ppm for 6 weeks, and 0.13 ppm for 30 weeks. Hepatic damage was more pronounced in the animals that died than in those that survived and, thus, may have been, at least partially, the result of autolysis (Treon et al. 1955).

2. HEALTH EFFECTS

Liver weights of rats were significantly reduced (8-9%) in females receiving doses of 0.11 and 0.5 ppm HCCPD for 1 or 2 weeks and 3-E% in males receiving doses of 0.01-0.2 ppm, 6 hours/day, 5 days/week for 13 weeks (Rand et al. 1982a). On the other hand, biochemical parameters, LDH, AST, AP, and ALT levels were not influenced by inhalation exposure to 0.01-0.5 ppm HCCPD for 1-13 weeks (Rand et al. 1982a). There were no changes in liver weights or tissue histopathology with intermediate-duration exposure of rats or mice to concentrations of 0.04-0.4 ppm HCCPD or chronic-duration exposures to 0.01-0.2 ppm (NTP 1994). The 13-week intermediate-duration exposure also had no dose-related effects on liver enzymes (ALT, AST, and LDH). These data suggest that HCCPD has some minimal effects on the liver enzymes in rats and mice at low concentrations and may cause necrotic lesions at high concentrations.

Renal Effects. Urine samples were collected from 41 workers exposed for 3-15 days to HCCPD at a waste water treatment plant as the result of an industrial release of this material into the sewage system (Morse et al. 1979). Proteinuria was identified in 6 of 41 workers immediately after exposure but not 3 weeks later. Urinalysis parameters were normal in the cleanup crew workers (Kominsky et al. 1980).

Relative to a group of 35 controls, 73 male operators employed for an average of 8.2 years (range 0.5-23 years) in a plant producing chlorinated hydrocarbons, including HCCPD, showed no evidence of damage to the renal tubules (Boogaard et al. 1993). The tests included measurement of urinary alanine aminopeptidase, N-acetyl-β-D-glucosaminidase, and retinol binding protein. Although total urinary protein concentrations did not differ between the two groups, urinary albumin was significantly higher in the exposed group. The difference, however, was not related to time of employment, and there was no difference in urinary albumin concentration in workers involved in the manufacture of HCCPD and those involved in the preparation of other chlorinated hydrocarbon. Thus, the effect was not considered to be due to the damage to the glomerulus caused by exposure to HCCPD.

Inhalation exposure of HCCPD caused renal tubular necrosis in rats, mice, guinea pigs, and rabbits with acute-duration exposure to concentrations of 0.3-66 ppm for 15 minutes to 2 weeks (7 hours/day, 5 days/week) and to intermediate-duration exposure to 0.3 ppm for 6 weeks and 0.13 ppm for 30 weeks, also for 7 hours/day, 5 days/week (Treon et al. 1955). No tissue damage was seen in rats exposed to 0.01-0.5 ppm for up to 13 weeks, although there was a slight reduction (10-l 1%) in average kidney weights in males and females receiving 0.5 ppm for 2 weeks and in males receiving 0.01-0.5 ppm for up to 13 weeks (Rand et al. 1982a).

2. HEALTH EFFECTS

Exposure of male rats to 0.01-0.2 ppm and female rats to 0.05-0.2 ppm for 15 months was associated with an increase in urine specific gravity (NTP 1994). The urine volume was reduced in the females exposed to 0.2 ppm. In companion studies of mice, the specific gravity was increased in the males with the 0.05 and 0.2 ppm exposures and the volume was increased in females exposed to the 0.2 ppm concentration. These findings suggest some deficit in renal function, but there were no observable changes in the tissues to suggest kidney damage, and no changes in kidney weights. Although the data are not completely consistent, HCCPD may affect the kidney, especially with acute, high-concentration exposures or more moderate long-term exposures.

Endocrine Effects. No reports of changes in human endocrine parameters or organs after inhalation exposure to HCCPD were found.

There were degenerative changes in the adrenal glands of rats, mice, guinea pigs, and rabbits after acuteduration exposures to concentrations of 0.3-66 ppm for periods of 15 minutes to 2 weeks. Similar changes occurred with intermediate-duration exposures to 0.3 ppm for 6 weeks, and 0.13 ppm for 30 weeks (Treon et al. 1955). These changes may have been the result of tissue autolysis in moribund animals.

The weights of the adrenal glands were significantly reduced in rats exposed to 0.5 ppm for 5-10 days (Rand et al. 1982a). The significance of the observation cannot be assessed quantitatively in the absence of measurements of hormone products. There were no histopathological changes in the adrenal glands of rats or mice with 13-week exposures to 0.04-0.4 ppm for 2 years (NTP 1994).

Dermal Effects. Skin irritation was one of the symptoms reported by plant workers (21%) and cleanup crew members exposed to HCCPD (>0.97 ppm) at a waste water treatment plant as a result of an industrial release of HCCPD into the sewage system (Kominsky et al. 1980; Morse et al. 1979).

Skin irritation in humans and animals are more likely a consequence of the direct action of HCCPD vapors on the skin rather than a systemic effect due to exposure to HCCPD through the lungs, and is discussed further in Section 2.2.3.

2. HEALTH EFFECTS

Body Weight Effects. No reports of weight loss in humans after inhalation exposure to HCCPD were found.

Rats exposed to 0.22 ppm HCCPD for 10 days did not gain weight at the same rate as the controls; at an exposure concentration of 0.5 ppm, the animals lost weight (Rand et al. 1982a). Once exposure ceased, the weight gain returned to normal, although the treated animals weighed less than the controls. Weight gains were decreased approximately 10% in male rats exposed to 0.04 ppm and greater, 16% in male mice exposed to 0.15 ppm, and 28% in male mice exposed to 0.4 ppm for 13 weeks, but not in females at any dose tested (NTP 1994).

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to HCCPD.

Rats exposed to 0.22 ppm HCCPD for 10 days ate less food than control animals (Rand et al. 1982a).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after inhalation exposure to HCCPD.

There were no histopathological changes in the spleens, thymus, or lymph nodes of rats or mice exposed to 0.04-0.4 ppm HCCPD for 13 weeks (NTP 1994; Rand et al. 1982a) or to 0.01-0.2 ppm for 2 years (NTP 1994). No studies were located that evaluated a broad range of immunological parameters; therefore, a reliable NOAEL cannot be identified for this end point.

2.2.1.4 Neurological Effects

Headaches were reported by 45% of 145 individuals after exposure to HCCPD at a waste water treatment plant for 3-15 days. Six weeks later, 18% of 177 questionnaire respondents were still experiencing headaches (Morse et al. 1979).

Some rats, mice, guinea pigs, and rabbits exposed to high concentrations of HCCPD (>41.6 ppm) by acute-duration inhalation experienced tremors (Treon et al. 1955). Rats and mice exposed to concentrations of 0.4-2 ppm HCCPD were described as listless after l-3 weeks of exposure for 6

hours/day, 5 days/week (NTP 1994). The higher the HCCPD concentration, the sooner the listlessness was noted.

The brain tissues of all rats, mice, guinea pigs, and rabbits that died due to HCCPD exposure showed diffuse degenerative changes with both acute- and intermediate-duration exposures (Treon et al. 1955). These changes may have been the result of tissue autolysis. There were no histopathological changes in the brains of rats at a dose of 0.5 ppm for l-2 weeks or in the brains of rats, mice, and monkeys at doses of 0.04-0.4 ppm for 13 weeks (NTP 1994; Rand et al, 1982a). No other indications of effects on the nervous system were noted.

The highest NOAEL values and all LOAEL values from each reliable study of neurological effects for each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1. Although the data are minimal, HCCPD vapors do appear to cause headaches in humans and some symptoms associated with impaired function of the nervous system in animals were evident.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to HCCPD.

In animals, there were no treatment-related histopathological lesions of the male reproductive organs (testes, prostate, seminal vesicle) or of the female reproductive organs (ovaries, uterus) in rats, mice, or monkeys exposed to vapors of HCCPD *at* concentrations up to 0.4 ppm for 13 weeks (NTP 1994; Rand et al. 1982a). However, lifetime exposure of female mice to 0.05 or 0.2 ppm resulted in inflammation and infection of the ovaries (NTP 1994). These infections were hypothesized to have shortened the lifespan of the afflicted animals. NTP (1994) suggested that the infections were caused by *Klebsiella* because this species has caused similar problems in mice during other NTP studies. It is not possible to identify a NOAEL for this end point or to reach any conclusions regarding the potential for HCCPD to cause reproductive effects, because studies evaluating a broad range of reproductive parameters related to reproductive function and success have not been conducted.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to HCCPD.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after inhalation exposure to HCCPD.

Male or female mice exposed to 0.01-0.2 ppm HCCPD for 13 weeks did not have an increase in reticulocyte micronuclei (NTP 1994). This indicates that HCCPD does not act as a clastogen causing chromosome breaks. Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer in humans after inhalation exposure to HCCPD.
There were no statistically significant increases in tumor incidence in rats or mice exposed to atmospheric concentrations of 0.01-0.2 ppm HCCPD for 6 hours/day, 5 days/week for 2 years (NTP 1994). The incidence of alveolar/bronchiolar carcinomas was significantly increased in male mice exposed to 0.5 ppm HCCPD for 26 or 42 weeks, but was within the historical range for the laboratory and, thus, was not definitely compound-related. There was a slight increase in the incidence of adenomas of the pituitary pars distalis in male rats and in thyroid follicle cell adenomas in female mice, but NTP did not consider these tumors to be related to HCCPD administration. On the basis of these data, the U.S. Department of Health and Human Services (DHHS) has determined that HCCPD is not a carcinogen in either male or female rats or mice (NTP 1994).

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding lethality in humans after oral exposure to HCCPD.

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HCCPD is moderately toxic to animals by the oral route of exposure. The LD_{50} (lethal dose, 50% kill) was 471 mg/kg administered in 5% peanut oil in a gavage study in male rats (Treon et al. 1955) and 584 mg/kg (in corn oil) for a group of male and female rats (IRDC 1972). There was a dose-response trend for the number of deaths per group with doses ranging from 261 to 1,344 mg/kg in male rats (Treon et al. 1955). The full dose range was not evaluated in the females. A dose of 877 mg/kg was lethal to over 90% of the males and females tested. The material tested was 93.3% pure; therefore, impurities could have contributed to the toxicity observed in this study, especially at the high exposure concentrations. Impurity concentrations in one 97.4% pure sample of HCCPD included 0.15% tetrachloroethylene, 0.5 1% hexachloro-1,3-butadiene, 1.73% octachlorocyclopentene, and 0.48% hexachloro-3-cyclopentene- l-one (Abdo et al. 1984). A 98% pure sample contained 0.4% hexachlorobutadiene and 1.5% hexachloro-3-cyclopentene-l-one (NTP 1994). Other impurities that have been reported in HCCPD include hexachlorobenzene, PCBs, and mirex (EPA 199la; HSDB 1998; WHO 1991). All exposure concentrations were adjusted to reflect exposure to HCCPD rather than the mixture for the Treon et al. 1955) results.

With repeated administration of HCCPD (purity 97.4% in corn oil) to rats, doses of 150 mg/kg/day caused mortality in 7 of 10 males and 5 of 10 females (Abdo et al. 1984). A low number of animal deaths (l-3) occurred in all lower dose groups including controls, but the increase in mortality was not dose-related.

Data on species other than the rat are more limited. A dose of 877 mg/kg administered in 5% peanut oil killed all of 3 exposed rabbits while a dose of 579 mg/kg killed only 1 and all survived a dose of 392 mg/kg (Treon et al. 1955). On the other hand, several rabbits (exact number not identified) did not survive 13 days of treatment (during pregnancy) with 75 mg!kg/day HCCPD in cottonseed oil (Murray et al. 1980). With intermediate-duration exposure, mice appeared to be less sensitive to HCCPD in corn oil than rats (Abdo et al. 1984). There were no deaths with 13-week exposures to 150 mg/kg/day, but all males and 3 females died during the first 2 weeks of exposure to doses of 300 mg/kg/day. On the other hand, in rats, 7 males and 5 females died with exposure to 150 mg!kg/day and 3 males and 3 females with exposure to 75 mg/kg/day. This is the reverse of the situation observed after inhalation exposure where mice were more sensitive than rats (Abdo et *al.* 1984). NTP (1994) hypothesized that the sensitivity of mice to inhalation exposure was the result of HCCPD-induced inflammation of the breathing passages and the narrower diameter of the air passages in mice.

2. HEALTH EFFECTS

An LD_{50} value and all reliable LOAEL values for lethality in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. Rats appear to be more sensitive to HCCPD than mice and rabbits, and males more sensitive than females via the oral route.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, or other systemic effects in humans or hematological musculoskeletal, dermal, or ocular effects in animals after oral exposure to HCCPD. Respiratory, cardiovascular, gastrointestinal, hepatic, renal, endocrine and body weight effects were observed in animals and are discussed below. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. Single doses of 261-1,959 mg/kg administered in 5% peanut oil caused labored breathing in rats and rabbits (Treon et al. 1955). Upon death or sacrifice, the lung tissues were hyperemic and edematous in animals given doses of 261 mg/kg/day or greater. Evidence of extensive hemorrhage of the lungs was reported in rats that received a single non-lethal dose of HCCPD (exact dose not specified; 96% pure) when the animals were sacrificed 21 days after dosing (Lawrence and Dorough 1982). On the other hand, there were no gross or histopathological changes in the lungs of rats exposed to doses of 75 and 150 mg/kg/day or in mice exposed to 150 and 300 mg/kg/day in corn oil for 13 weeks (Abdo et al. 1984). These differences in results may be due to gavage procedures. Lung damage may be more severe when inhalation of volatilized HCCPD occurs during dosing.

Cardiovascular Effects. Single doses of 261-1,959 mg/kg administered in 5% peanut oil caused degenerative changes in the hearts of rats and rabbits (Treon et al. 1955) but there were no gross or histopathological changes in the hearts of rats exposed to doses of 75 and 150 mg/kg/day or mice exposed to 150 and 300 mg/kg/day in corn oil for 13 weeks (Abdo et al. 1984). The changes seen in the study by Treon et al. (1955) may have been the result of tissue autolysis in moribund animals.

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene - Oral

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
	ACUTE EXPOSURE							
	Death							
1	Rat	once				584	(LD_{50})	IRDC 1972
2	Rat	once				261 M	(LD_{Lo} in males)	Treon et al. 1955
						471 M	(LD_{50} in males)	
3	Mouse (B6C3F1)	1-2 wk 5 d/wk 1x/d				300 M	(100% mortality)	Abdo et al. 1984
						300 F	(30% mortality)	
4	Rabbit (New Zealand)	13 d Gd 6-18 1x/d				75 F	(increased maternal death during pregnancy)	Murray et al. 1980
5	Rabbit	once				579 F	(1/3 rabbits died)	Treon et al. 1955
	Systemic							
6	Rat	once	Resp			261 F	(pulmonary hyperemia and edema, retarded respiration rate)	Treon et al. 1955
			Cardio			261 F	(degenerative changes in heart)	
			Gastro			261 F	(diarrhea, necrotizing gastritis)	
			Hepatic			261 F	(liver degeneration and necrosis)	
			Renal			261 F	(renal tubular necrosis)	
			Endocr			261 F	(degenerative changes in adrenal glands)	

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
7	Rabbit (New Zealand)	13 d Gd 6-18 1x/d	Bd Wt		75 F (unspecified decreased maternal body weight)		Murray et al. 1980
8	Rabbit	once	Resp			579 F (hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			579 F (degenerative changes in the heart)	
			Gastro			579 F (diarrhea)	
			Hepatic			579 F (degenerative changes)	
			Renal			579 F (necrosis of tubular epithelia)	
			Endocr			579 F (degenerative changes in the adrenal glands)	
	Neurological						
9	Rat	once			261 F (lethargy)	579 F (degenerative changes in brain)	Treon et al. 1955
10	Rabbit	once			168 F (lethargy)	579 F (degenerative changes in brain)	Treon et al. 1955
	Developmental						
11	Mouse (CD-1)	5 d Gd 8-12 1x/d		45			Chernoff and Kavlock 1982
12	Mouse	5 d Gd 8-12 1x/d		45			Gray and Kavlock 1984
13	Mouse	5 d Gd 8-12		45			Gray et al. 1986

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
14	Mouse	10 d Gd 6-15 1x/d		75			Murray et al. 1980
15	Rabbit (New Zealand)	13 d Gd 6-18 1x/d		75			Murray et al. 1980
	INTERMEDIATE EXPOSURE						
	Death						
16	Rat (Fischer- 344)	13 wk 5 d/wk 1x/d				75 (death in 10% of males)	Abdo et al. 1984
	Systemic						
17	Rat (Fischer- 344)	13 wk 5 d/wk 1x/d	Resp	150			Abdo et al. 1984
			Cardio	150			
			Gastro	10	19 (forestomach epithelial hyperplasia)		
			Hemato	150			
			Hepatic	150			
			Renal	19[b]	38 (nephrosis)		
			Bd Wt	19 M 38 F		38 M (body weight gain reduced 75 F 21% in males; 28% in females)	

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
18	Mouse (B6C3F1)	13 wk 5 d/wk 1x/d	Resp	300			Abdo et al. 1984
			Cardio	300			
			Gastro	19	38 (focal inflammation, hyperplasia of fore-stomach)		
			Hepatic	300			
			Renal	38	75 (nephrosis)		
			Endocr	300			
			Bd Wt	75 M 75 F		150 M (reduced body weight 39%) 150 F (reduced body weight 21%)	
	Immunological/Lymphoreticular						
19	Mouse (B6C3F1)	13 wk 5 d/wk 1x/d		300			Abdo et al. 1984
	Neurological						
20	Rat (Fischer- 344)	13 wk 5 d/wk 1x/d		150			Abdo et al. 1984
21	Mouse (B6C3F1)	13 wk 5 d/wk 1x/d		300			Abdo et al. 1984

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Reproductive						
22	Mouse (B6C3F1)	13 wk 5 d/wk 1x/d		300			Abdo et al. 1984

[a]The number corresponds to entries in Figure 2-2.

[b]Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.1 mg/kg/day; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Cardio = cardiovascular; d = day(s); F = female (G) = gavage; Gastro = gastrointestinal; Gd = gestational day (s); (GO) = gavage in oil; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LD_{Lo} = lethal dose, low; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s); x = times

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

Acute (≤14 days)

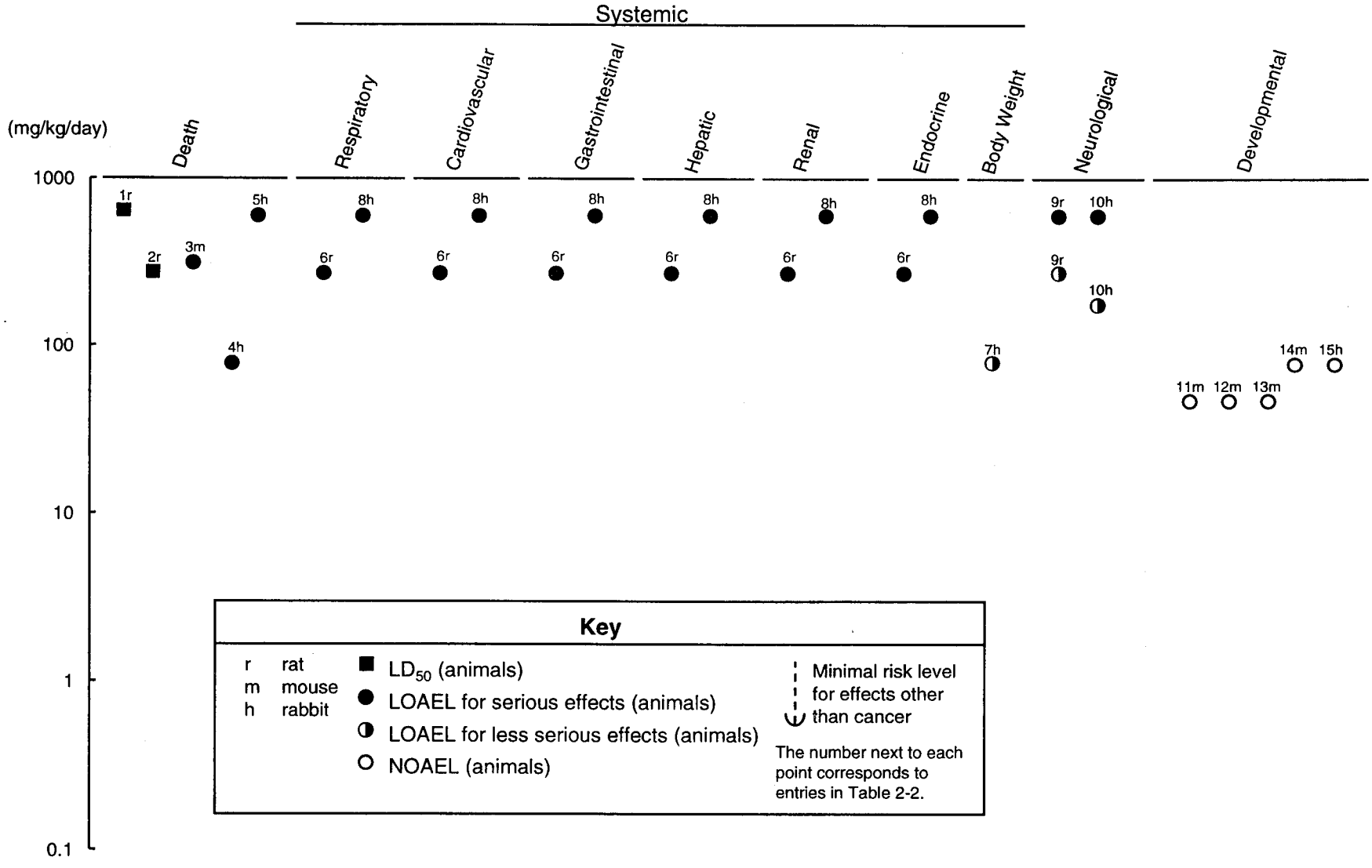
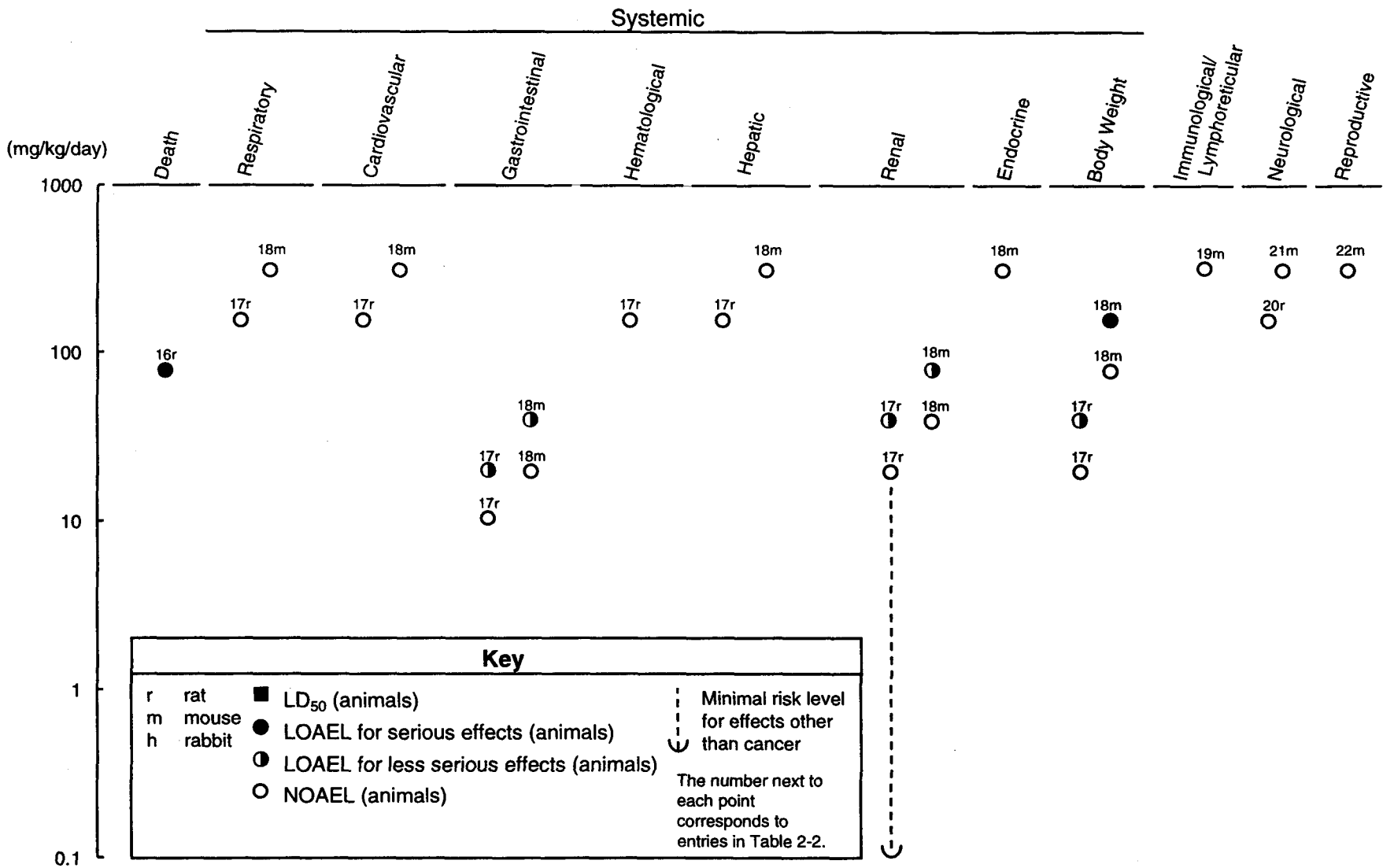


Figure 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene - Oral (cont.)

Intermediate (15-364 days)



2. HEALTH EFFECTS

Gastrointestinal Effects. Rats and rabbits experienced diarrhea following single oral doses of HCCPD (93.3% purity in peanut oil); the exact doses associated with the diarrhea were not specified. In some rats given an oral dose of 261-1,959 mg/kg, acute necrotic lesions of the forestomach were noted (Treon et al. 1955). After 13-week exposures to HCCPD administered in corn oil, inflammation and epithelial hyperplasia of the forestomach were present in female rats given doses of 19 mg/kg/day and greater, and in males with doses of 38 mg/kg/day and greater (Abdo et al. 1984). The severity of the lesions was directly related to dose. No effects were seen in either sex with a dose of 10 mg/kg/day. A similar pattern was seen in mice with inflammation and hyperplasia at doses of 38 mg/kg/day or greater (Abdo et al. 1984). The location of lesion suggests that they result from direct contact of the tissues with HCCPD during dosing.

Hepatic Effects. High acute oral doses of HCCPD (261-1,959 mg/kg administered in 5% peanut oil) were associated with liver necrosis and tissue degeneration in rats; doses of 579 and 877 mg/kg had the same effects in rabbits (Treon et al. 1955). However there were no changes in liver weights or histopathological changes in the livers of rats exposed to doses of 75 and 150 mg/kg/day, or of mice exposed to 150 and 300 mg/kg/day in corn oil for 13 weeks (Abdo et al. 1984). These differences in effects may reflect the ability of the liver to detoxify the lower, but not the higher, concentrations of HCCPD or tissue autolysis in animals killed through exposure.

Renal Effects. The kidneys also appear to be a target tissue for HCCPD toxicity. Degenerative lesions in the tubules resulted from single-dose exposures administered in 5% peanut oil of 261-l ,959 mg/kg in rats and 579-877 mg/kg in rabbits (Treon et al. 1955). Lesions were also noted in the terminal sections of the proximal tubules of the kidney cortex in rats given 38-150 mg/kg/day HCCPD and mice (female) given 70-300 mg/kg/day in corn oil for 13 weeks (Abdo et al. 1984). There were changes in epithelial cell structure. Brown granular pigment debris protruded into the lumen. Tubular necrosis was present in 70% of the male mice receiving the 300 mg/kg/day d ose, but this lesion was morphologically distinct from that seen in the other animals. It should be noted that hexachlorobutadiene was present as an impurity (0.5%) in the HCCPD used for this study. Since hexachlorobutadiene is a renal toxin, it may have contributed to the lesions observed, particularly those at the highest dose. No effects on the kidney tubules were apparent in rats with doses of 19 mg/kg/day or in mice with doses of 38 mg/kg/day (Abdo et al. 1984).

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Endocrine Effects. No effects on endocrine tissues were reported for humans exposed to HCCPD by the oral route.

Degenerative changes in the adrenal tissues resulted from exposure to single doses of 261-l ,959 mg/kg HCCPD in rats and doses of 579 and 877 mg/kg administered in 5% peanut oil in rabbits (Treon et al. 1955). These changes may have resulted from tissue autolysis. In a 13-week study using exposure of up to 150 mg!kgIday in rats and 300 mg/kg in mice administered in corn oil, there were no reported histopathological changes in the adrenals of either species (Abdo et al. 1984).

Body Weight Effects. Maternal weight loss was observed in rabbits administered 75 mg/kg/day in cottonseed oil on gestation days 6-18 in a teratogenic study. The magnitude of the weight loss was not reported (Murray et al. 1980). Male and female rats and mice experienced dose-related diminished weight gains when compared to controls after exposure to HCCPD in corn oil for 13 weeks (Abdo et al. 1984). Male rats were affected more than females and rats more than mice. Body weights in male rats were reduced 21-58% at dose levels of 38 mg/kg/day or greater. In females, comparable weights were reduced 28-36%, but weight loss first occurred in the 75 mg/kg/day or greater dose groups. Body weights in male mice were reduced 39% at dose levels of 150 mg/kg/day. No data were provided for the 300 mg/kg/day dose group (highest dose tested) because all the males died. In females, comparable weights were reduced 21-44% in the 150 mg/kg/day or greater dose groups. No effect on weight gain was noted in rats at a dose of 19 mg/kg/day or in mice at a dose of 75 mg/kg/day.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals after oral exposure to HCCPD.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to HCCPD.

Rats exposed to single doses administered in 5% peanut oil of 168-1,959 mg/kg HCCPD and rabbits exposed to 168-877 mg/kg were described as lethargic in the period immediately after exposure (Treon et al. 1955). During postmortem examination of tissues, degenerative lesions of the brain were observed in

the rats and rabbits that succumbed to exposure and also in the rats that survived. No histopathological lesions of the brain were noted in rats exposed to 150 mg/kg/day or mice exposed to 300 mg/kg/day in corn oil for 13 weeks (Abdo et al. 1984). The data suggest that brain lesions occur only with exposures to high oral doses of HCCPD.

All LOAEL values from each reliable study of neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding the reproductive effects in humans after oral exposure to HCCPD. Animal studies demonstrated HCCPD did not cause treatment-related effects on the testes, seminal vesicle, prostate, airwaves, and uterus in rats exposed to concentrations up to 150 mg/kg/day or in mice up to 300 mg/kg/day in corn oil for 13 weeks (Abdo et al. 1984). A multigeneration study evaluating a wide range of parameters regarding reproductive function and success has not been conducted. Accordingly, a reliable NOAEL value cannot be determined for this end point.

2.2.2.6 Developmental Effects

No studies were located regarding the developmental effects in humans after oral exposure to HCCPD

In animals, studies of the developmental toxicity of HCCPD have been limited to screening tests that evaluated effects following exposure during gestation. HCCPD was not embryotoxic, fetotoxic, or teratogenic in mice exposed to the compound at dose levels up to 75 mg/kg/day in cottonseed oil during gestation days 6-15 or in rabbits at corresponding doses during gestation days 6-18 (Murray et al. 1980). It should be noted that the compound was not maternally toxic in mice, but weight loss was noted in rabbits, and there were some rabbits that died (number not specified).

Mice that received HCCPD (45 mg/kg/day in corn oil) during gestation days 8-12 did not show developmental effects (Chernoff and Kavlock 1982). When offspring of mice that were administered HCCPD (45 mg/kg/day in corn oil) during gestation days 8-12 were evaluated over a 250-day postnatal

period (including through puberty and breeding), there were no adverse effects on postnatal viability, growth, locomotor activity, or reproductive function (Gray and Kavlock 1984; Gray et al. 1986).

The highest NOAEL values for developmental effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

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

Data on animals are limited to a study evaluating dominant lethality in mice (Litton Bionetics 1978b). HCCPD did not induce genetic damage in germ cells in male mice exposed to doses up to 1 mg/kg for 5 days. Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

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

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding lethality in humans after dermal exposure to HCCPD.

Dermal doses of 569 mg/kg and greater in 10% Ultrasene were lethal to rabbits when applied to a shaved area encircling the trunk and covered by a rubber sleeve for 24 hours (Treon et al. 1955). The higher the dose, the shorter the survival time for the animals. None of the animals died with a dermal application of a 401 mg/kg dose, although one was in poor condition and probably would have died naturally if it had not been sacrificed at 21 days. In a separate study, a dermal dose of 200 mg/kg led to the death of 2 male rabbits exposed for 24 hours. HCCPD was nonlethal in guinea pigs and monkeys when 0.05 mL of solutions of up to 90% HCCPD in mineral oil were applied to the skin (Treon et al. 1955).

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When an unspecified quantity of HCCPD was placed in the conjunctival sac of the right eye of 5 rabbits for only 5 minutes and then washed away, the quantity of material absorbed was lethal to all the animals within 9 days (IRDC 1972).

The LOAEL values for lethality in rabbits after acute-duration dermal exposure to HCCPD are recorded in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, body weight or other systemic effects in humans after dermal exposures to HCCPD.

There are no data for gastrointestinal, hematological, and musculoskeletal effects in animals. Data are available for respiratory, cardiovascular, hepatic, renal, endocrine dermal, ocular, and body weight effects after dermal exposure to HCCPD in animals. These effects are discussed below. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-3.

Respiratory Effects. Workers were exposed to HCCPD vapors for 3-15 days at a waste water treatment plant as a result of an inadvertent industrial release (Kominsky et al. 1980; Morse et al. 1979). Complaints included nasal irritation, and sinus congestion. These effects were more likely a consequence of the direct action of the HCCPD vapor on the mucous membranes, rather than systemic effects due to exposure to HCCPD through the lungs.

The lungs of rabbits that were dermally exposed to HCCPD (93.3% pure) were congested with blood and fluid (Treon et al. 1955). Some studies were conducted using the undiluted compound. Others were conducted using 10% (v/v) in Ultrasene. The exact doses associated with these effects cannot be determined because the authors did not directly correlate descriptions of effects with specific doses. It is presumed that the lung effects were seen in all exposed animals at doses of 401-5,719 mg/kg/day. The HCCPD was applied to a shaved area of skin encircling the trunk that was covered by a rubber sleeve for 24 hours, limiting any opportunity for inhalation exposure.

Table 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference
ACUTE EXPOSURE								
Death								
Rabbit	once 4 hr					365 mg/kg	(3/6 rabbits died)	IRDC 1972
Rabbit	once					200 M mg/kg	(2/2 died within 14 days)	IRDC 1972
Rabbit	once 24 hr					84 mg/kg	(all animals died within 6 days)	IRDC 1972
Rabbit	once 5 min					84 mg/kg	(all animals died within 9 days)	IRDC 1972
Rabbit	once 24 hr					569 mg/kg	(1/3 died)	Treon et al. 1955
Systemic								
Human	3-15 d	Dermal		0.97	(irritation of skin)			Kominsky et al. 1980
		Ocular		0.97	(irritation of eyes)			
Monkey	3 d 1x/d	Dermal				1 mg/cm	(skin irritation and necrosis)	Treon et al. 1955
Monkey	once	Dermal	1.6 mg	3.2 mg	(skin discoloration and irritation)			Treon et al. 1955
Rat	4 hr	Ocular		65.9 ppm	(eye irritation)			Treon et al. 1955
Rat	2.5-3.6 hr	Ocular		1.25 ppm	(eye irritation)			Treon et al. 1955

Table 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL			Reference
				Less Serious		Serious	
Rat	0.25 hr	Ocular		11.6 ppm	(eye irritation)		Treon et al. 1955
Rat	5 d 7 hr/d	Ocular		0.3 ppm	(irritation of eyelids)		Treon et al. 1955
Mouse	0.25 hr	Ocular		17.4 ppm	(eye irritation)		Treon et al. 1955
Rabbit	once	Dermal		200 mg/kg	(dermal irritation and discoloration)		IRDC 1972
		Bd Wt	2000 M	200 F mg/kg	(weight loss - amount not specified)		
Rabbit	0.25 hr	Ocular		11.6 ppm	(eye irritation)		Treon et al. 1955
Rabbit	2.5-3.6 hr	Ocular		1.25 ppm	(eye irritation)		Treon et al. 1955
Gn pig	2.5-3.6 hr	Ocular		1.25 ppm	(eye irritation)		Treon et al. 1955
Gn pig	once	Dermal	0.8 mg	31.7 mg	(skin discoloration and irritation)		Treon et al. 1955
Gn pig	0.25 hr	Ocular		11.6 ppm	(eye irritation)		Treon et al. 1955
Neurological							
Rabbit	once 4 hr			365 mg/kg	(ataxia and hypoactivity)		IRDC 1972

Table 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference
INTERMEDIATE EXPOSURE						
Systemic						
Monkey	13 wk 5 d/wk 6 hr/d	Ocular	0.2 ppm			Rand et al. 1982a
Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d	Ocular	0.2 ppm			Rand et al. 1982a
Rat	6 wk 5 d/wk 7 hr/d	Ocular		0.3 ppm	(irritation of eyes and mucous membranes)	Treon et al. 1955
Rat	30 wk 5 d/wk 7 hr/d	Bd Wt	0.13 ppm			Treon et al. 1955
Mouse	30 wk 5 d/wk 7 hr/d	Ocular	0.13 ppm			Treon et al. 1955
Rabbit	6 wk 5 d/wk 7 hr/d	Ocular		0.3 ppm	(eye irritation during exposure)	Treon et al. 1955
Rabbit	30 wk 5 d/wk 7 hr/d	Ocular	0.13 ppm			Treon et al. 1955
Gn pig	6 wk 5 d/wk 7 hr/d	Ocular		0.3 ppm	(eye irritation)	Treon et al. 1955

Table 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Gn pig	30 wk 5 d/wk 7 hr/d	Ocular	0.13 ppm			Treon et al. 1955

d = day(s); Gn Pig = guinea pig; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; min = minute(s); NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = times

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Nasal irritation, accompanied by nasal discharge and nasal lesions, was also observed in animals exposed to HCCPD vapors (IRDC 1972; Rand et al. 1982a; Treon et al. 1955). Contact of the vapors with the olfactory membranes most likely contributed to these effects. At vapor concentrations of 41.6 ppm or higher there was sneezing, mucus discharge from the nose, and salivation in rats, mice, guinea pigs, and rabbits (Treon et al. 1955). These signs were manifested almost immediately. Irritation of the mucous membranes took several minutes to appear with exposure concentrations of 11.1 or 12.4 ppm, but it took several hours to appear when the exposure concentration s were 0.9 or 1.4 ppm (Treon et al. 1955). Necrotizing or suppurative inflammation of the nasal passages was present in rats and mice after exposure to 0.4 ppm HCCPD for 13 weeks or 0.2 ppm for 2 years (NTP 1994).

Cardiovascular Effects. Rabbits exposed to single dermal doses of 569-5,919 mg/kg and greater displayed degenerative changes in the heart as determined by gross necropsy (Treon et al. 1955). This may have been the result of tissue autolysis.

Hepatic Effects. Rabbits exposed to single dermal doses of 401-5,719 mg/kg displayed necrosis of the liver as determined by gross necropsy (Treon et al. 1955). Degenerative changes persisted even 21 days after the exposure period in the animals that survived exposure.

Renal Effects. Rabbits exposed to single dermal doses of 401-5,719 mg/kg displayed degeneration and necrosis of the kidney tubules as determined by gross necropsy (Treon et al. 1955). These changes were still apparent 21 days after exposure period when the animals that survived the exposure period were sacrificed.

Endocrine Effects. No reports of endocrine effects in humans after dermal exposure to HCCPD were found.

Rabbits that were dermally exposed to HCCPD (401-5,719 mg/kg) had degenerative changes of the adrenal glands that were still apparent in survivors 21 days after exposure (Treon et al. 1955).

2. HEALTH EFFECTS

Dermal Effects. Workers were exposed to HCCPD vapors for 3-15 days at a waste water treatment plant as a result of an inadvertent industrial release (Kominsky et al. 1980; Morse et al. 1979). Dermal complaints included skin irritation. These effects were more likely a consequence of the direct action of the HCCPD vapor on the skin, rather than systemic effects due to exposure to HCCPD through the lungs.

Brief periods of exposure to 19.2 ppm HCCPD for several seconds by one cleanup crew worker using no protective equipment at a waste water treatment plant caused skin irritation of the face and neck (Kominsky et al. 1980). Three workers wearing half-face protectors complained of skin irritation after exposure to 7.1 ppm for several seconds. Another four workers also reported skin irritation.

HCCPD in either its pure form or in solution appears to have a pronounced effect upon the epidermis based on results in guinea pigs, monkeys, and rabbits (Treon et al. 1955). At lesion-forming doses the skin became discolored (purple-colored) and inflamed; ulceration and fissuring of the surface followed (IRDC 1972; Treon et al. 1955). Eventually the ulcerated area became encrusted. If the animal did not die, the lesions healed with time. In one monkey, the lesion site was still hairless and scarred 13 months after exposure (Treon et al. 1955).

Ocular Effects. Brief periods of exposure to 19.2 ppm HCCPD for several seconds by one cleanup crew worker using no protective equipment at a waste water treatment plant caused lacrimation (Kominsky et al. 1980). Three workers wearing half-face protectors complained of lacrimation and soreness around the eyes after exposure to 7.1 ppm for several seconds.

Eye irritation was one of the major symptoms reported by humans exposed to HCCPD vapors for 3-15 days at a waste water treatment plant as a result of an inadvertent industrial release (Kominsky et al. 1980; Morse et al. 1979). From the 145 individuals who responded to a questionnaire immediately after exposure occurred, 86% complained of eye problems; in a follow-up questionnaire 6 weeks later, 16% of 177 respondents were still experiencing ocular irritation. Tearing and redness of the eyes were present in five individuals on the day of exposure.

Eye irritation accompanied by lacrimation was also observed in animals exposed to HCCPD vapors (IRDC 1972; Rand et al. 1982a; Treon et al. 1955). Contact of the vapors with the eye most likely contributed to these effects. At vapor concentrations of 41.6 ppm or higher the eyes were closed. There was reddening of

the eyelids and tearing in rats, mice, guinea pigs, and rabbits (Treon et al. 1955). These signs were manifested almost irnrnediately.

Unexpectedly, there were no reports of ocular irritation in the intermediate- or chronic-duration studies of HCCPD conducted by NTP (1994). When an unidentified amount of HCCPD was placed in the right conjunctival eye sac for only 5 minutes, it caused severe eye irritation (IRDC 1972). When the material was left in place for 24 hours, it caused corrosion of the tissues as well (IRDC 1972).

Body Weight Effects. No reports of body weight effects in humans after dermal exposure to HCCPD were found.

Weight loss occurred in rabbits even with a nonlethal dose (IRDC 1972; Treon et al. 1955).

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after dermal exposure to HCCPD.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to HCCPD.

Rabbits exposed to single dermal doses of HCCPD (401-5,719 mg/kg) displayed degenerative changes in the brain as determined by gross necropsy (Treon et al. 1955). These changes were still apparent 21 days after exposure in survivors. Exposure to 856 mg applied to the shaved shin of rabbits was accompanied by ataxia, hypoactivity, and a depressed breathing pattern (IRDC 1972).

2. HEALTH EFFECTS

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

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to HCCPD.

2.3 TOXICOKINETICS

Absorption of HCCPD occurs throughout the lungs, gastrointestinal tract, and skin based on both toxicokinetic data and the occurrence of toxic effects in animals exposed through these routes (Dorough and Ranieri 1984; El Darreer et al. 1983; Lawrence and Dorough 1981, 1982; Mendenhale 1977; Treon et al. 1955). The low levels of labeled HCCPD in the blood after oral dosing, when compared to inhalation dosing, may be evidence of poor gastrointestinal absorption due to binding to the gastrointestinal contents. Absorbed HCCPD is distributed to the liver, kidneys, and lungs. There is some tendency for this material to distribute to in adipose tissues. Distribution in rats differs from that in mice. The highest concentrations are found in the kidneys of rats and the livers of mice.

There have been no studies of the metabolism of HCCPD. Four to five radiolabeled compounds were isolated in extracts from the urine of exposed rats and seven from fecal matter, but these compounds were not identified (Dorough and Ranieri 1984). There was negligible degradation to carbon dioxide. Since HCCPD has a strong tendency to participate in cycloaddition reactions, it is possible that some of the materials excreted in the urine are the products of HCCPD reaction with cellular or extracellular biomolecules. Some of the fecal metabolites may be formed by the result of interaction with intestinal microbes.

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Absorbed HCCPD and/or its products are excreted principally via the kidneys; some material is also excreted in the bile. Unabsorbed material is removed with the fecal matter; some appears to remain free, and some is bound to the fecal solids.

2.3.1 Absorption

No data were located regarding absorption of HCCPD in humans by any exposure route. In rats, the route of exposure appears to have a significant effect on absorption. The low levels of radiolabel from ^{14}C-HCCPD in the blood after oral dosing, as compared to the intravenous and inhalation routes, may be evidence of poor gastrointestinal absorption.

2.3.1 .1 Inhalation Exposure

Rats absorbed and retained an average of 83.9% of the radioactivity associated with the inhaled labeled compound during a l-hour exposure period (Lawrence and Dorough 1981). Retention increased to 95.2% after 2 hours (Lawrence and Dorough 1982).

2.3.1.2 Oral Exposure

The route of exposure appears to have a significant effect on absorption. The low levels of ^{14}C in the blood and tissues after oral dosing of rats with ^{14}C-HCCPD and the relatively large amount in the feces suggest that HCCPD is poorly absorbed from the gastrointestinal tract (Dorough and Ranieri 1984; Lawrence and Dorough 1982; Mehendale 1977; Yu and Atallah 1981). Estimates of absorption range from 25 to 40% (Dorough and Ranieri 1984; Lawrence and Dorough 1982; Mehendale 1977). In one study, a portion of the ingested HCCPD reacted with the contents of the gastrointestinal tract and was not available for absorption. When HCCPD was added to the contents of a rat's stomach, only 50% of what was added could be extracted with hexane. The unextractable HCCPD was found in both the liquid and solid fractions of the stomach contents (Lawrence and Dorough 1982).

The dosing medium may have an effect on the amount of HCCPD absorbed. In the work by Treon et al. (1955), the dosing vehicle was peanut oil. In the study by Abdo et al. (1984), corn oil was used. These two oils differ in their degree of unsaturation and, thus, in the number of double bonds that are potential reaction sites for HCCPD. If HCCPD reacted with double bonds in fatty acids, it would be less

bioavailable from the more unsaturated fat (corn oil). The LD_{50} for HCCPD in peanut oil was 471 mg/kg in male rats (Treon et al. 19.55) while the LD_{50} for HCCPD in corn oil was 630 mg/kg (IRDC 1972), suggesting that there is a slight difference in bioavailability.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption of HCCPD in humans or animals after dermal exposure. However, absorption through both skin and ocular membranes does occur in amounts leading to effects on target tissues (liver and kidney) and sometimes death (IRDC 1972; Treon et al. 1955).

2.3.2 Distribution

No studies were located regarding the distribution of HCCPD in human tissue after any route of exposure.

In rats and mice, liver and kidney tissues are sites of HCCPD distribution with all routes of compound administration. In rats, higher levels accumulate in the kidneys than in the liver. In mice, the situation is reversed. When dosing occurs by the inhalation route, there is a high concentration of material in the lungs. The brain and fat have very low concentrations of HCCPD label, suggesting that the metabolites of this material are not lipid soluble.

2.3.2.1 Inhalation Exposure

The site of uptake, like the trachea and lungs of rats showed the highest concentration of ^{14}C-radiolabel 72 hours after inhalation exposure to a dose of 0.024 mg/kg labeled HCCPD. The concentration in the trachea was 107 ng/g and the concentration in the lungs was 7 1.5 rig/g (Lawrence and Dorough 1981, 1982). The concentration of ^{14}C in the kidneys (29.5 ng/g) was 8 times that in the liver (3.6 ng/g). Fat tissue was not a site of retention following inhalation of HCCPD. Only 11.4% of the administered dose was found in the tissues at 72 hours; 2% was found in the lungs and 7.8 % in the carcass.

Little or no radioactivity was present in the fat tissue or in the brain of rats 6 and 72 hours after exposure to ^{14}C-HCCPD (El Dareer et al. 1983). The largest percentage of the total dose remained in the lungs and kidneys at both 6 and 72 hours after exposure. The amount of ^{14}C-HCCPD in the lungs decreased from 4.5 to 1.6% in 66 hours and that in the kidneys decreased from 3.6 to 1.7%. At 72 hours, about 20% of the

radiolabel in the kidneys was unextractable, indicating some binding to tissues; the remainder was water soluble. In the lungs, 47% was unextractable and 53% was water soluble (El Dareer et al. 1983).

2.3.2.2 Oral Exposure

When rats were given a single dose of 25 mg/kg [^{14}C]HCCPD in corn oil, the concentration of radioactivity in blood rose slowly, reaching its maximum level at 4 hours (Yu and Atallah 1981). Blood levels were then relatively stable over the next 4 hours. The tissues were analyzed for the presence of label from HCCPD between 8 and 120 hours after compound administration. At both 8 and 24 hours, the highest concentration of label was in the kidneys. The liver contained 30-40% of the amount in the kidneys (Yu and Atallah 1981). Moderate amounts were present in the blood, lungs, adipose deposits, and gonads. At the end of 8 hours, the amount of label recovered from the carcass was 41%, the digestive system contained 36.3%, and the remaining tissues contained 4.1%. Similar results were found at the end of 24 hours when single doses of 2.5 or 25 mg/kg were administered in corn oil (Dorough and Ranieri 1984). The affinity of the gonadal tissue differed for males and females. The concentration in the ovaries peaked at 24 hours at 11.6 ppm with a 25 mg/kg dose, and was 0.98 ppm at the end of 3 days. The concentration in the testes was not determined at 24 hours, but was 0.32 ppm at the end of 3 days, one-third the concentration in the ovaries at that time.

When doses of 17.7 or 25 mg/kg were given to rats and the tissue metabolites were monitored after 72 hours, the amount (% of dose) in the kidneys was about twice that in the liver with the 25 mg/kg dose; the concentrations in the liver and kidneys were roughly equal for the 17.7 mg/kg dose (Yu and Atallah 1981). For both doses, 12-13% of the label that remained in the tissues at 72 hours was present in the adipose tissue.

The tissue distribution in mice differs from that in rats. In mice, the highest concentration of radiolabel from a single dose of 2.5 or 25 mg/kg was found in the liver rather than the kidneys (Dorough and Ranieri 1984). The amount in the kidneys was between 33 and 50% of that in the liver. The adipose tissues and gonads contained moderate concentrations of the radiolabel and the muscle and brain, low concentrations. As with the rats, the mouse ovaries had a higher affinity for HCCPD than the testes as demonstrated by the concentrations of label 3 days after compound administration.

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In both rats and mice, the tissue distribution pattern for radioactivity derived from [^{14}C]HCCPD was similar for single doses and multiple doses (0.06, 0.3, or 1.5 mg/kg/day in the diet for 30 days). For rats in the high-dose group, the concentration of label in the kidneys increased rapidly, reaching homeostasis at a concentration of about 7 ppm in about 10 days (Dorough and Ranieri 1984). The concentrations in the fat and ovaries also increased rapidly, reaching about 4 ppm for the fat and about 3 ppm for the ovaries. Steady state was reached in 10 days for the ovaries, but not until about 20 days for the fat tissues. The concentration in the liver reached steady state near the end of the 30-day treatment period and was roughly 50% of the value for the kidneys. Low levels of label were found in muscle (0.5 ppm) and brain (0.3 ppm). Once exposure ceased, tissue levels decreased quickly in the first 20 days post-treatment for all tissues except the fat. For both brain and muscle, the tissue concentration remained stable for the last 20 days of observation.

In mice, the concentration of label in the liver increased rapidly, reaching homeostasis at about 5 ppm in 7 days with a dose of 4.2 mg/kg/day (Dorough and Ranieri 1984). The concentration in the fat and ovaries also increased rapidly and was nearly equivalent to that in the liver. Steady state was reached by about 20 days for the ovaries (3 ppm) and fat (5 ppm). The concentration in the kidneys was about 50% of that in the liver. Low levels of label were found in muscle (0.8 ppm) and brain (0.2 ppm). Once exposure ceased, tissue levels decreased quickly in the first 10 post-treatment days for all tissues except the fat. For both brain and muscle, the tissue concentration remained stable for the last 20 days of observation.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of HCCPD in the tissues of humans or animals after dermal exposure.

2.3.2.4 Other Effects

Seventy-two hours after an intravenous dose of 0.59 mg/kg ^{14}C-HCCPD in Emulphore EL-620 and ethanol:water, 1: 1:4 (v/v), 39.0% remained in the tissues of rats. The following levels of ^{14}C-HCCPD label were observed: liver 13.9%, kidneys 1.2%, tail section 1.4% (site of injection), intestine 0.7%, lungs 0.3%, brain 0.l%, skin (ears) <0.l%, remaining carcass 18.4%, and blood 2.9% (El Dareer et al. 1983). Since an elevated level of ^{14}C-HCCPD label remained in the blood at 72 hours, the highest concentrations of

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^{14}C-HCCPD label in the liver and kidney after intravenous administration may be due to the added presence of blood in those tissues.

In a separate study, there was little difference in the percentage of radiolabel that was recovered 24 or 48 hours after 0.7 mg/kg HCCPD was administered intravenously in Emulphor® EL-620 (Yu and Atallah 1981). At 24 hours, 37% of the label was recovered and at 48 hours, 38% was recovered. The amount in the blood at 24 hours (15%) was less than that at 48 hours (26%). The kidneys contained 2-3% of the dose at both times and the liver contained about 5%. The amount in fat at 24 hours (1.2%) was greater than that at 48 hours (0.2%). The lungs contained 0.7-0.8% of the label.

Oral preexposure of rats to HCCPD at 0.05 mg/kg/day for 3 days increased the concentration of HCCPD in the kidneys from a challenge intravenous dose of ^{14}C-HCCPD. The hepatic concentration, biliary excretion, and blood decay curves appeared to be unaltered by preexposure to HCCPD (Mehendale 1977).

2.3.3 Metabolism

No studies were located concerning the metabolism of HCCPD in humans. Complete oxidation of this material is apparently limited, based on the small amount of radiolabel that is excreted as carbon dioxide (<1%) after exposure to ^{14}C-HCCPD in rats by the oral, inhalation, and intravenous routes (El Dareer et al. 1983).

Based on the levels of radioactivity in the blood following intravenous administration, [^{14}C]HCCPD was rapidly metabolized and distributed to blood, liver, kidneys, and lungs before being distributed to the peripheral tissues (Yu and Atallah 198 1). There is some metabolism of HCCPD by bacteria in the gastrointestinal tract (Yu and Atallah 1981).

When rat urine was extracted with a mixture of hexane and cyclohexanol, approximately 70% of the radiolabel from HCCPD dissolved in the organic phase (Mehendale 1977). Thin layer chromatography (TLC) of this extract suggested the presence of four labeled compounds in the urine; these compounds were not identified. Most of the HCCPD urinary metabolites or derivatives were considered to be nonpolar.

In a different study, ethyl acetate extraction of acidified urine recovered 33% of the radiolabel. When the aqueous phase was refluxed for 30 minutes and re-extracted with ethyl acetate, an additional 10% of the

radiolabel was recovered (Yu and Atallah 198 1). The urinary extracts were chromatogrammed using silica gel plates and a relatively nonpolar solvent (toluene/acetone/acetic acid, 75:20:5); 5 fractions were identified. Most of the material was polar, as indicated by the fact that Rf values were low. An additional 36% of the label was water soluble. These results indicate that urinary metabolites or derivatives are predominantly polar rather than nonpolar and are not in agreement with those of Mehendale (1977).

Identification of the chromatogram fractions using mass spectroscopy (MS) was not possible due to the presence of coextractives, several compounds in one fraction, and the polar nature of the metabolites (Yu and Atallah 1981). One major fraction was purified by high pressure liquid chromatography (HPLC). Based on its elution, this compound did not correspond to either HCCPD or any of four HCCPD potential metabolites (hexachloro-2-cyclopentanone, hexachloro-3-cyclopentanone, hexachloro-indone, or octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene- 1,8-dione).

Using TLC and a toluene/acetone/acetic acid solvent system, fecal matter was found to contain seven radioactive fractions (Yu and Atallah 1981). None of these fractions corresponded with the four potential metabolites listed above. With the fecal matter, only 10.6% of the label was recovered in an ethyl acetate extract, and 6.8% was relatively polar, based on its movement in the solvent system. Another 32% of the label was extracted from the fecal matter after refluxing with acid. A portion of the fecal label (21%) was found as unextractable solids and 25% was water soluble. In a separate rat study, 20% of the fecal label was extracted in benzene after continuous feeding of 0.06 or 0.3 mg/kg/day HCCPD in the diet for 30 days, but only 7-12% was extracted with a dose of 1.5 mg/kg/day (Dorough and Ranieri 1984).

The affinity that HCCPD (or its products) has for the Clara cells in the lungs and the production of electron-lucent granules in these cells after inhalation exposure situations (Rand et al. 1982b) suggests that HCCPD may interact with the microsomes in rats and monkeys to form a metabolite (possibly a free radical) that binds to secretory molecules and changes their ability to be transported from the cell. When the granular pigments that are found in the lungs and nasal passages after long-term inhalation exposure to HCCPD were stained with reagents to detect mucopolysaccarides, mucoproteins, carbohydrates, iron, reducing substances, and acid fast substances, all tests were negative except those for reducing substances (NTP 1994). These results support the classification of the pigment as lipofuscin or ceroid material (substances that are formed through free-radical-induced crosslinking of cellular lipids. These results do not confirm the presence of either of these complexes.

It is also possible that HCCPD rather than a metabolite could react directly with cellular alkenes in a spontaneous Diels-Alder cycloaddition reaction. The occurrence of such a non-enzymatic reaction could explain why HCCPD causes effects at the point of contact for all exposure routes. It also explains the tissue-binding properties of HCCPD.

2.3.4 Elimination and Excretion

No data were identified for excretion of HCCPD by humans after any route of exposure. Based on animal data, the route of exposure appears to have a significant effect on elimination and retention. In rats, inhaled ^{14}C-HCCPD was primarily excreted by the kidneys, and the oral dose was primarily eliminated in the feces. These differences may be attributable to the poor absorption from the gastrointestinal tract (El Dareer et al. 1983; Lawrence and Dorough 1981).

2.3.4.1 Inhalation Exposure

Inhaled ^{14}C-HCCPD was excreted primarily in the urine (33.1%) of rats with a smaller percentage eliminated in the feces (23.1%) 72 hours after dosing (Lawrence and Dorough 1981, 1982). Most of the radiolabel was eliminated in the first 24 hours; only 70% of the radiolabel was recovered.

Higher values for rat urinary and fecal excretion were obtained after inhalation exposures that resulted in absorbed doses of 1.3-1.8 mg/kg HCCPD (El Dareer et al. 1983). The urine contained 41% of the label after 6 hours and 40% after 72 hours. The label in the feces entered the gastrointestinal tract with the bile. Only about 1% of the label was exhaled as carbon dioxide, indicating that the pulmonary route is not a major route of excretion as suggested by Mehendele (1977).

2.3.4.2 Oral Exposure

The amount of radiolabel found in rat urine in a 72-hour period after single oral doses of 2.5-61 mg/kg ranged from 13 to 35% and the amount in the feces ranged from 64 to 80% (Dorough and Ranieri 1984; El Dareer et al. 1983; Lawrence and Dorough 1982; Yu and Atallah 1981). In each case, most of the label was excreted in the first 24 hours. About 16-18% of the radiolabel entered the fecal matter with the bile (Dorough and Ranieri 1984; Lawrence and Dorough 1981). Less than 1% of HCCPD was metabolized to carbon dioxide; there were trace amounts that were exhaled as volatiles other than carbon dioxide (≤0.3%)

(El Dareer et al. 1983). In mice, the urine contained 15% of the dose after 72 hours and the feces contained 74% following a dose of 25 mg/kg HCCPD dissolved in corn oil (Dorough and Ranieri 1984).

When HCCPD was given to rats at doses of 0.06, 0.3, or 1.5 mg/kg/day in feed for 30 days, urinary excretion of label ranged from 5 to 9% at the end of the exposure period and fecal excretion ranged from 62 to 69% (Dorough and Ranieri 1984). When mice were fed 0.2,0.8, or 4.2 mg/kg/day under the same study conditions, urinary excretion ranged from 7 to 12% and fecal excretion ranged from 54 to 68%.

In one study, some of the HCCPD in the feces was volatile and was considered to be unmetabolized (El Dareer et al. 1983). In another study, some of the fecal label was bound to insoluble matter (Yu and Atallah 1981). Fecal microbes appear to metabolize HCCPD rather rapidly. The half-life for degradation of HCCPD in a spiked fecal homogenate was 6.2 hours in the presence of mercuric chloride and 1.6 hours in the absence of mercuric chloride (Yu and Atallah 1981). Mercuric chloride is a bacterial inhibitor and, thus, minimized microbial metabolism when it is present in the medium.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of HCCPD by humans or animals after dermal exposure.

2.3.4.4 Other Exposure

Data are available from two studies that evaluated the excretion of radiolabel from ^{14}C-HCCPD after intravenous dosing. When a dose of 0.01 mgkg in dimethylsulfoxide or a 10:4:1: mixture of saline, propylene glycol, and ethanol was given to rats, 22% was excreted in the urine and 3 1% in the feces over 72 hours (Lawrence and Dorough 1982). A total of 85% of the label was recovered. With a 0.59 mg/kg in emulphor, ethanol, water (1:1:4) intravenous dose, rats excreted 16% in the urine and 34% in the feces (El Dareer et al. 1983). A very small amount of label (0.02%) was excreted as exhaled carbon dioxide and other volatiles.

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

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

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

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

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately

described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

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

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

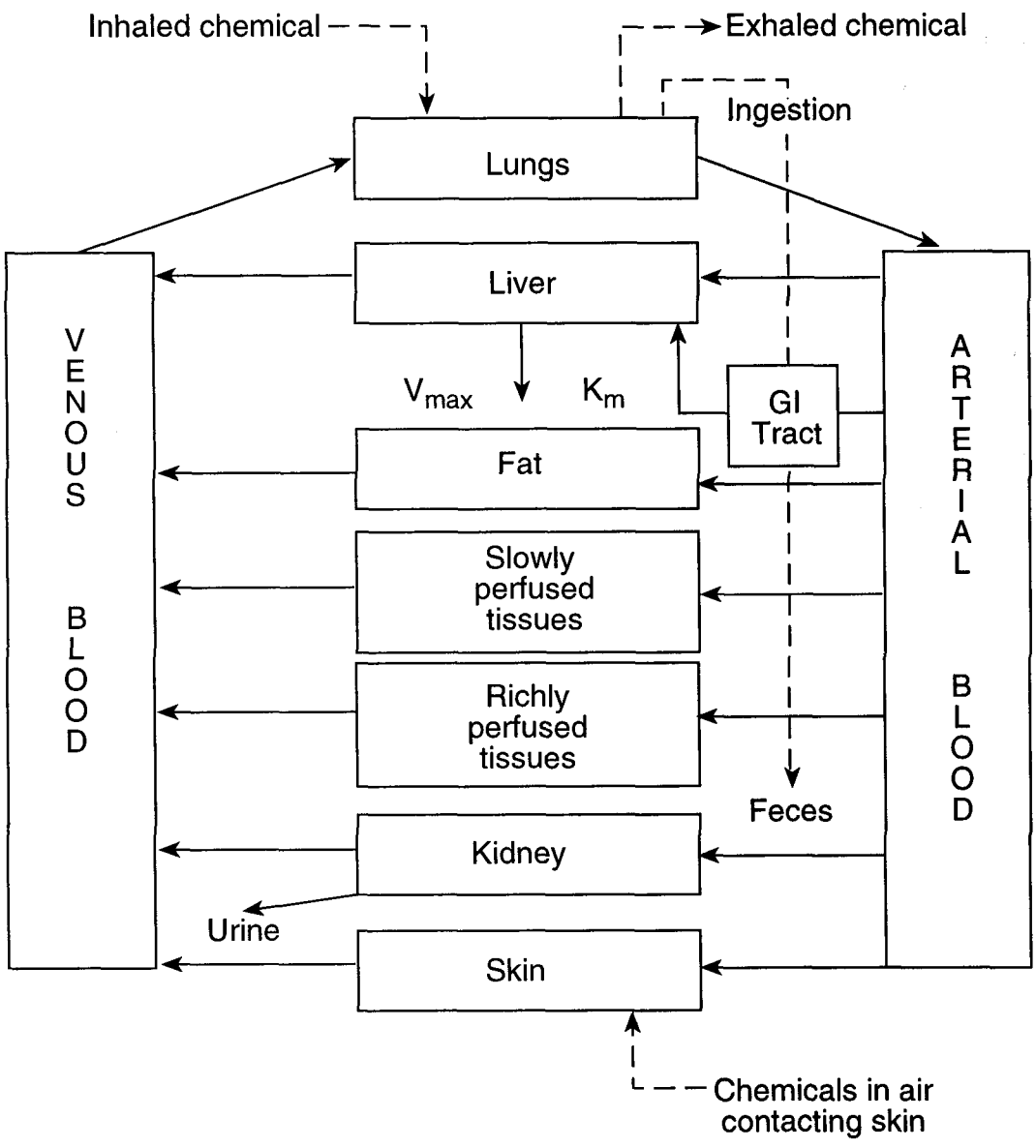
No PBPK models for HCCPD were found in the literature. The existing kinetic data (see Section 2.3) are insufficient for developing a model.

2.4 MECHANISMS OF ACTION

Little information was located regarding the mechanism of action of HCCPD. It can be postulated, however, that some of its toxic properties are a consequence of its reactivity in Diels-Alder reactions where a conjugated diene combines with a substituted or unsubstituted alkene (a dienophile) in a cycloaddition reaction (EPA 1991a; Morrison and Boyd 1983). Biological tissues contain a large number of potential reactants for cycloaddition reactions (quinones, sterols, 2-alkenoic acids, unsaturated fatty acids, and unsaturated fatty acid derivatives). HCCPD can also undergo addition and substitution reactions (EPA 199la) or be oxidized by way of the mixed function oxidase system (Rand et al. 1982b).

The attack of HCCPD on tissues can be regarded as a 2-phase phenomenon. Primary lesions are formed by direct contact of the material with exposed tissues (nasal passages, lungs, forestomach, and skin) (Abdo et al. 1984; Rand et al. 1982a ;Treon et al. 1955). These lesions can be hypothesized to result from reactions of HCCPD or one of its metabolites with epithelial cells impairing function and resulting in cell death. Once exposure ceases, new cells replace the damaged ones, and slow recovery begins (Rand et al.

Figure 2-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

1982a; Treon et al. 1955). Secondary lesions form at sites distant from the point of contact when systemic circulation carries unreacted HCCPD or a metabolite to lungs, liver, kidney, heart, brain, and adrenals. These tissues may become targets for HCCPD by virtue of their physiological function (liver and kidney) or the tendency for their cell products or membrane components to react with HCCPD or an HCCPD metabolite (lung, adrenal).

There are minor changes in Clara cells of the lung epithelium in rats and monkeys when exposure occurs by the inhalation route (Rand et al. 1982b). Electron-lucent inclusions become apparent in the affected cells. There, inclusions could represent the reaction products of HCCPD or a microsomal metabolite with the carbon double bonds in phospholipids, prostaglandins, eicosanoids, and other molecules within the lung tissues. Alternatively, the changes in the lung could be the result of free radical modification of the cellular molecules that form the yellow-brown pigment found in the epithelial cells of the respiratory tract after long-term exposure (NTP 1994). Clara cells have particularly rich concentrations of microsomes and enzymes of the mixed function oxidase system.

Effects of HCCPD on the brain may also be a reflection of the reaction of either HCCPD or a metabolite with brain lipids. Degenerative brain effects were not seen in rats exposed to low inhalation concentrations of up to 0.2 ppm (6 hours a day, 5 days a week) for 13 weeks (Rand et al. 1982a), but they were seen with acute exposure to higher dose (Treon et al. 1955). At low exposure levels, the reactivity of HCCPD makes it unlikely that reactive species would be present in the blood at high enough concentrations to cause significant change in a secondary site such as the brain, but at higher doses, transport of reactive material across the blood-brain barrier is possible.

The effects of HCCPD on the adrenal glands (Rand et al. 1982a; Treon et al. 1955) may be a reflection of its ability to combine with the unsaturated carbons in sterols produced by this gland. The hydroxyl functional group of a sterol is on a carbon adjacent to the double bond and can activate that bond to cycloaddition reactions. Such reactions would require exposure to large doses of HCCPD so that reactive material would reach the adrenal gland.

2. HEALTH EFFECTS

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

HCCPD is a highly volatile, reactive liquid that has entered the environment primarily as a result of its use in the manufacture of pesticides and flame-retardant chemicals. In recent years, limited use of pesticides synthesized from HCCPD has decreased the possibility of exposure to pesticide residues among most members of the population. Exposure to materials at hazardous waste sites is still possible.

Some data pertaining to human exposures to HCCPD (100-200 people) come from an incident where waste water treatment plant workers and clean-up crews members were exposed after an industrial discharge. Irritation of the eyes, skin, and breathing passages were the primary complaints of those exposed. Less frequently, there were complaints of nausea and headaches. Issues relevant to children are explicitly discussed in Section 2.6, Children's Susceptibility, and Section 5.6, Exposures of Children.

Animal studies confirm the observation that HCCPD vapors irritate the eyes and breathing passages. In addition, the hmg epithelium is damaged by HCCPD contact, leading to edema, hemorrhage, and fibrosis. The extent of damage is related to the dose. Even doses that cause no histopathological changes that can be seen under the light microscope cause ultrastructural changes in Clara cells that are visible by electron microscopy, and accumulation of granular pigmented material in the epithelial cells of the nose, trachea, and lungs.

High oral and dermal doses also cause lung damage in exposed animals. At least a portion of the damage observed may be the result of inhalation of HCCPD vapors during dosing and thereby may not be due to systemic toxicity. The effective doses for inhalation exposures are lower than those for oral and dermal exposures. Reaction of HCCPD with the contents of the gastrointestinal tract or the cellular constituents of the epidermis seems to limit oral and dermal uptake.

Liquid HCCPD causes lesions at the point of tissue contact with oral and dermal dosing. Lesions form in the rat forestomach when HCCPD is administered by gavage. When administered dermally, lesions form at the point of skin contact.

2. HEALTH EFFECTS

Other target tissues for HCCPD, based on animal studies, are the kidneys, liver, ovaries, adrenals, brain, and heart. Damage to the kidney tubules was seen with intermediate-duration oral doses of 38 mg/kg/day in rats and 70 mg/kg/day in mice, and tubular necrosis was apparent in rats, mice, guinea pigs, and rabbits acutely exposed to concentrations as low as 0.3 ppm and intermediate-duration exposures as low as 0.13 ppm. Effects on the liver (minimal weight changes) are not definitive at low doses. Lesions appeared in the liver, brain, adrenals, and heart with high doses and, in mice, ovarian inflammation was associated with chronic exposure to low doses of HCCPD.

HCCPD appears to have no histological effects on the male reproductive organs of rats and mice. There have been no reproductive studies of HCCPD to determine if it affects fertility and embryogenesis. Studies in mice and rabbits indicate that HCCPD is not developmentally toxic at doses of up to 45 mg/kg/day.

Minimal Risk Levels for HCCPB

Inhalation MRLs

- An MRL of 0.01 ppm has been derived for intermediate-duration inhalation exposure (15-364 days) to HCCPD .

This MRL was calculated using a LOAEL of 0.2 ppm based on structural effects on the bronchial epithelial cells of rats (Rand et al. 1982b). Electron microscopic examination revealed a statistically significant increase in the mean number of electron-lucent inclusions in the Clara cells at a concentration of 0.01 ppm or greater. The importance of this finding is not clear; nevertheless, it does show that the pulmonary lining can be affected. Clara cells are nonciliated cells that line the terminal bronchioles and contribute materials to the extracellular lining of the peripheral airways. In addition, they contain mixed function oxidases that are active in detoxifying inhaled contaminants. Thus, Clara cells are biomarkers of exposure, and not effect.

Since HCCPD is a category 1 gas, a $NOAEL_{HEC}$ was calculated. An RGDR of 1.95 was calculated using the surface area of the entire respiratory tract. An uncertainty factor of 30 (3 for extrapolation from humans to animals using a $NOAEL_{HEC}$ and 10 for human variability) was used in the calculation of the MRL. Exposure concentrations were not normalized over time due to the high reactivity of HCCPD and its

tendency to form lesions on directly exposed tissues. The chemical exerts a direct contact effect, and the effects are concentration- rather than time-dependent.

- An MRL of 0.2 ppb has been derived for chronic-duration (365 days or more) inhalation exposure to HCCPD.

This MRL was derived from the NTP (1994) bioassay where yellow-brown granular pigmentation of the nasal epithelium, trachea, and/or bronchioles was noted in rats after 15 months or 2 years of exposure to concentrations of 0.01-0.2 ppm HCCPD for 6 hours a day, 5 days a week. In all cases, the nasal tissues were affected to a greater extent than the lungs or trachea, suggesting that pigment formation was an *in situ* reaction resulting from the contact of the vapor with the mucosa, which increases the half-life of some mucosal components. The survival of the exposed animals did not differ from the controls, suggesting that the pigment had, at best, a minimal effect on organ function. Since HCCPD is a category 1 gas, a $LOAEL_{HEC}$ was calculated. An RGDR of 2.4 was calculated using the surface area of the entire respiratory tract. An uncertainty factor of 90 (3 for minimally adverse cellular changes, 3 for extrapolation from humans to animals using a $LOAEL_{HEC}$ and 10 for human variability) was used in the calculation of the MRL. Exposure concentrations were not normalized over time due to the high reactivity of HCCPD and its tendency to form lesions on contact with exposed tissues. The chemical exerts a direct contact effect, and the effects are concentration- rather than time-dependent.

An MRL was not derived for acute-duration inhalation exposure. An acute-duration exposure study was available for workers in a sewage treatment plant who were exposed to HCCPD as a result of a large industrial release (Kominsky et al. 1980; Morse et al. 1979). Workers experienced breathing difficulties and tracheobronchial irritation as well as sore throat and chest discomfort. Exposure duration was presumed to be from 3 to 5 days. Concentrations to which the workers were exposed could not be firmly established. Because exposure duration or concentration could not be determined with certainty, these data are not adequate for deriving an acute MRL. ACGIH also adopted the 0.01 ppm (0.01 mg/m^3) exposure limit for HCCPD (ACGIH 1998).

HCCPD caused inflammation and hyperplasia in nasal and lung epithelium in rats exposed to a concentration of 0.5 ppm (highest concentration) for 5 days and allowed to recover for 21 days, but no effects were seen at concentrations of 0.1 I ppm or less for up to 10 days of exposure except for a marginal reduction in liver weight and a slight decrease in body weight (Rand et al. 1982a). The usefulness of these

data are limited due to a high mortality in the high-dose group. Three of the 5 exposed males died either during the 5-day exposure period or during the 2 l-day recovery period. The resulting MRL calculated from this study would be lower than the intermediate-duration inhalation MRL calculated from Rand et al. (1982a) (see above). Therefore, the calculated intermediate-duration inhalation MRL is protective of acute exposures.

Oral MRLs.

- An MRL of 0.1 mg/kg/day has been derived for intermediate-duration (15-364 days) oral exposure to HCCPD.

This MRL was calculated using a NOAEL of 19 mg/kg/day based on the absence of renal lesions in rats exposed to HCCPD for 13 weeks, 5 days/week (Abdo et al. 1984). Lesions were seen in the terminal sections of the proximal tubules at a LOAEL of 38 mg/kg/day. Doses were normalized to account for a 5 days a week exposure and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied. A NOAEL of 10 mg/kg/day and a LOAEL of 19 mg/kg/day were observed for epithelial hyperplasia and inflammation of the forestomach in female rats. However, humans lack an anatomical equivalent to the rat forestomach. Accordingly, the NOAEL of 10 mg/kg/day for this end point was not used as the basis for the MRL.

No data were located on effects of acute-duration oral exposure in humans or animals except single highdose exposures (261-1,959 mg/kg/day) in rats that resulted in death (IRDC 1972; Treon et al. 1955). An acute MRL for this exposure route has not been derived.

No data were located on the effects of chronic-duration oral exposure in humans or animals. A chronic MRL for this exposure route has not been derived.

Death. No studies were located regarding lethality in humans after exposure to HCCPD. HCCPD was lethal to animals by all exposure routes (Abdo et al. 1984; NTP 1994; Rand et al. 1982a; Treon et al. 1955). Compound concentrations, duration, and route of exposure influenced lethality. Exposure by the inhalation route appeared to be most toxic (NTP 1994; Rand et al. 1982a; Treon et al. 1955); oral exposure is less toxic because HCCPD binds to the contents of the gastrointestinal tract (Abdo et al. 1984; Lawrence and Dorough 1982). Mice seem to be more susceptible to death than rats following inhalation

exposure to HCCPD (NTP 1994; Treon et al. 1955) while rats are more susceptible than mice when exposure is oral (Abdo et al. 1984). The small diameter of the air passages, which become even narrower as the result of HCCPD-induced inflammation, may explain the high incidence of death in mice with inhalation exposure. Guinea pigs are less likely to be affected than rats, mice, and rabbits, and appear to have an adaptive response to intermediate-duration, low-dose exposures (Treon et al. 1955). Adaptive responses were not apparent in rats, mice, and rabbits. The lowest lethal concentration for oral exposures was 0.04 ppm in mice (NTP 1994) and 75 mg/kg/day in rats (Abdo et al. 1984). Exposure to 0.2 ppm for 2 years decreased the longevity of female mice (NTP 1994).

Animal data suggest that HCCPD could be lethal to humans if there were a sudden release of a large amount of vapor from a drum or other vessel at a hazardous waste site resulting in acute exposures to a high concentration. The odor, appearance, and irritating effects of the vapors on the eyes and nose (Kominsky et al. 1980; Morse et al. 1979) would alert the victim to the presence of a noxious substance. The toxicity of HCCPD makes the use of protective equipment advisable at any site where contact with this material is possible.

Systemic Effects.

All systems appear to be vul,nerable to HCCPD toxicity with the exception of the musculoskeletal and hematological systems. The musculoskeletal system has not been thoroughly evaluated in any of the studies of HCCPD toxicity.

Respiratory Effects. The lungs are vulnerable to HCCPD after exposure by every route. In humans acutely exposed to concentrations of greater than 0.97 ppm (100-200 people, exact concentration not known) as the result of an industrial discharge, respiratory complaints (tracheobronchial irritation and discomfort, sore throats, cough, chest discomfort, and breathing difficulty) were reported (Kominsky et al. 1980; Morse et al. 1979). Pulmonary function tests and chest X-rays were normal for those individuals examined (Kominsky et al. 1980). When one individual was exposed to 19.2 ppm for several seconds, he experienced shortness of breath and chest discomfort (Kominsky et al. 1980). Respiratory irritation was reported by workers and cleanup crew members exposed to HCCPD at a waste water treatment plant (Kominsky et al. 1980). Exposed individuals complained of nasal irritation and sinus congestion. These effects were more likely a consequence of the direct action of the HCCPD vapor on the mucus membranes than systemic effects due to exposure through the lungs.

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Nasal irritation accompanied by nasal discharge was observed in animals exposed to HCCPD vapors (Rand et al. 1982a; Treon et al. 1955). Nasal lesions caused by concentrations of 0.022-0.5 ppm HCCPD over a 5-10-day period healed within 3 weeks (Rand et al. 1982a). In animals, concentrations of less than 0.9 ppm HCCPD for durations of 2 days or less, or a concentration of 0.13 ppm for up to 30 weeks caused no overt symptoms of respiratory distress (Treon et al. 1955). However, at higher concentrations, breathing patterns became irregular and the animals were gasping for breath. Even under conditions where there were no apparent effects on respiration, the tissues of the bronchi and alveoli were inflamed, hyperemic, and edematous (Treon et al. 1955). The higher exposure concentration, the more severe the tissue inflammation. A yellow-brown pigment was found in the nasal cavity, lungs, and/or trachea of all rats and mice exposed to concentrations of 0.01-0.2 ppm for 15-24 months (NTP 1994). A hyaline or fibrinoid membrane and proliferation of fibrous tissue into the bronchus, bronchiole, and alveoli appeared with the most severe lung necrosis (Treon et al. 1955).

Under exposure conditions where there were no apparent histopathological effects (0.01 ppm for 14 weeks), electron microscopy of the Clara cells of the alveolar epithelium of rats revealed electron-lucent granules. These same inclusions were seen in one monkey exposed to 0.2 ppm for 14 weeks (Rand et al. 1982b). Additional research will be necessary to determine if these inclusions are associated with impaired cell function and to evaluate the influence of species differences in respiration rates and Clara cell structure on the occurrence of granules. The increased values for hemoglobin concentration and hematocrit observed after 12 weeks in male rats exposed to 0.01 ppm HCCPD, females exposed to 0.05 ppm, and males and females exposed to 0.2 ppm (Rand et al. 1982a) provide some support for impaired lung function. Some rats exposed to 0.4 ppm for 13 weeks also had increased hemoglobin and hematocrit values (NTP 1994). These changes could reflect a compensatory physiological response to impaired oxygen transfer across the alveolar membranes.

Sudden releases of HCCPD vapors from containers at hazardous waste sites pose the greatest risk to people who live in these areas. If there were a release of HCCPD into the air at or near a hazardous waste site, it is highly likely that some effects on the respiratory system would be experienced by exposed individuals, even with low exposure concentrations. Low-level exposure concentrations (1-19.2 ppm) can cause respiratory irritation within seconds or minutes, although this effect was observed in only one exposed person (Kominsky et al. 1980; Morse et al. 1979). Direct contact with HCCPD vapors would be likely to cause damage. It is important for workers at sites that may contain HCCPD to use proper protective equipment.

2. HEALTH EFFECTS

Cardiovascular Effects. There are minimal data from human HCCPD exposure situations that relate to the cardiovascular system. In several humans, the levels of LDH and AST were elevated (Kominsky et al. 1980; Morse et al. 1979). These enzymes can be released to the systemic circulation following damage to the heart muscle or liver. However, because these enzymes are not exclusively associated with heart damage, their presence cannot be regarded as evidence that HCCPD has a direct effect on the heart in the absence of other tests of heart function.

Diffuse degeneration of the heart muscle was seen in animals after inhalation, oral, and dermal exposures (Treon et al. 1955). The amount of tissue damage was directly related to the dose and may have been at least partly due to tissue autolysis. Tissue damage was seen in rats at concentrations of 0.3 ppm and greater for inhalation exposures and 26 mg/kg and greater for oral exposures. The doses associated with tissue damage were not specified for dermal exposures (Treon et al. 1955). There was no histopathological examination of the tissues and no testing for cardiac function in this study. There were no histopathological changes in the hearts of rats or mice exposed to concentrations of 0.04-0.4 ppm for 13 weeks or 0.01-0.2 ppm for 2 years (NTP 1994). There was an increase in relative heart weight in male rats exposed to 0.4 ppm, but not in male rats at lower doses (0.04 and 0.15 ppm). Female rats and mice of both sexes were not affected.

Although the data from the NTP (1994) studies indicate that the risk is minimal at low doses, it is premature to draw any conclusions concerning the potential for cardiovascular damage resulting from human exposure to HCCPD in the environment.

Gastrointestinal Effects. Humans exposed to HCCPD through inhalation had some complaints of nausea and abdominal cramps (Morse et al. 1979). No other gastrointestinal symptoms were reported. Rats given single oral doses of 261-1,959 mg/kg had diarrhea (Treon et al. 1955), but this effect was not reported for inhalation exposure to concentrations of 0.04-2 ppm for up to 13 weeks (NTP 1994) or oral doses of up to 150 mg/kg/day in rats and 300 mg/kg/day in mice (Abdo et al. 1984). With single doses of 261 mg/kg and with daily doses of 10 mg/kg for 13 weeks, inflammation, hyperplasia, and necrotic lesions appeared in the forestomach of rats (Abdo et al. 1984; Treon et al. 1955). There were no observable effects on the stomach lining in rats at doses of 19 mg/kg/day or less (Abdo et al. 1984). It is possible that erosion of the gastrointestinal epithelium might occur as a result of contact exposure to HCCPD through contaminated drinking water or foods. However, humans do not have a forestomach and, thus, may not respond to HCCPD exposure in the same manner as rats. In addition, it is unlikely that exposure of this kind would

occur. No histopathological changes were seen in the esophagus, stomach, or intestines of rats and mice that were exposed to 0.01-0.2 ppm HCCPD vapors over a 2-year period (NTP 1994).

Hematological Effects. The only effects of HCCPD on hematological parameters (slightly elevated packed red cell volumes, hemoglobin concentration, and erythrocyte count) were seen in animals (NTP 1994; Rand et al. 1982a). These effects were a compensatory response to hemorrhagic damage to the lungs following inhalation exposure rather than direct effects on hematopoiesis (Rand et al. 1982a). No hematological effects were observed in animals when exposure occurred by the oral or dermal route. Exposure of humans to HCCPD at hazardous waste sites is unlikely to cause hematological effects unless there is hemorrhagic damage to the lung.

Hepatic Effects. Elevated values for LDH, AST, ALT, and/or AP were seen in a small number (about 18) of the 145 waste water treatment workers and 97 clean-up crew members after exposure to HCCPD at a sewage treatment plant. These enzymes were not elevated in blood samples taken three or more weeks after the initial samples (Kominsky et al. 1980; Morse et al. 1979). For eight of the cleanup crew members, these biochemical indices of possible liver damage were abnormal in more than one blood sample (Kominsky et al. 1980).

In animals, mild to moderate liver damage was a common manifestation of exposure to HCCPD by all routes in the studies by Treon et al. (1955). Exposure concentrations ranged from 0.13 to 66 pm and exposure durations ranged from 15 minutes to 30 weeks for inhalation conditions. For the oral route, single doses of 168-1,959 mg/kg were given, and for the dermal route, single doses of 401-5,719 mg/kg were used. These changes may have been the result of autolysis of tissues following death. Liver weights were slightly reduced with inhalation exposures of 0.01-0.5 ppm for 5 days to 13 weeks (Rand et al. 1982a), but not with 13-week inhalation of 0.04-0.4 ppm HCCPD vapors by rats or mice (NTP 1994) or oral exposures of up to 150 mg/kg/day for 13 weeks in rats and up to 300 mg/kg/day in mice (Abdo et al. 1984). The biochemical parameters, LDH, AST, ALT, and AP were not influenced by inhalation exposure to 0.01-0.5 ppm HCCPD (Rand et al. 1982a). It is not clear whether or not exposure to HCCPD could have an impact on liver function in individuals exposed to this substance at hazardous waste sites. Available evidence indicates that the risks of hepatic damage are minimal.

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Renal Effects. Urine samples were collected from workers and cleanup crew members exposed to HCCPD at a waste water treatment plant. Proteinuria was the only abnormality seen; it was identified in six workers immediately after exposure, but not 3 weeks later (Morse et al. 1979).

Inhalation, oral, and dermal exposure to HCCPD caused renal tubular necrosis in animals (Treon et al. 1955). Inhalation exposure concentrations ranged from 0.13 to 66 pm and durations ranged from 15 minutes to 30 weeks. For oral exposures, single doses of 168-1,958 mg/kg were given and for dermal exposures, the doses were 40 l-5,719 mg/kg.

No kidney damage was seen in rats or mice exposed by inhalation to 0.01-0.4 ppm for 13 weeks (NTP 1994; Rand et al. 1982a), or to 0.01-0.2 ppm for 2 years (NTP 1994). However, 15-month exposures to 0.01-0.2 ppm were associated with an increase in volume and/or specific gravity in the urine in both rats and mice (NTP 1994).

Lesions were located in the terminal sections of the proximal tubules of the kidney cortex of rats given 38-150 mg/kg/day HCCPD and female mice given 75-300 mg/kg/day by gavage for 13 weeks (Abdo et al. 1984). There were changes in renal epithelial cell structure, and brown granular pigment debris protruded into the lumen of the kidney tubules.

Based on animal data, chronic exposure to HCCPD from a hazardous waste site might result in impaired kidney function due to changes in tubules.

Dermal Effects. Dermal irritation was a symptom reported by workers and cleanup crew members exposed to HCCPD at a waste water treatment plant (Kominsky et al. 1980). Exposed individuals complained of skin irritation. These effects were more likely a consequence of the direct action of the HCCPD vapor on the skin than systemic effects due to exposure through the lungs.

If there were a release of HCCPD into the air at or near a hazardous waste site, it is highly likely that some effects on the skin would be experienced by exposed individuals even with low exposure concentrations. Direct contact with liquid HCCPD would be likely to cause chemical burns and ulceration. It is important for workers at sites that may contain HCCPD to use proper protective equipment.

2. HEALTH EFFECTS

Ocular Effects. Eye irritation was one of the major symptoms reported by workers and cleanup crew members exposed to HCCPD at a waste water treatment plant (Kominsky et al. 1980; Morse et al. 1979). From the 145 individuals who responded to a questionnaire immediately after the exposure incident, 59% complained of eye problems; in a follow-up questionnaire 6 weeks later, 9% of 177 respondents were still experiencing ocular irritation. Eye irritation occurred with exposure concentration as low as 0.009 ppm (Kominsky et al. 1980). These effects were more likely a consequence of the direct action of the HCCPD vapor on the mucus membranes than systemic effects due to exposure through the lungs.

Eye irritation accompanied by lacrimation was observed in animals exposed to HCCPD vapors (Rand et al. 1982a; Treon et al. 1955). Nasal lesions caused by concentrations of 0.022-0.5 ppm HCCPD over a 5-10-day period healed within 3 weeks (Rand et al. 1982a).

If there were a release of HCCPD into the air at or near a hazardous waste site, it is possible that some effects on the eyes would be experienced by exposed individuals even with low exposure concentrations. It is important for workers at sites that may contain HCCPD to use proper protective equipment.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to HCCPD.

Rats exposed to HCCPD vapors (0.5 ppm) for 10 days ate less food than controls and they also lost weight. At lower doses (0.022 and 0.01 ppm), the weight gain was diminished (Rand et al. 1982a). Decreases in weight gain were also noted in male rates and male mice with 13-week inhalation exposure to 0.4 ppm HCCPD (NTP 1994) and with oral exposures to 38 mg/kg/day in rats and 75 mg/kg/day in mice (Abdo et al. 1984).

There were degenerative changes in the adrenal glands of rats, mice, guinea pigs, and rabbits after inhalation, oral, and dermal exposures to HCCPD (Treon et al. 1955). The weights of the adrenal glands were also significantly reduced in rats exposed to 0.5 ppm for 10 days (Rand et al. 1982a). However, no changes in the histopathology of the adrenal glands were seen with 13-week exposures of rats and mice to 0.04-0.4 ppm or lifetime exposures to 0.01-0.2 ppm (NTP 1994). Adrenal function was not monitored in any of the studies of HCCPD toxicity.

2. HEALTH EFFECTS

Immunological and Lymphoreticular Effects. There are no human data to indicate that HCCPD affects the immunological system; in the animal studies that have been conducted, there were no histopathological effects on the spleen or thymus (NTP 1994; Rand et al. 1982a). No data were identified from a study designed to monitor immunological response to xenobiotic materials.

Neurological Effects. Exposure to HCCPD vapors was associated with headaches in 45% of 145 individuals who responded to a questionnaire after being exposed at a waste water treatment plant (Morse et al. 1979). As much as 6 weeks later, 18% of 177 respondents were still experiencing headaches. Tremors were noted in animals acutely exposed to HCCPD vapor concentrations of 41.6 ppm or greater (Treon et al. 1955). Rats exposed to concentrations of 0.4-2 ppm were described as listless after l-3 weeks of exposure (NTP 1994). The higher the dose, the sooner the listlessness was noted. It must be remembered that these same doses were also lethal. Thus, the listless behavior could well have been a symptom of impending death rather than HCCPD neurotoxicity. Scattered degenerative brain lesions were seen following acute- and intermediate-duration doses of 0.13 ppm or more, or acute oral doses of 579 mg/kg/day or more. With dermal exposure, the doses associated with effects on the brain were not specified (Treon et al. 1955).

Based on these data, individuals could get headaches if they are exposed to HCCPD at a hazardous waste site where vapors are released into the air.

Reproductive Effects. No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure. Limited data suggest that HCCPD did not adversely affect reproductive organs in rats exposed to vapors of HCCPD (up to 0.5 ppm) or in rats or mice after oral exposure to 150 or 300 mg/kg/day (Abdo et al. 1984). A lack of adverse effects on male reproduction has been confirmed in a dominant lethal test in mice (Litton Bionetics 1978b). Fertility index, implantation/pregnancy, and average resorption/pregnancy in females mated to treated males were comparable to untreated controls. Although this test is used primarily to assess mutagenic potential, it can be used as supplemental data in the overall assessment of the reproductive potential of chemical contaminants.

No multi-generational reproduction studies evaluating reproductive function and success have been located. However, maternal toxicity was associated with oral exposure to 75 mg/kg/day in cottonseed oil during

gestation (Murray et al. 1980). Thus, reproductive toxicity potential of HCCPD cannot be established with certainty.

Long-term exposure of female mice to HCCPD was associated with an increased incidence of suppurative ovarian inflammation which was hypothesized to be caused by a *Klebsiella* infection in the NTP mouse colony (NTP 1994). Studies of HCCPD distribution in both rats and mice showed that the concentrations in the ovaries were relatively high. Changes in cell chemistry resulting from the presence of HCCPD may help to explain why exposure was associated with an increased risk for infection.

Developmental Effects. Acute-duration oral studies in animals suggest that HCCPD is not developmentally toxic in offspring of mice and rabbits administered doses of 75 mg/kg/day (Murray et al. 1980). Further, there appeared to be no effects on postnatal development with exposure to 45 mg/kg/day in mice evaluated for up to 250 days (Gray and Kavlock 1984; Gray et al. 1986). Based on these considerations, HCCPD does not seem likely to pose significant risk to human development.

Genotoxic Effects. No studies were located regarding the genotoxic effects of HCCPD in humans after inhalation, oral, or dermal exposure. In *in vivo* tests, HCCPD did not induce dominant lethals in mice following oral exposure or recessive lethal mutations in *Drosophila* (Table 2-4). The absence of gene mutation and chromosomal aberrations suggests that HCCPD does not cause significant genetic damage in humans at low exposure concentrations. For the most part, *in vitro* tests employing bacterial assays or mammalian cell cultures were negative, with two exceptions (Table 2-5). Results were positive in one bacterial assay evaluating DNA damage potential (Matsui et al. 1989). Because other genotoxic end points were negative and the carcinogenic potential of HCCPD is not confirmed, the importance of a positive response in the DNA assay is not clear. It should be further noted that other studies evaluating the same end point are not available. Thus, the reproducibility of this response has not been determined. In a second assay that evaluated Chinese hamster ovary cells, HCCPD caused sister chromatid exchanges (SCE) and chromosomal aberrations with and without metabolic activation (NTP 1994). It should be noted that there was no clear dose-response relationship in the SCE assay. Further, a sufficient number of cells were not scored for chromosomal aberrations at the highest dose tested due to high cytotoxicity of HCCPD. Accordingly, the overall importance of the positive response for chromosomal aberrations is reduced. For these reasons, it is difficult to speculate regarding the potential for HCCPD to induce DNA damage and chromosomal aberrations in humans.

Table 2-4. Genotoxicity of HCCPD *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Mouse/micronucleus assay	Chromosomal aberrations	–	NTP 1994
Mouse/dominant lethal assay	Chromosomal aberrations	–	Litton Bionetics 1978b
Eukaryotic organisms:			
Insect			
Drosophila/sex-linked recessive lethal assay	Gene mutation	–	Mason et al. 1992
Drosophila/sex-linked recessive lethal assay	Gene mutation	–	NTP 1994

– = negative result; + = positive result

Table 2-5. Genotoxicity of HCCPD *In Vitro*

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA 1535, TA 1538	Gene mutation	–	No data	Greim et al. 1977
S. typhimurium TA 100, TA 1535, TA 1537, TA 998	Gene mutation	–	–	NTP 1994
S. typhimurium TA 1535, TA 1537, TA 98, 100	Gene mutation	–	–	Haworth et al. 1983
Escherichia coli K12	Gene mutation	–	No data	Greim et al. 1977
E. coli K12	Gene mutation	–	–	Goggelman et al. 1978
Bacillus subtilis Rec - assay	DNA damage	+	+	Matsui et al. 1989
Mammalian cells:				
Mouse/L5178Y/Lymphoma assay	Gene mutation	–	–	Litton Bionetics 1978a
Chinese hamster ovary cells	Sister chromatid exchanges	+	+	NTP 1994
Chinese hamster ovary cells	Chromosomal aberrations	+	+	NTP 1994

– = negative results; + = positive results

Cancer. There were no data from studies in humans pertaining to the carcinogenicity of HCCPD. NTP conducted 2-year bioassays of HCCPD in mice and rats, and concluded that it is not a carcinogen in either species (NTP 1994). Although the incidence of alveolar/bronchiolar carcinomas was significantly increased in male mice exposed to 0.5 ppm HCCPD for 26 or 42 weeks, the incidence was within the historical range for the laboratory and was not seen in animals exposed to 0.2 ppm for 2 years. There was also a slight increase in the incidence of adenomas of the pituitary pars distalis in male rats and thyroid follicle cell adenomas in female mice, but these tumors were not considered to be compound-related.

2.6 CHILDREN'S SUSCEPTIBILITY

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

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with the developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on the developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and

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

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

There are no data describing the health effects, developmental or otherwise, of HCCPD in children. It is unlikely that children will be directly exposed to HCCPD. Nor are there any data describing the health effects of HCCPD in immature animals, except for prenatal developmental studies. HCCPD was not embryotoxic, fetotoxic, or teratogenic in mice exposed to the compound at oral dose levels up to 75 mg/kg/day during gestation days 6-15 or in rabbits at corresponding doses during gestation days 6-18 (Murray et al. 1980). It should be noted that the compound was not maternally toxic in mice, but weight loss was noted in rabbits and some rabbits died. Mice that received oral doses of HCCPD (45 mg/kg/day) during gestation days 8-12 did not show developmental effects (Chernoff and Kavlock 1982). When offspring of mice that were administered oral doses of HCCPD (45 mg/kg/day) during gestation days 8-12 were evaluated over a 250-day postnatal period (including the period through puberty and breeding), there were no adverse effects on postnatal viability, growth, locomotor activity, and reproductive function (Gray and Kavlock 1984; Gray et al. 1986). There is no information on whether HCCPD can cross the placenta or accumulate in breast milk either in animals or humans.

2. HEALTH EFFECTS

2.7 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAWNRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to HCCPD are discussed in Section 2.7.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by HCCPD are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organisms ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the

biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.9, Populations That Are Unusually Susceptible.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to HCCPD

There are no specific biomarkers for HCCPD except the compound itself. Studies with the radiolabeled compound indicate that HCCPD and several metabolites are excreted in the urine and feces (Dorough and Ranieri 1984; El Dareer et al. 1983; Lawrence and Dorough 1981, 1982; Yu and Atallah 1981). The metabolites have not yet been identified and have only been classified as polar and nonpolar. HCCPD can also be identified in blood.

2.7.2 Biomarkers Used to Characterize Effects Caused by HCCPD

Evaluation of humans exposed to HCCPD did not identify any unique adverse health effects (Kominsky et al. 1980; Morse et al. 1979). Minimal-to-mild abnormalities in liver function tests (LDH, AST, ALT, AP, bilirubin) were observed in a small percentage of waste water treatment plant workers exposed to sewage contaminated with HCCPD (Kominsky et al. 1980; Morse et al. 1979). However, many other xenobiotic reports of compounds, as well as several physiological conditions, can cause increased levels of these enzymes. Initial reports of compound-induced proteinuria following HCCPD exposure could not be confirmed (Morse et al. 1979). Urinary porphyrin excretion in a group of 40 industrial workers exposed to HCCPD was found to be an unsuitable parameter for monitoring long-term exposure (Nagelsmit et al. 1979) because the values for the exposed individuals were not significantly different from those for controls.

In studies of rats, mice, guinea pigs, rabbits, and monkeys using the inhalation, oral, and dermal routes of exposure, adverse effects were seen in the lungs, liver, kidneys, and stomach (Treon et al. 1955). Following long-term inhalation exposure, a yellow-brown pigment formed in the epithelium of the nose, trachea, and lungs with vapor concentrations as low as 0.01 ppm (NTP 1994). The presence of pigment in the epithelial cells of the nose would be a useful biomarker for long-term exposure. Inhalation exposure to HCCPD also caused the appearance of electron-lucent granules in lung epithelial Clara cells. The Clara cell changes are not appropriate biomarkers of effects because undesirable invasive procedures would be necessary to obtain tissue specimens for analysis.

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Studies of Japanese quail dosed with 100-300 mg/kg/day HCCPD for 15 days showed no macroscopic or microscopic fluorescence of porphyrins in the intestines, intestinal contents, liver, or kidneys (Nagelsmit et al. 1979). Quail were used as test animals because they are highly sensitive to porphyrinogenic chlorinated xenobiotics.

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

2.8 INTERACTIONS WITH OTHER CHEMICALS

No data were located pertaining to interactions of HCCPD with other compounds. Based on the chemical properties of this material, interactions with materials that provide reactive alkene functional groups, especially those with an electron withdrawing substituent on the carbons adjacent to the double bond, are expected. Interactions with these materials preceding exposure would be expected to reduce HCCPD concentration.

In one oral exposure study, the sample HCCPD contained 0.5% hexachlorobutadiene as an impurity (Abdo et al. 1984). Because hexachlorobutadiene is also a renal toxin, the authors postulated that the renal lesions seen in the male mice at the highest dose (300 mg/kg) were due to the combined effects of both compounds.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to HCCPD than will most persons exposed to the same level of HCCPD in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of HCCPD, or compromised function of target organs affected by HCCPD. Populations who are at greater risk due to their unusually high exposure to HCCPD are discussed in Section 5.6, Populations With Potentially High Exposure.

People with preexisting lung, kidney, or liver damage may be more at risk than the general population in the event of HCCPD exposure because of compromised organ function. Asthmatics are probably also likely to be more affected. In two studies of human exposure to HCCPD in the workplace, respiratory

symptoms predominated (Kominsky et al. 1980; Morse et al. 1979). There was also transient elevation of serum enzyme levels (e.g., LDH, AST, ASL, and AP) and proteinuria, suggesting potential effects of HCCPD on the liver and kidneys (Morse et al. 1979). Animal studies have confirmed the potential respiratory, renal, and hepatic toxicity of HCCPD. Animal studies also suggest that males are generally more susceptible to HCCPD toxicity than females (Abdo et al. 1984; NTP 1994; Rand et al. 1982a).

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to HCCPD. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to HCCPD. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.10.1 Reducing Peak Absorption Following Exposure

Humans may be exposed to HCCPD by inhalation, ingestion, or dermal contact. Exposure may be prevented by wearing respiratory protection, protective clothing, and gloves. Inhalation and ingestion have been associated with lung, liver, and kidney damage in animals (Abdo et al. 1984; Rand et al. 1982a, 1982b), although comparable data do not exist for humans. Several methods can be used to reduce absorption and thereby reduce the severity of the lesions.

If inhalation of HCCPD has occurred, it is recommended that patient be removed to fresh air. Humidified supplemental oxygen (100%) may be administered as required (HSDB 1998).

In cases of ingestion, measures are usually taken to limit gastrointestinal absorption and accelerate excretion. If patients have ingested small amounts of HCCPD, milk or water may be administered to dilute the ingested compound if the patient can swallow and has good gag reflex (Bronstein and Currance 1988; Stutz and Janusz 1988). In cases where substantial amounts of the compound have been ingested, vomiting may be induced if the patient is alert and not at risk of convulsing. Syrup of ipecac may be used for this purpose; however, it is most effective if administered within 30 minutes of ingestion (HSDB 1998). Gastric aspiration and lavage are recommended to empty the stomach of patients with severe respiratory distress or for those that are unconscious. Measures must be taken to prevent aspiration of gastric contents

into the lungs. Administration of activated charcoal to absorb the HCCPD and saline cathartics to speed fecal excretion are other measures which may be employed following ingestion of HCCPD.

In order to reduce absorption of HCCPD through the skin, areas of the skin that have come in contact with the compound should be washed thoroughly with soap and water. If the compound is splashed into the eyes, irrigation with large amounts of water for at least 15 minutes is recommended (Bronstein and Currance 1988; HSDB 1998; Stutz and Janusz 1988).

2.10.2 Reducing Body Burden

HCCPD that is absorbed in the body is distributed to the lung, liver, and kidney (Lawrence and Dorough 198 1). Although the major routes of elimination are the urine and feces, the disparity between elimination and retention as a function of route is not fully understood. It should be noted that the metabolic fate and the identity of metabolites have not been fully characterized: In the absence of data, it is difficult to speculate on methods for reducing HCCPD in body tissues. Considering the reactivity of HCCPD, it is unlikely that dialysis or hemoperfusion would be effective in reducing body burden.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

The primary effects associated with exposure to HCCPD are in the lung, kidney, liver, and stomach. The mechanism of toxicity for these effects is not well understood, but may involve binding of the HCCPD with cell constituents which leads to cell death. The lack of data on metabolic fate of the compound and mechanism of action for these effects precludes any speculation regarding methods that would reduce toxic effects. Administration of natural products containing dieneophiles may be a possible method of interfering with the mechanism of action in the gastrointestinal tract.

2.11 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of HCCPD is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of

a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of HCCPD.

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

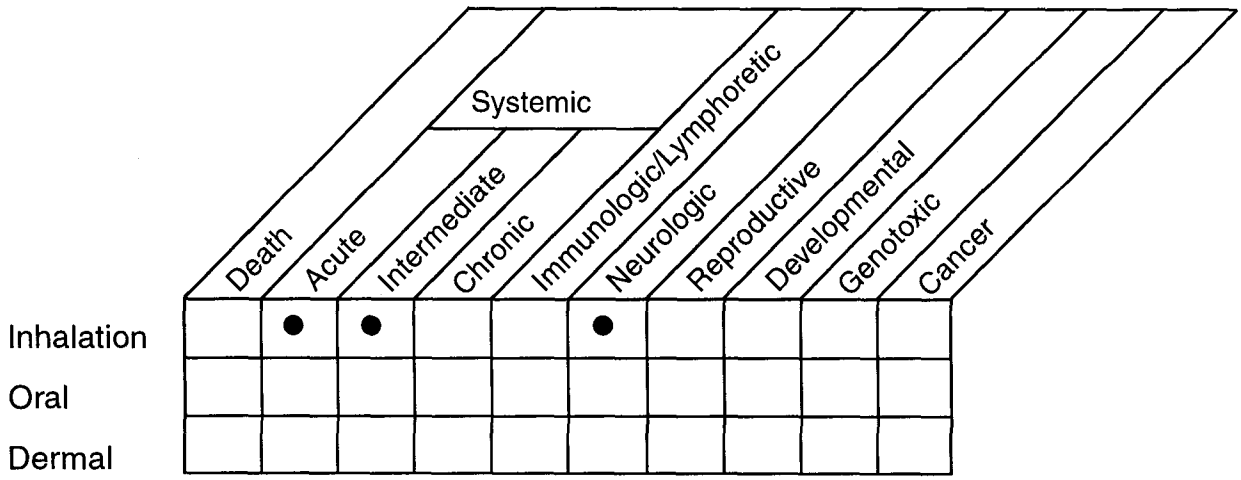
2.11.1 Existing Information on Health Effects of HCCPD

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to HCCPD are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of HCCPD. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989b), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

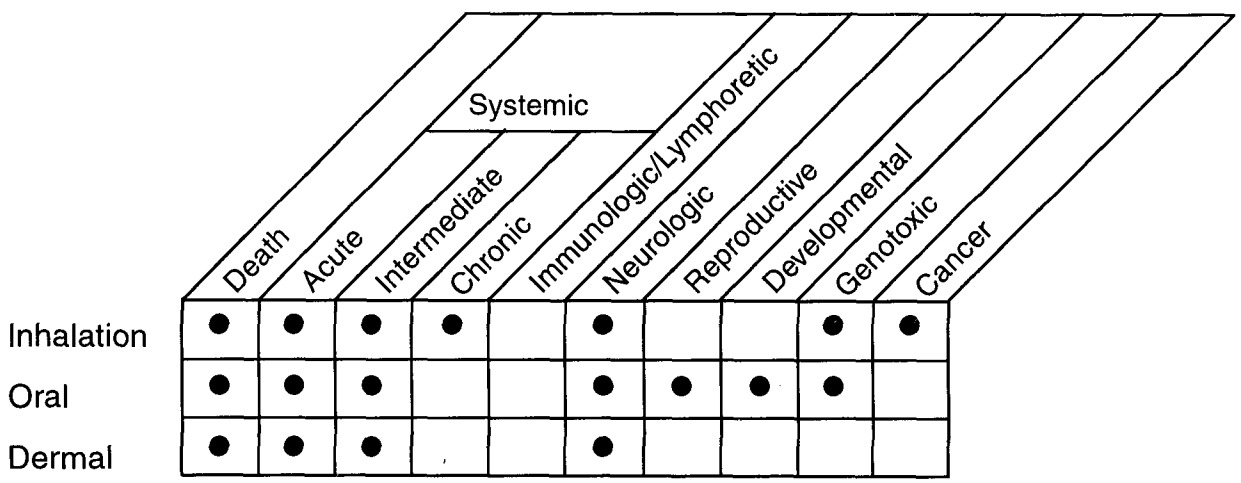
As indicated in Figure 2-4, there are very few studies available on the health effects of HCCPD in humans. No studies were located regarding oral exposure. There are several reports of the effects of acute- or intermediate-duration inhalation and dermal exposure in the workplace (Kominsky et al. 1980; Morse et al. 1979). For the most part, these reports focused on systemic (respiratory, cardiovascular, gastrointestinal, hepatic, renal, dermal, and ocular) and neurological effects. Effects of HCCPD on human development, reproduction, genotoxicity, and cancer incidence have not been evaluated, although there have been studies of cancer incidence among workers involved in the manufacture of pesticides prepared from HCCPD (Shindell and Ulrich 1986; Wang and MacMahon 1979).

More data are available in animals and include studies by the inhalation, oral, and dermal routes of exposure. These exposure routes have focused on lethality and systemic effects (respiratory, cardiovascular, gastrointestinal, hepatic, renal, dermal, and ocular). There has been minimal evaluation of

Figure 2-4. Existing Information on Health Effects of HCCPD



Human



Animal

● Existing Studies

neurological and immunological effects. There are data available on the histopathological effects of HCCPD on the spleen, thymus, and reproductive organs after inhalation and oral exposure. It should be noted that effects on reproductive functions have not been evaluated. There are studies in animals on the effects of HCCPD on development after oral exposure, but not after inhalation or dermal exposure. The carcinogenic potential of HCCPD has been studied in rats and mice using the inhalation route of exposure.

2.11.2 Identification of Data Needs

Acute-Duration Exposure. In humans involved with the cleanup of HCCPD at a waste water treatment plant, an exposure concentration as low as 0.009 ppm caused symptoms of eye irritation, and exposure to 19.2 ppm for only a few seconds affected respiration (Kominsky et al. 1980; Morse et al. 1979). Thus, acute human exposures are a concern when there are environmental releases of HCCPD.

Single-dose exposures to HCCPD were evaluated in several animal species using all three routes of administration (Treon et al. 1955). The doses used for the oral and dermal routes were lethal in most instances and caused substantial damage to the lungs, liver, kidney, brain, and adrenals in all cases. A broader range of doses was tested by the inhalation route. There were substantial effects on most of the same tissues. Based on the data from single-dose exposures, the inhalation route seems to cause the most profound physiological effects. Some effects on blood parameters, body weight, and liver and kidney weight occur with lo-day exposures to 0.5 ppm for 6 hours per day (Rand et al. 1982a). Additional testing of acute inhalation exposure situations in animals in order to detect subtle cellular changes that accompany low-dose, short-term exposures is justified because human exposures to a sudden release of HCCPD vapors from a container at or near hazardous waste sites during cleanup would be very serious.

Intermediate-Duration Exposure. There are no well-conducted studies of intermediate-duration exposure of humans to HCCPD by any route. There are well conducted oral and inhalation intermediateduration studies of HCCPD in animals but no studies using the dermal route. One kinetic study in mice (Dorough and Ranieri 1984) provides some information on the distribution of HCCPD and its metabolites after oral administration. Rats displayed minimal but significant decreases in liver weight after 13 weeks at the lowest vapor concentration tests (0.01 ppm) and in kidney weight (males only) at the highest concentration tested (0.2 ppm) (Rand et al. 1982a). Comparable effects were not observed in the liver with doses of up to 0.4 ppm. A concentration of 0.2 ppm caused a significant increase in the presence of electron-lucent granules in Clara cells from rat lungs; monkey lungs were also affected at 0.2 ppm (Rand

et al. 1982b). The data from this study were used to develop the intermediate-duration inhalation MRL of 2.0 ppb for HCCPD.

A NOAEL of 10 mg/kg/day in rats was identified in a 13-week oral study (Abdo et al. 1984). The LOAEL in this study was 19 mg/kg/day based on hyperplasia of the forestomach, a site that is lacking in humans. Accordingly, the NOAEL of 10 mg/kg/day for forestomach hyperplasia was not selected for use in deriving an MRL. However, nephrosis was present in both mice and rats at higher dose levels. The NOAEL of 19 mg/kg/day for nephrotic lesions in rats was used to derive an intermediate-duration oral MRL of 0.1 mg/kg/day from the study by Abdo et al. (1984). Additional research evaluating intermediate-duration exposures is not recommended at this time.

Chronic-Duration Exposure and Cancer. There are no human studies of chronic-duration exposure to HCCPD or of the tumorigenic effects of this compound. Long-term inhalation studies in animals have been conducted, but the oral and dermal routes have not been studied. There are no available pharmacokinetic data for chronic exposure by any route. There were no effects noted after chronic inhalation exposures except for the changes in the epithelium of the respiratory tract (NTP 1994). A yellow-brown pigment formed in the mucosal epithelium of the nose, trachea, and lungs; hyperplasia was noted in the nose; and there was squamous metaplasia of the larynx in female rats. A critical burden of 20-21 ppm-weeks appeared to be necessary for tissue pigmentation. The occurrence of pigmentation in nasal passages at a LOAEL of 0.01 ppm was used to derive an MRL for chronic-duration inhalation exposure of 0.03 ppb. Because there are differences in the effects of HCCPD after inhalation and oral exposures, a long-term study using the oral route, with emphasis on defects in kidney function and possible ulceration of the stomach lining, may be justified. HCCPD was determined to be noncarcinogenic in rats and mice on the basis of the NTP (1994) bioassay. Occupational exposure data are limited to parameters other than carcinogenicity (Kominsky et al. 1980; Morse et al. 1979). However, in light of the results of the NTP (1994) bioassay, no additional studies of the carcinogenic potential of HCCPD are recommended at this time.

Genotoxicity. HCCPD has been tested in several in vitro and in vitro test systems to determine the compounds ability to cause gene mutation (Greim et al. 1977; Haworth et al. 1983; Litton Bionetics 1978a; Mason et al. 1992; NTP 1994), DNA damage (Matsui et al. 1989), and chromosomal aberrations (Litton Bionetics 1978b; NTP 1994). Because HCCPD appears to lack genotoxic potential in several test

systems evaluating different end points, additional testing is not needed at this time. Although HCCPD is highly cytotoxic, potential human exposures are likely to fall within the concentration ranges already tested.

Reproductive Toxicity. No studies were located regarding the effects of HCCPD on human reproduction. Acute- and intermediate-duration inhalation exposure in rats, mice, and monkeys (NTP 1994; Rand et al. 19821 Rand et al. 1982a) and intermediate-duration oral exposure in rats and mice (Abdo et al. 1984) did not reveal effects on either male or female reproductive organs. Ovarian inflammation was observed in female rats and mice after long-term inhalation exposure, but this may have been due to bacterial infection (NTP 1994). One kinetic study suggests that after a single oral exposure in mice, the testes appeared to have a lower affinity for HCCPD than the ovaries (Dorough and Ranieri 1984). In the absence of information of the effect of the compound on reproductive function, occupational exposure studies and one-generation studies in animals by the inhalation, oral, and dermal routes would be useful in judging whether reproductive toxicity is an area of concern in humans following exposure to HCCPD.

Developmental Toxicity. The effects of HCCPD have been studied on development (up to 2.50 days of age) after oral exposure in mice (Gray et al. 1986; Gray and Kavlock 1984) and rabbits (Murray et al. 1980). The compound did not cause adverse effects on development, even at doses that were maternally toxic (75 mg/kg/day) (Murray et al. 1980). It should also be noted that systemic effects (kidney lesions) have been seen at lower doses (19 mg/kg/day) (Abdo et al. 1984) than those employed in oral developmental studies (45 and 75 mg/kg/day). Based on these considerations and the fact that the compound is not readily absorbed orally, additional testing by this route may not be useful at this time. On the other hand, HCCPD can be absorbed more readily after inhalation contact. No information on developmental toxicity is available by this route, nor is there any kinetic information that supports HCCPD's potential for developmental toxicity. Because environmental exposure to HCCPD may occur in humans at hazardous waste sites, additional animal studies by the inhalation route would enhance our understanding of the potential effects of the compound on human development.

Immunotoxicity. There have been no studies of the immunotoxicity of HCCPD by any exposure route. This compound does not appear to have effects on the spleen or thymus after inhalation or oral exposure, but there are many aspects of immunotoxicity that have not been evaluated (Abdo et al. 1984; NTP 1994; Rand et al. 1982a). A well conducted study of the immunotoxicity of this compound after inhalation exposure is needed. There is no information to suggest that the potential of HCCPD to cause immune effects would be route- or species-specific.

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Neurotoxicity. Inhalation exposure to HCCPD for 3-15 days was associated with complaints of headaches in workers in a waste water treatment plant (Morse et al. 1979). High-concentration acuteduration inhalation exposures (>41.6 ppm) in animals caused tremors (Treon et al. 1955), and longer-term exposures were associated with lethargy (NTP 1994). Diffuse degeneration of the brain was seen in animals following inhalation, oral, and dermal exposures (Treon et al. 1955). Accordingly, detailed investigation of the brain lesions that are observed with HCCPD exposure is justified. Additional neurotoxicity studies evaluating functional end points after inhalation exposure that might be relevant to the occupational setting are needed. In addition, attention should be paid to the effects of HCCPD on unsaturated brain lipids and neurotransmitter derivatives of the aromatic amino acids. These molecules have the potential to react with this conjugated diene. There is no information to suggest that the potential of HCCPD to cause neurological effects would be route- or species-specific.

Epidemiological and Human Dosimetry Studies. No epidemiological studies of HCCPD exposure in humans were identified. This material is a reactant in the manufacture of a number of pesticides (aldrin, dieldrin, chlordane, and heptachlor). The toxicity of these pesticides makes it difficult to evaluate occupational exposure to the HCCPD in workers that manufacture or use these pesticides. There would be problems differentiating the effects of the pesticides from the effects of HCCPD. HCCPD is also used in the manufacture of flame-retardant materials. An epidemiological study of lung, liver, and kidney function in workers who made or used any low-toxicity HCCPD-based, flame-retardant materials would be helpful in establishing cause/effect relationships and in future monitoring of individuals living near hazardous waste sites by possible identifying biomarkers of exposure or effect.

Biomarkers of Exposure and Effect.

Exposure. HCCPD and some unknown metabolites have been excreted in the urine and feces of humans and rats, but only HCCPD is useful as a biomarker because none of the urinary or fecal metabolites have been identified (Dorough and Ranieri 1984; Elia et al. 1983; Mehendale 1977; Yu and Atallah 1981). HCCPD can also be measured in the blood (DeLeon et al. 1980a). No data were located regarding the fate of the chlorine from HCCPD. If isotopic labeling experiments were to identify a unique chlorine-containing metabolite, it might be possible to use extraction from urine and analysis for total organic halogen (TOX) as a biomarker of exposure.

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Effect. Inadequate information is available at the present time regarding biomarkers of effect for acuteand intermediate-duration exposures to HCCPD. Additional tests of liver and renal function in workers exposed to HCCPD would be useful (Kominsky et al. 1980; Morse et al. 1979). With a larger database on HCCPD-associated changes in liver enzymes such as LDH, AST, ALT, AP, and glutamyltransferase (GGT) following HCCPD exposure it might be possible to use these enzymes as biomarkers of effect. The presence of yellow-brown granular pigment in the nasal epithelium appears to be a biomarker for chronic inhalation exposure (NTP 1994).

Absorption, Distribution, Metabolism, and Excretion. Little is known concerning the mechanism of HCCPD absorption or the mechanism of compound metabolism. Data on distribution to tissues in rats demonstrate that absorption occurs through the inhalation, oral, and dermal exposure routes (El Dareer et al. 1983; Lawrence and Dorough 1981,1982). The liver, kidneys, lungs, fat, and ovaries contain the highest amount of label (Dorough and Ranieri 1984; El Dareer et al. 1983; Yu and Atallah 198 1). HCCPD and/or unidentified HCCPD metabolites are excreted in urine, fecal matter, and bile. The metabolites that were extracted and separated by TLC appeared to be largely polar. It has been hypothesized that when exposure occurs by the oral route, much of the HCCPD binds to the contents of the gastrointestinal tract or is metabolized by intestinal microbes and is excreted with fecal matter (Lawrence and Dorough 1982; Yu and Atallah 1981). Additional studies to identify the metabolites of HCCPD are a priority in further understanding HCCPD toxicity. From this information, a metabolic scheme could be constructed. Additional research on the ability of HCCPD to bind to natural products would be helpful in understanding metabolism and for use in developing mitigation measures. Studies using labeled chlorine rather than labeled carbon would also be valuable in elucidating the toxicokinetic properties of HCCPD.

Comparative Toxicokinetics. There is some evidence that there are species differences in toxicity. Monkeys and guinea pigs are less susceptible to inhalation toxicity than rats, mice, and rabbits (Rand et al. 1982a, 1982b; Treon et al. 1955). Rats are more susceptible to oral toxicity than mice (Abdo et al. 1984) and mice are more susceptible to inhalation toxicity than rats (NTP 1994; Treon et al. 19.55). Males appear to be more sensitive than females (Abdo et al. 1984; Rand et al. 1982a).

Before additional studies of comparative toxicokinetics are conducted, it is important to establish the mechanism of toxicity for the most sensitive response. An understanding of the mechanism will make it possible to evaluate the contribution that anatomical and physiological species differences make to the observed differences in HCCPD toxicity. Differences in the diameters of the bronchioles may be the

critical factor in respiratory toxicity. Regardless, there is a need for a well-conducted pharmacokinetic study of HCCPD.

Methods for Reducing Toxic Effects. There are no compound-specific methods for reducing toxic effects. The mitigation measures suggested are general procedures that apply to inhalation and oral toxins as a group and are not unique to HCCPD (Bronstein and Currance 1988; HSDB 1998; Stutz and Janusz 1988). Before research efforts are devoted to compound-specific mitigation techniques, more must be learned concerning the mechanism of toxicity. The toxicity of HCCPD and the lack of compound-specific methods for mitigating toxicity make it important to use proper protective equipment in any situation where HCCPD exposure is possible.

Children's Susceptibility. Data needs relating to developmental effects are discussed above under Developmental Toxicity. There are no data describing the effects of HCCPD exposure either on children or postnatal animals. As pointed out in Chapter 5, there are still hazardous waste scenarios that could result in children's exposure. Should that occur, information on the kinetics of HCCPD in children, and how it differs from that in adults, would be useful. In addition, information on lung and liver toxicity and ocular sensitivity would help define children's susceptibility; these organs are known to be targets in either adult animals or humans.

Studies in animals on the effect of prenatal exposure to HCCPD on postnatal survival and growth suggest that HCCPD has little effect on these parameters (Chernoff and Kavlock 1983; Gray and Kavlock 1984; Gray et al. 1986). The studies that exist are primarily extended screening studies. Pharmacokinetic information, including distribution and metabolism, for the developing human or animal is also lacking, especially information on whether HCCPD or its metabolites cross the placenta or are excreted in breast milk. Since HCCPD appears to target the liver, kidney, and the central nervous system, and since these systems undergo further development in the infant and young child, additional information in these areas would aid in determining whether HCCPD presents a unique risk to children.

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

2.11.3 Ongoing Studies

No ongoing studies of HCCPD were identified.