Toxicological Profile for Hexachlorocyclopentadiene (HCCPD)

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute-, intermediate-, and chronic-duration exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute-, intermediate-, and chronic-duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA Section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health-related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under Section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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July 1999	Final toxicological profile released

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Hexachlorocyclopentadiene (HCCPD) is a highly volatile, reactive liquid. HCCPD is an anthropogenic chemical that has entered the environment primarily because of its use in the production of chlorinated pesticides and flame-retardant chemicals. Restriction of pesticides synthesized from HCCPD has decreased the possibility of exposure to HCCPD and pesticide residues among most members of the general population. Exposure to materials containing HCCPD at hazardous waste sites is still possible.

The potential for persistence of HCCPD in the environment is low. Due to its high vapor pressure, HCCPD is most likely released to the environment through volatilization, especially from surface waters and soils. The main degradation processes expected include photolysis and photooxidation, hydrolysis, and, to a lesser extent, biodegradation. HCCPD in the air is expected to degrade with estimated half-lives ranging from 5 hours to <1 day, which limits its potential for long-range transport. HCCPD in water is expected to degrade rapidly, with half-lives for photolysis of ~2–4 minutes and half-lives for hydrolysis of ~3–5.45 days.

Occupational exposure to HCCPD is most likely to occur via inhalation and dermal routes. The general population may be exposed to HCCPD through inhalation of air contaminated with this chemical and ingestion of drinking water contaminated with this chemical.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the noncancer toxicity of HCCPD in humans is limited to reports by wastewater treatment plant (WWTP) workers and cleanup crew members exposed after an inadvertent industrial release. No occupational studies evaluating health effects in workers exposed during regular manufacture or use of HCCPD are available. Additionally, no observational epidemiological studies of workers or the public are available for HCCPD. Further information on the noncancer toxicity of HCCPD comes from inhalation and oral studies in animals. Data following dermal exposure are very limited in humans and animals.

In laboratory animals, evaluation of available dose-response data by route and duration indicates that sensitive noncancer targets of HCCPD toxicity are respiratory and hematological effects following

inhalation exposure (Figure 1-1). Ovarian inflammation was noted in mice following chronic-duration inhalation exposure; however, the causal relationship between the effect and HCCPD exposure could not be determined due to apparent association with stress-induced susceptibility to an infection in the mouse colony (see Section 2.16). Due to this, female reproductive (ovarian) effects were not considered as potential sensitive effects or included in Figure 1-1. The oral database is very limited; the only potential targets identified below doses associated with lethality include the gastrointestinal tract and kidney (Figure 1-2). General toxicity (decreased body weight) was also observed at similar doses. A systematic review of sensitive target organs/systems by exposure route resulted in the following hazard identification conclusions:

- Respiratory effects are a presumed health effect for humans following inhalation exposure.
- Gastrointestinal effects are a presumed health effect for humans following oral exposure.
- Hematological (red blood cell) effects are suspected health effects for humans following inhalation exposure; white blood cell effects are not classifiable as to the hazard to humans.
- Renal effects are a presumed health effect for humans following oral exposure.

Respiratory Effects (Inhalation Route). The respiratory tract is sensitive to HCCPD toxicity after inhalation exposure; findings are attributed to compound reactivity upon contact with respiratory tissues at the portal of entry. WWTP workers and cleanup crew members reported respiratory symptoms including coughing, nose and throat irritation, and difficulty breathing following inhalation of HCCPD vapors from an inadvertent industrial discharge (Kominsky et al. 1980; Morse et al. 1979). Acute-duration inhalation exposure studies in animals identified increased or labored respiration or abnormal respiratory patterns at concentrations ≥0.5 ppm (Alexander et al. 1980a; Jackson and Hardy 1986, 1987; Rand et al. 1982a). Sneezing and altered respiratory rates/patterns were observed in rodents at intermediate-duration exposures of ≥0.56 ppm (Clark 1981; NTP 1994). Histopathological evaluation identified changes to the nasal, tracheobronchial, and/or pulmonary epithelium in rats and mice at ≥0.385 and ≥0.2 ppm, respectively; these changes consisted of inflammation (suppurative or necrotizing) or metaplasia at nonlethal concentrations (Clark 1981; NTP 1994) and hemorrhaging or necrosis at lethal concentrations (NTP 1994). Nasal and pulmonary lesions were observed in mice exposed to 0.2 ppm HCCPD for 2 years, while no lesions were observed in rats under the same exposure conditions (NTP 1994).

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to HCCPD

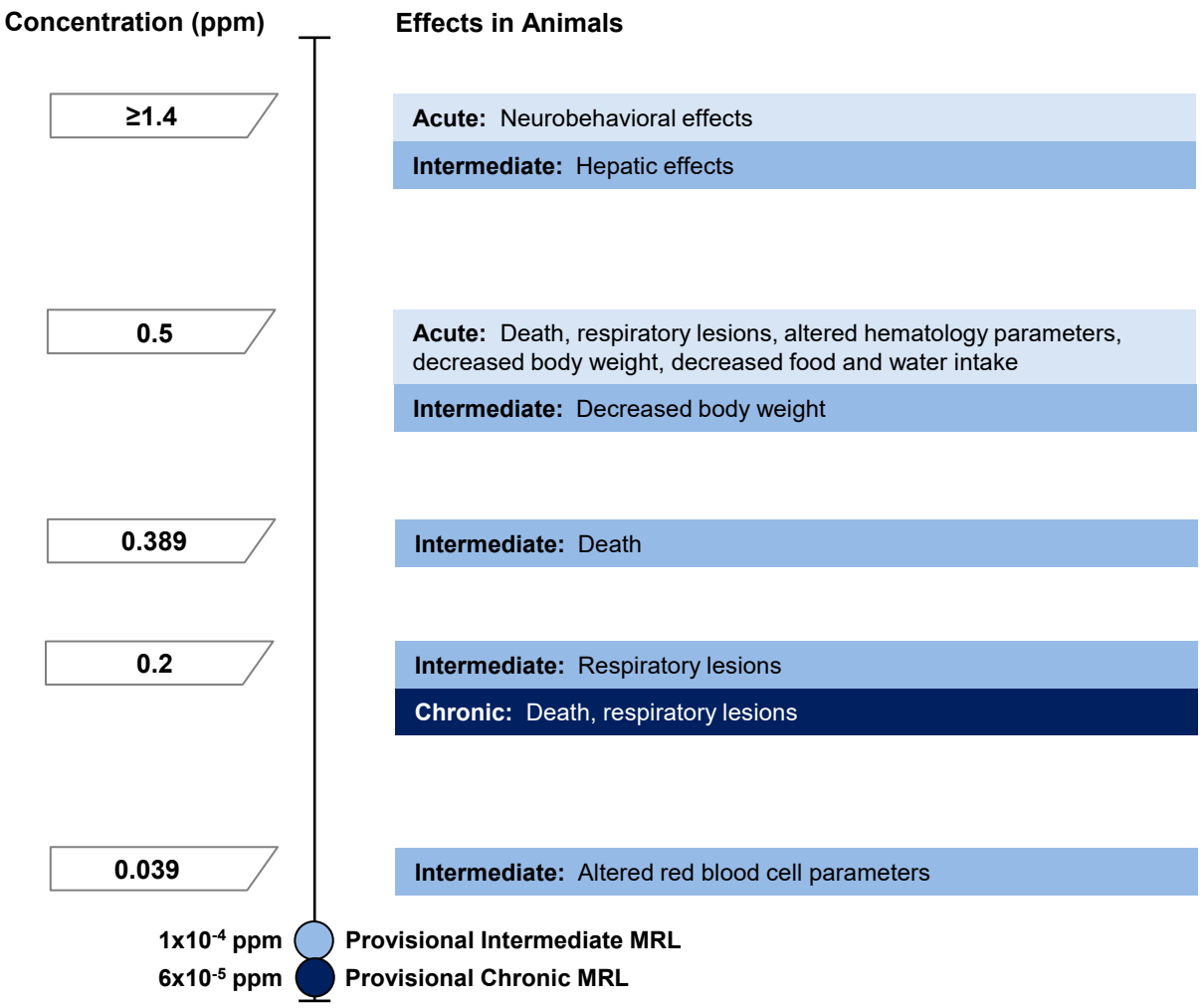
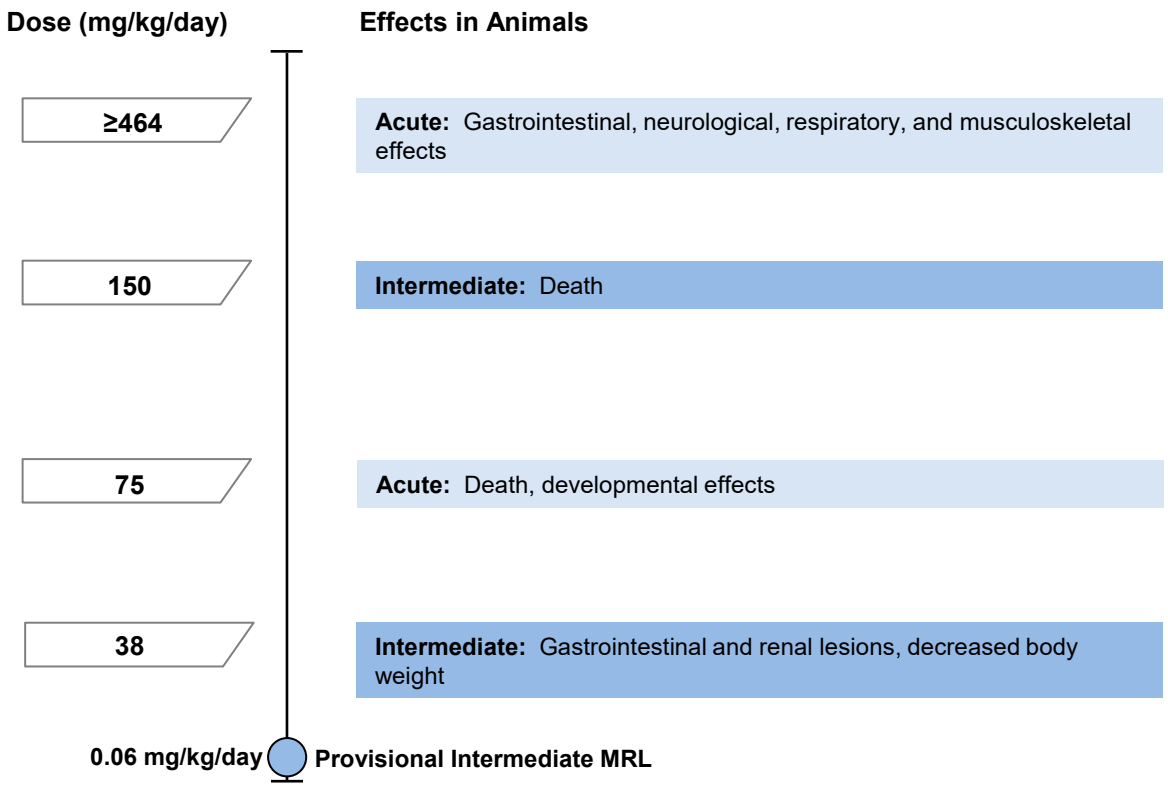


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to HCCPD



Gastrointestinal Effects (Oral Route). The gastrointestinal tract is sensitive to HCCPD after oral exposure; findings are attributed to compound reactivity upon contact with gastrointestinal tissues at the portal of entry. No human data are available evaluating potential gastrointestinal effects of HCCPD following oral exposure. Diarrhea was reported in rodents administered single oral doses of ≥464 mg/kg (Dean 1977; Gardner 1986a); this effect was not reported at lower doses in intermediate-duration studies up to 150 mg/kg/day in rats or 300 mg/kg/day in mice (Abdo et al. 1984). In the only available intermediate-duration oral study in animals, focal inflammation and epithelial hyperplasia of the forestomach were observed in rats and mice exposed to ≥38 and ≥75 mg/kg/day, respectively (Abdo et al. 1984). While humans lack a forestomach, analogous lesions could occur in the proximate portions of the human gastrointestinal tract, including oral, pharyngeal, and/or esophageal tissues, due to portal-of-entry reactivity following oral exposure to HCCPD.

Hematological Effects (Inhalation Route). No changes in blood counts were observed in workers exposed to HCCPD at a WWTP following an inadvertent industrial discharge (Kominsky et al. 1980). Alterations in red blood cell parameters, primarily elevated red blood cell counts and hemoglobin levels,

were reported in rats following acute- and intermediate-duration inhalation exposure to HCCPD at concentrations of 0.5 and ≥0.14 ppm, respectively (Clark 1981; NTP 1994; Rand et al. 1982a); similar findings were observed in mice at intermediate-duration inhalation concentrations ≥0.039 ppm (NTP 1994). Based on the absence of histopathological changes to bone marrow, observed red blood cell effects have been hypothesized to be a compensatory response to hemorrhagic damage to the lungs following inhalation exposure rather than direct effects on hematopoiesis (Rand et al. 1982a). However, rats showed sex-specific findings (females were less sensitive), and there were inconsistencies between the main 13-week (comprehensive) study and the 13-week specialized hematological study conducted by NTP (1994). In mice, findings were limited and inconsistent with respect to alterations in red blood cell parameters after exposure for 13–42 weeks (NTP 1994). Additionally, no hematological effects were observed in the 2-year inhalation studies in rats or mice at concentrations up to 2 ppm (NTP 1994). No consistent effects on white blood cell parameters were observed with inhalation exposures in animal studies (Clark 1981; NTP 1994; Rand et al. 1982a).

Renal Effects (Oral Route). No human data are available to assess the potential for HCCPD to cause renal toxicity. In the only available oral study in animals evaluating the kidney, HCCPD produced toxic nephrosis in male and female rats at ≥38 mg/kg/day and in female mice at ≥75 mg/kg/day (Abdo et al. 1984). Toxic nephrosis was not identified in male mice, but acute tubular necrosis was identified in male mice exposed to 300 mg/kg/day. Available toxicokinetic data indicate that HCCPD and/or its metabolites distribute to the kidneys in both rats and mice after oral dosing; however, the highest distribution is to the kidney in the rat and to the liver in the mouse (Dorough and Ranieri 1984). This observed difference in distribution may explain the observed species sensitivity.

Cancer Effects. There were no data from studies in humans pertaining to the carcinogenicity of HCCPD. The National Toxicology Program (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 for 26 or 42 weeks and evaluated at 2 years, the incidence was within the historical range for the laboratory and was not elevated 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 exposure-related since the incidences were similar to the historical control means, were within the historical control range, or did not exhibit a dose-dependency. Based on these results, the U.S. Environmental Protection Agency (EPA) determined that HCCPD is not likely to be a human carcinogen by the inhalation route (IRIS 2003). The International

Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of HCCPD (IARC 2025). The U.S. Department of Health and Human Services (HHS) has not evaluated a cancer classification category for HCCPD (NTP 2021).

1.3 MINIMAL RISK LEVELS (MRLs)

As illustrated in Figure 1-3, available inhalation data for HCCPD suggest that the respiratory and hematological systems are the most sensitive targets for toxicity. The inhalation database was considered adequate for derivation of provisional intermediate- and chronic-duration MRLs. As discussed in Section 1.2, ovarian effects observed in the chronic-duration mouse study were not considered as potential sensitive effects due to potential confounding by a utero-ovarian infection (see Appendix A for details). Therefore, female reproductive effects are not included in Figure 1-3.

As illustrated in Figure 1-4, gastrointestinal, renal, and body weight effects appear to be the most sensitive targets of HCCPD toxicity following oral exposure. The oral database was considered adequate for derivation of a provisional intermediate-duration MRL for HCCPD. The acute- and chronic-duration oral data were insufficient for deriving MRLs.

The provisional MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of HCCPD – Inhalation

Available data indicate that the hematological and respiratory systems are the most sensitive targets of HCCPD inhalation exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals. No reliable dose response data were available for humans.

Figure 1-4. Summary of Sensitive Targets of HCCPD – Oral

Available data indicate that the gastrointestinal tract, renal system, and body weight are the most sensitive targets of HCCPD oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

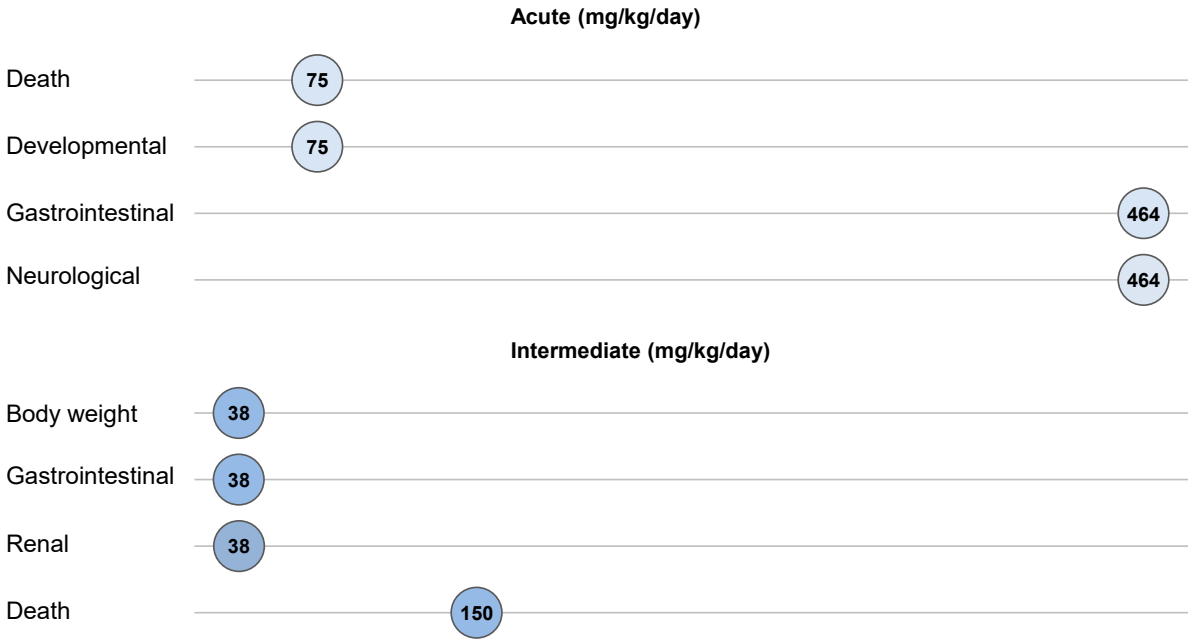


Table 1-1. Provisional Minimal Risk Levels (MRLs) for HCCPD[a]

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	None	–	–	–	–	–
	Intermediate	**$1x10^{-4}$ ppm** ($1x10^{-3}$ mg/m^3)	Nasal suppurative inflammation in rats	$NOAEL_{HEC}$	0.00344 ppm	UF: 30	NTP 1994
	Chronic	**$6x10^{-5}$ ppm** ($7x10^{-4}$ mg/m^3)	Nasal suppurative inflammation in mice	$BMCL_{HEC}$	0.0019 ppm	UF: 30	NTP 1994
Oral	Acute	None	–	–	–	–	–
	Intermediate	**0.06 mg/kg/day**	Combined incidence of forestomach epithelial hyperplasia and focal inflammation in rats	$BMDL_{ADJ}$	5.5 mg/kg/day	UF: 100	Abdo et al. 1984: Velsicol 1981b
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.

ADJ = adjusted for intermittent exposure; BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 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. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

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 by health effects. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to HCCPD, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to HCCPD was also conducted; the results of this review are presented in Appendix C.

Human and animal inhalation studies are presented in Table 2-1 and Figure 2-2, animal oral studies are presented in Table 2-2 and Figure 2-3, and human and animal dermal studies are presented in Table 2-3. Due to the limited nature of the database, several older studies lacking quantitative data reporting are included in Chapter 2 to provide data potentially relevant for hazard identification; however, data that are only reported qualitatively (i.e., histopathological data lacking incidence data) are not included in Tables 2-1, 2-2, or 2-3.

Levels of significant exposure (LSEs) 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. Effects have been classified into “less serious LOAELs” or “serious LOAELs (SLOAELs).” “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 endpoint 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 endpoints. 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.

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

The health effects of HCCPD have been evaluated in 2 human studies and 68 animal studies. As illustrated in Figure 2-1, most of the health effect data come from dermal and inhalation studies in animals. In both human and animal studies, the ocular effects observed in HCCPD inhalation studies are likely attributable to direct contact with HCCPD vapors. Therefore, ocular effects from inhalation studies are counted as dermal exposure in Figure 2-1 and are listed in the dermal LSE table.

The available human studies were predominantly focused on evaluation of dermal, ocular, and respiratory effects in WWTP workers and cleanup crew members following an inadvertent industrial release of HCCPD. For these studies, exposure was evaluated as HCCPD vapor levels in air.

For animal data, inhalation and oral studies are available for most health effects. Acute-, intermediate-, and chronic-duration studies are available for the inhalation route, while only acute- and intermediate-duration studies are available for the oral route. The dermal animal database is mostly limited to ocular and dermal effects, largely following exposure to HCCPD vapor. The most examined endpoints in animal studies were death, respiratory, hepatic, renal, and ocular.

A systematic review was conducted on potential targets of HCCPD exposure, which included respiratory and hematological effects for inhalation exposure and gastrointestinal and renal effects following oral exposure (see Appendix C for details).

- **Respiratory Effects.** Respiratory effects are a presumed health effect associated with HCCPD exposure via inhalation based on inadequate evidence in humans and a high level of evidence in animals. WWTP workers and cleanup crew members reported respiratory symptoms including coughing and respiratory tract irritation after exposure to HCCPD vapors following an inadvertent industrial release. Several animal studies have reported altered respiratory patterns following single or repeated exposures to HCCPD. Upon histopathological examination, nonneoplastic lesions of the nasal, tracheobronchial, and pulmonary regions were consistently observed in mice and rats exposed for intermediate durations to concentrations ≥0.2 or ≥0.385 ppm, respectively. Chronic-duration exposure to 0.2 ppm resulted in similar lesions in mice, but not rats. Observed lesions (suppurative, serous, or necrotizing inflammation; epithelial hyperplasia) are consistent with chronic irritation at the portal of entry.

- **Gastrointestinal Effects.** Gastrointestinal effects are a presumed health effect associated with HCCPD exposure via oral exposure based on no human data and a high level of evidence in animal studies. Diarrhea was reported in rodents following exposure to high acute doses ≥464 mg/kg. Forestomach lesions (epithelial hyperplasia and focal inflammation) were observed in rats and mice following intermediate-duration exposures of ≥38 and ≥75 mg/kg/day, respectively. Although humans lack a forestomach, effects associated with HCCPD are consistent with chronic irritation at the portal of entry. Thus, the upper gastrointestinal tract is presumably vulnerable to toxicity following oral exposure to HCCPD.

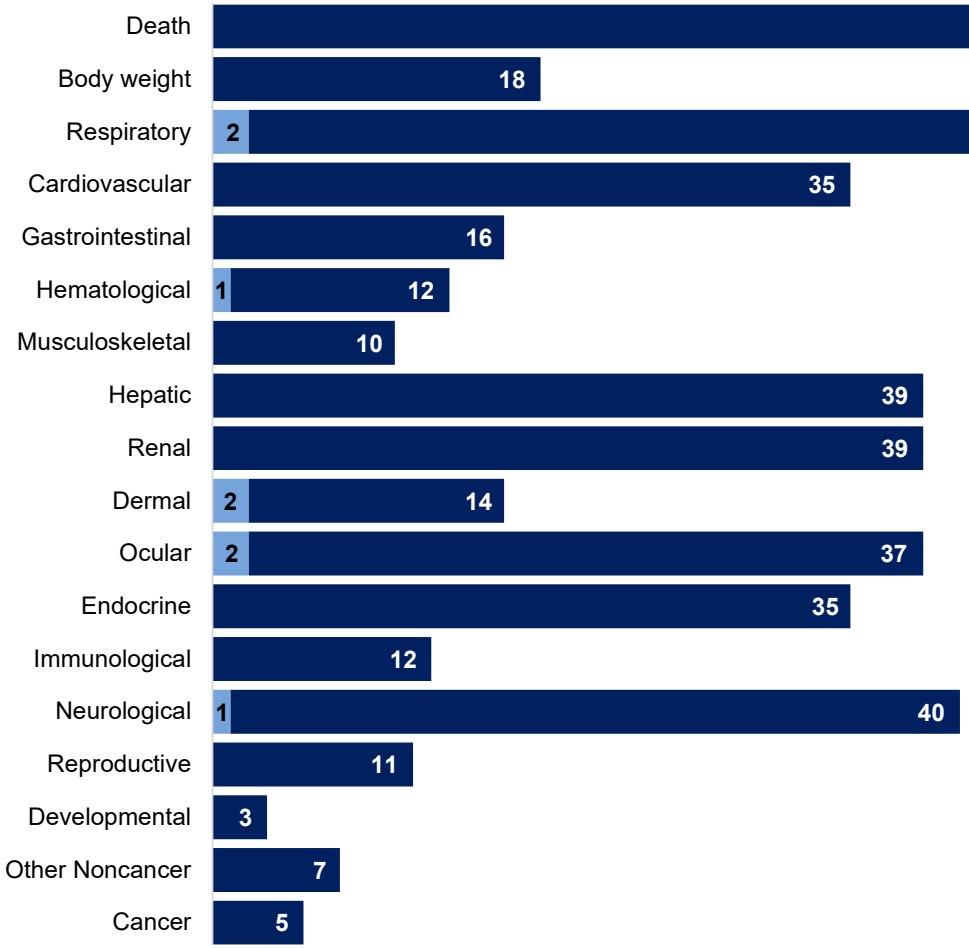
- **Hematological Effects.** Hematological effects, specifically red blood cell parameters, are a suspected health effect associated with HCCPD exposure via inhalation based on inadequate data in humans and a moderate level of evidence in animals. No changes in blood counts were observed in WWTP workers after exposure to HCCPD vapors following an inadvertent industrial release. Several acute- and intermediate-duration inhalation studies reported altered red blood cell parameters (e.g., increased hemoglobin, red blood cell counts, and packed cell volume) at concentrations as low as 0.14 and 0.039 ppm in rats and mice, respectively; however, these findings were not consistent across sexes or species nor were they reproducible in targeted analyses by the same researchers. Observed red blood cell effects may be attributable to compromised gas exchange following tissue damage to the respiratory tract, as no evidence of bone marrow hyperplasia was observed in rodents following repeated inhalation exposure to HCCPD. White blood cell effects are not classifiable as to the hazard to humans based on no data in humans and inadequate evidence in animals. Available studies did not find consistent evidence of alterations in white blood cell parameters in rats or mice following intermediate- or chronic-duration inhalation exposure to HCCPD.

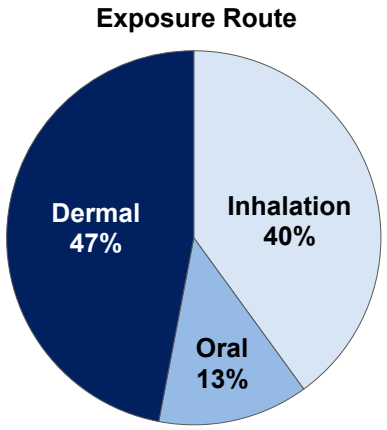
- **Renal Effects.** Renal effects are a presumed health effect associated with oral exposure to HCCPD based on no human data and a high level of evidence in animal studies. Renal lesions, specifically toxic nephrosis, were observed in rats and mice following intermediate-duration exposures to ≥38 and ≥75 mg/kg/day, respectively. Acute tubular necrosis was observed in male mice at a higher dose (300 mg/kg/day). Available toxicokinetic data indicate that HCCPD and/or

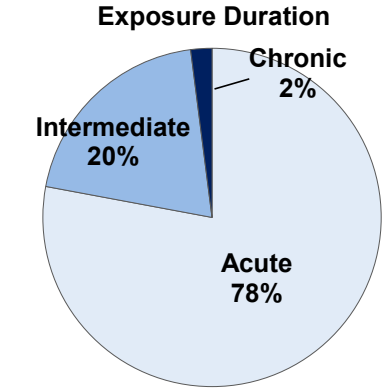
its metabolites distribute to the kidneys of both rats and mice after oral dosing; however, it will accumulate to a higher degree in rats.

Figure 2-1. Overview of the Number of Studies Examining HCCPD Health Effects*

Most studies examined the potential death, respiratory, neurological, renal, hepatic, and ocular effects of HCCPD
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 70 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Alexander et al. 1980a; Rand et al. 1982a									
1	Rat (Sprague-Dawley) 10 M, 10 F	1–2 weeks 5 days/week 6 hours/day (WB)	0, 0.022, 0.11, 0.5	LE, CS, BW, FI, HE, BC, GN, OW, HP	Death			0.5 M	10/10 died or were sacrificed in moribund condition
					Bd wt	0.11		0.5	Decreased terminal body weight in females (29%) and males (32%)
					Resp	0.11		0.5	Labored respiration; increased absolute lung weight; bronchiole inflammation, hyperplasia, and epithelial erosion
					Cardio	0.5			
					Hemato	0.11	0.5		Males: total white blood cell and lymphocyte counts reduced Females: neutrophils increased Both: red blood cell count, packed cell volume, and hemoglobin increased
					Hepatic	0.5			
					Renal	0.5			
					Immuno	0.5			
					Neuro	0.5			
					Other noncancer	0.11	0.5		Decreased food and water intake
Jackson and Hardy 1986									
2	Rat (Wistar) 5 M, 5 F	1 hour (WB)	0, 1.67, 2.38, 3.53, 6.25, 8.30	LE, CS, BW, FI, WI, OW, GN	Death			3.69	LC_{50}
					Bd wt	1.67		2.38	Decreased body weight at death or scheduled sacrifice (3-weeks post exposure) in males (41%) and females (26%)
					Resp		1.67		Abnormal respiratory pattern
					Other noncancer		1.67		Decreased food consumption

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Jackson and Hardy 1987									
3	Rat (Wistar) 5 M, 5 F	4 hours (WB)	0, 1.68, 1.83, 3.31, 3.47	LE, CS, BW, FI, WI, GN, OW	Death			2.9	LC_{50}
					Bd wt			1.68 M	23% decreased body weight at scheduled sacrifice (4 weeks post exposure)
						1.68 F		1.83 F	24% decreased body weight at death or scheduled sacrifice (4 weeks post exposure)
					Resp		1.68		Abnormal respiratory pattern
					Other noncancer		1.68		Decreased food consumption
OxyChem 1972									
4	Rat (Carworth CFE) 10 M	4 hours (WB)	176, 1,760	LE, CS, GN	Death			176	10/10 died within 48 hours
Rand et al. 1982a									
5	Rat (Sprague-Dawley) 10 M, 10 F	4 hours (WB)	0.28, 1.4, 2.5, 3.1, 3.3, 3.4, 4, 5.8	LE, CS, BW	Death			3.5 F	LC_{50}
								1.6 M	LC_{50}
					Bd wt	0.28			
							1.4 F		17% body weight loss
								1.4 M	25% body weight loss
					Neuro	0.28	1.4	5.8	LOAEL: Sedation SLOAEL: Ataxia
Treon et al. 1955									
6	Rat 4 NS	2 days 7 hours/day (WB)	3.2	LE, CS, GN	Death			3.2	4/4 died
Treon et al. 1955									
7	Rat 4 NS	3 days 7 hours/day (WB)	1.4	LE, CS, GN	Death			1.4	3/4 died

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Treon et al. 1955									
8	Rat 4 NS	2.6–3.6 hours (WB)	1.4, 3.1, 7.1, 12.4, 12.7, 46.5, 56.9, 70.4	LE, CS, GN	Death			3.1	2/4 died
Treon et al. 1955									
9	Rat 4 NS	7 hours (WB)	1.5, 3.2, 6.7	LE, CS, GN	Death			3.2	3/4 died
Treon et al. 1955									
10	Rat 4 NS	5 days 7 hours/day (WB)	0.33, 1.0, 1.6	LE, CS, GN	Death			1	4/4 died
Treon et al. 1955									
11	Rat 4 NS	0.25–1.25 hours (WB)	1.4, 1.5, 3.1, 7.2. 13.0, 13.8, 19.4, 20.0, 20.2, 69.1, 69.2	LE, CS, GN	Death			7.2	2/4 died
Treon et al. 1955									
12	Rat 4 NS	4 hours (WB)	73.6	LE, CS, GN	Death			73.6	4/4 died
Treon et al. 1955									
13	Mouse 5 NS	0.25–1.25 hours (WB)	1.4, 1.5, 3.1, 7.2, 13.0, 13.8, 19.4, 20.0, 20.2, 69.1, 69.2	LE, CS, GN	Death			7.2	5/5 died
Treon et al. 1955									
14	Mouse 5 NS	4 hours (WB)	73.6	LE, CS, GN	Death			73.6	5/5 died

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Treon et al. 1955									
15	Mouse 5 NS	2 days 7 hours/day (WB)	3.2	LE, CS, GN	Death			3.2	4/5 died
Treon et al. 1955									
16	Mouse 5 NS	3 days 7 hours/day (WB)	1.4	LE, CS, GN	Death			1.4	5/5 died
Treon et al. 1955									
17	Mouse 5 NS	7 hours (WB)	1.5, 3.2, 6.7	LE, CS, GN	Death			1.5	4/5 died
Treon et al. 1955									
18	Mouse 5 NS	2.6–3.6 hours (WB)	1.4, 3.1, 7.1, 12.4, 12.7, 46.5, 56.9, 70.4	LE, CS, GN	Death			3.1	4/5 died
Treon et al. 1955									
19	Mouse 5 NS	5 days 7 hours/day (WB)	0.33, 1.0, 1.6	LE, CS, GN	Death			1	4/5 died
Treon et al. 1955									
20	Rabbit 3 NS	4 hours (WB)	73.6	LE, CS, GN	Death			73.6	3/3 died
Treon et al. 1955									
21	Rabbit 3 NS	3 days 7 hours/day (WB)	1.4	LE, CS, GN	Death			1.4	3/3 died
Treon et al. 1955									
22	Rabbit 3 NS	5 days 7 hours/day (WB)	1, 1.6	LE, CS, GN	Death			1	3/3 died

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Treon et al. 1955									
23	Rabbit 3 NS	2.6–3.6 hours (WB)	1.4, 3.1, 7.1, 12.4, 12.7, 46.5, 56.9, 70.4	LE, CS, GN	Death			1.4	2/3 died
Treon et al. 1955									
24	Rabbit 3 NS	7 hours (WB)	1.5, 3.2, 6.7	LE, CS, GN	Death			1.5	3/3 died
Treon et al. 1955									
25	Rabbit 3 NS	0.25–1.25 hours (WB)	1.4, 1.5, 3.1, 7.2. 13.0, 13.8, 19.4, 20.0, 20.2, 69.1, 69.2	LE, CS, GN	Death			3.1	2/3 died
Treon et al. 1955									
26	Rabbit 3 NS	2 days 7 hours/day (WB)	3.2	LE, CS, GN	Death			3.2	3/3 died
INTERMEDIATE EXPOSURE									
Alexander et al. 1980b; Rand et al. 1982a, 1982b									
27	Monkey (Cynomolgus) 6 M, 6 F	14 weeks 5 days/week 6 hours/day (WB)	0, 0.01, 0.05, 0.2	LE, CS, BW, FI, HE, BC, UR, OP, GN, OW, HP, OF	Bd wt	0.2			
					Resp	0.2			
					Cardio	0.2			
					Gastro	0.2			
					Hemato	0.2			
					Musc/skel	0.2			
					Hepatic	0.2			
					Renal	0.2			
					Ocular	0.2			
					Endocr	0.2			
					Immuno	0.2			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Neuro	0.2			
					Repro	0.2			
					Other noncancer	0.2			
Alexander et al. 1980b; Huntingdon Research Centre 1980; Rand et al. 1982a, 1982b									
28	Rat (Sprague-Dawley) 40 M, 40 F	14 weeks 5 days/week 6 hours/day (WB)	0, 0.01, 0.05, 0.2	LE, CS, BW, FI, WI, HE, BC, UR, OP, GN, OW, HP	Bd wt	0.2			
					Resp	0.2			
					Cardio	0.2			
					Gastro	0.2			
					Hemato	0.2			
					Musc/skel	0.2			
					Hepatic	0.2			
					Renal	0.2			
					Ocular	0.2			
					Endocr	0.2			
					Immuno	0.2			
					Neuro	0.2			
					Repro	0.2			
					Other noncancer	0.2			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Clark 1981									
29	Rat (Wistar) 18 M, 18 F	30 weeks 5 days/week 6 hours/day (WB)	0, 0.06, 0.14, 0.56	LE, CS, BW, FI, WI, HE, BC, UR, GN, OW, HP	Death			0.56	4/18 males and 2/18 females died
					Bd wt	0.56			
					Resp	0.14	0.56 F	0.56 M	Females: perivascular/peribronchiolar inflammatory cell infiltration; sneezing Males: bronchiolar epithelial ulceration/thinning and perivascular/peribronchiolar inflammatory cell infiltration; sneezing
					Cardio	0.56			
					Gastro	0.56			
					Hemato	0.14 F	0.56 F		Decreased lymphocyte counts
						0.06 M	0.14 M		Increased red blood cell counts, hemoglobin, hematocrit, and neutrophil counts; decreased lymphocyte percentage
					Musc/skel	0.56			
					Hepatic	0.56			
					Renal	0.56			
					Dermal	0.56			
					Ocular	0.56			
					Endocr	0.56			
					Immuno	0.56			
					Neuro	0.56			
					Repro	0.56			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Other noncancer	0.56			
NTP 1994									
30	Rat (Fischer-344) 10 M, 10 F	13 weeks 5 days/week 6 hours/day (WB)	0, 0.039, 0.146, 0.385, 0.941, 2.065	LE, CS, BW, HE, BC, GN, OW, HP	Death			0.941	100% mortality during first 4 weeks
					Bd wt	0.385			
					Resp	0.385 F			
						0.146[b] M	0.385 M		Nasal squamous metaplasia and suppurative inflammation; suppurative and necrotizing inflammation of the bronchus/bronchiole; increased absolute and relative lung weights
								0.941	Increased respiration rate and mouth breathing; suppurative inflammation and hemorrhaging in the alveolus; necrotizing inflammation of the nose, larynx, trachea, and bronchus/bronchiole
					Cardio	0.385			
					Gastro	0.385			
					Hemato	0.146	0.385		Males: increased packed cell volume, hemoglobin, red blood cell count, and MCHC Females: decreased red blood cell count and increased MCV
					Musc/skel	0.385			
					Hepatic	0.385			
					Renal	0.385			
					Endocr	0.385			
					Immuno	0.385			
					Neuro	0.385			
					Repro	0.385			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1994									
31	Rat (Fischer-344) 20 M, 20 F	13 weeks 5 days/week 6 hours/day (WB)	0, 0.039, 0.385, 2.065	LE, HE, BC, UR	Death			2.065	100% mortality
					Hemato	0.039	0.385		Males: increased MCV; Females: increased MCV, packed cell volume, hemoglobin, and red blood cell count
					Hepatic	0.385	2.065		Increased AST
					Renal	2.065			
NTP 1994									
32	Mouse (B6C3F1) 10 M	42 weeks 5 days/week 6 hours/day (WB)	0, 0.5	LE, CS, BW, GN, OW, HP	Death			0.5	14% decreased survival at 45 weeks
					Bd wt		0.5		Decreased body weight (19%) and body weight gain (42%) at the end of the exposure period
					Resp		0.5		Suppurative inflammation of the nose, trachea, and lungs
					Gastro	0.5			
					Hepatic	0.5			
					Renal	0.5			
					Endocr	0.5			
					Immuno	0.5			
					Repro	0.5			
NTP 1994									
33	Mouse (B6C3F1) 20 M, 20 F	13 weeks 5 days/week 6 hours/day (WB)	0, 0.039, 0.389, 2.142	LE, HE, BC, UR	Death			2.142	100% mortality
					Hemato		0.039 F		Increased MCHC
						0.039 M	0.389 M		Increased MCHC
					Hepatic	2.142			
					Renal	2.142			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1994									
34	Mouse (B6C3F1) 10 M	26 weeks 5 days/week 6 hours/day (WB)	0, 0.5	LE, CS, BW, GN, OW, HP	Bd wt	0.5			
					Resp		0.5		Nasal suppurative inflammation
NTP 1994									
35	Mouse (B6C3F1) 10 M	33 weeks 5 days/week 6 hours/day (WB)	0, 0.2	LE, CS, BW, GN, OW, HP	Bd wt	0.2			
					Resp		0.2		Nasal suppurative inflammation
					Gastro	0.2			
					Hepatic	0.2			
					Renal	0.2			
					Immuno	0.2			
					Neuro	0.2			
					Repro	0.2			
NTP 1994									
36	Mouse (B6C3F1) 10 M, 10 F	13 weeks 5 days/week 6 hours/day (WB)	0, 0.039, 0.146, 0.389, 0.949, 2.142	LE, CS, BW, HE, BC, OW, HP	Death			0.949 F	10/10 died
								0.389 M	5/10 died
					Bd wt	0.389			
					Resp	0.146	0.389		Females: focal serous or suppurative inflammation of the nose Males: squamous metaplasia in the trachea, focal serous or suppurative inflammation of the nose
					Cardio	0.389			
					Gastro	0.389			
					Hemato	0.146 F	0.389 F		Decreased MCV
						0.389 M			
					Musc/skel	0.389			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic	0.389			
					Renal	0.389			
					Endocr	0.389			
					Immuno	0.389			
					Neuro	0.389			
					Repro	0.389			
CHRONIC EXPOSURE									
NTP 1994									
37	Rat (Fischer-344) 50 M, 50 F	104 weeks 5 days/week 6 hours/day (WB)	0, 0.01, 0.05, 0.2	LE, CS, BW, UR, GN, OW, HP	Bd wt	0.2			
					Resp	0.2			
					Cardio	0.2			
					Gastro	0.2			
					Hemato	0.2			
					Musc/skel	0.2			
					Hepatic	0.2			
					Renal	0.2			
					Dermal	0.2			
					Endocr	0.2			
					Immuno	0.2			
					Neuro	0.2			
					Repro	0.2			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1994									
38	Mouse (B6C3F1) 50 M, 50 F	103 weeks 5 days/week 6 hours/day (WB)	0, 0.01, 0.05, 0.2	LE, BW, GN, OW, HP	Death			0.2 F	57% mortality
					Bd wt	0.2			
					Resp	0.05[c]	0.2		Males: nasal suppurative inflammation, alveolar epithelium hyperplasia, and suppurative inflammation of the lung Females: nasal suppurative inflammation ($BMCL_{10}$ for nasal suppurative inflammation in females = 0.0052 ppm)[c]
					Cardio	0.2			
					Gastro	0.2			
					Hemato	0.2			
					Musc/skel	0.2			
					Hepatic	0.2			
					Renal	0.2			
					Dermal	0.2			
					Endocr	0.2			
					Immuno	0.2			
					Neuro	0.2			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Repro	0.01 F	0.05 F	0.2 F	LOAEL: Suppurative inflammation of the ovaries SLOAEL: Severe ovarian suppurative inflammation (associated with increased lethality)
						0.2 M			

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive a provisional intermediate-duration inhalation MRL of $1x10^{-4}$ ppm based on a NOAEL of 0.146 ppm, which was converted into a $NOAEL_{HEC}$ of 0.00344 ppm and divided by an uncertainty factor of 30 (10 for human variability and 3 for animal to human extrapolation after dosimetric adjustment).
[c]Used to derive a provisional chronic-duration inhalation MRL of $6x10^{-5}$ ppm based on a $BMCL_{10}$ of 0.052 ppm, which was converted into a $BMCL_{HEC}$ of 0.0019 ppm and divided by an uncertainty factor of 30 (10 for human variability and 3 for animal to human extrapolation after dosimetric adjustment).

Green shading indicates the study selected for derivation of provisional inhalation MRLs.

AST = aspartate aminotransferase; BC = blood chemistry; Bd wt or BW = body weight; BMCL = benchmark concentration lower confidence limit; $BMCL_{10}$ = 95% lower confidence limit on the benchmark concentration (subscripts denote benchmark response: i.e., 10 = concentration associated with 10% extra risk); Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; HEC = human equivalent concentration; Hemato = hematological; HP = histopathology; Immuno = immunological; LC_{50} = median lethal concentration; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MRL = Minimal Risk Level; Musc/skeletal = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OP = ophthalmology; OW = organ weight; Repro = reproductive; Resp = respiratory; SLOAEL = serious lowest-observed-adverse-effect level; UR = urinalysis; (WB) = whole body; WI = water intake

Figure 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Inhalation
Acute (≤14 days)

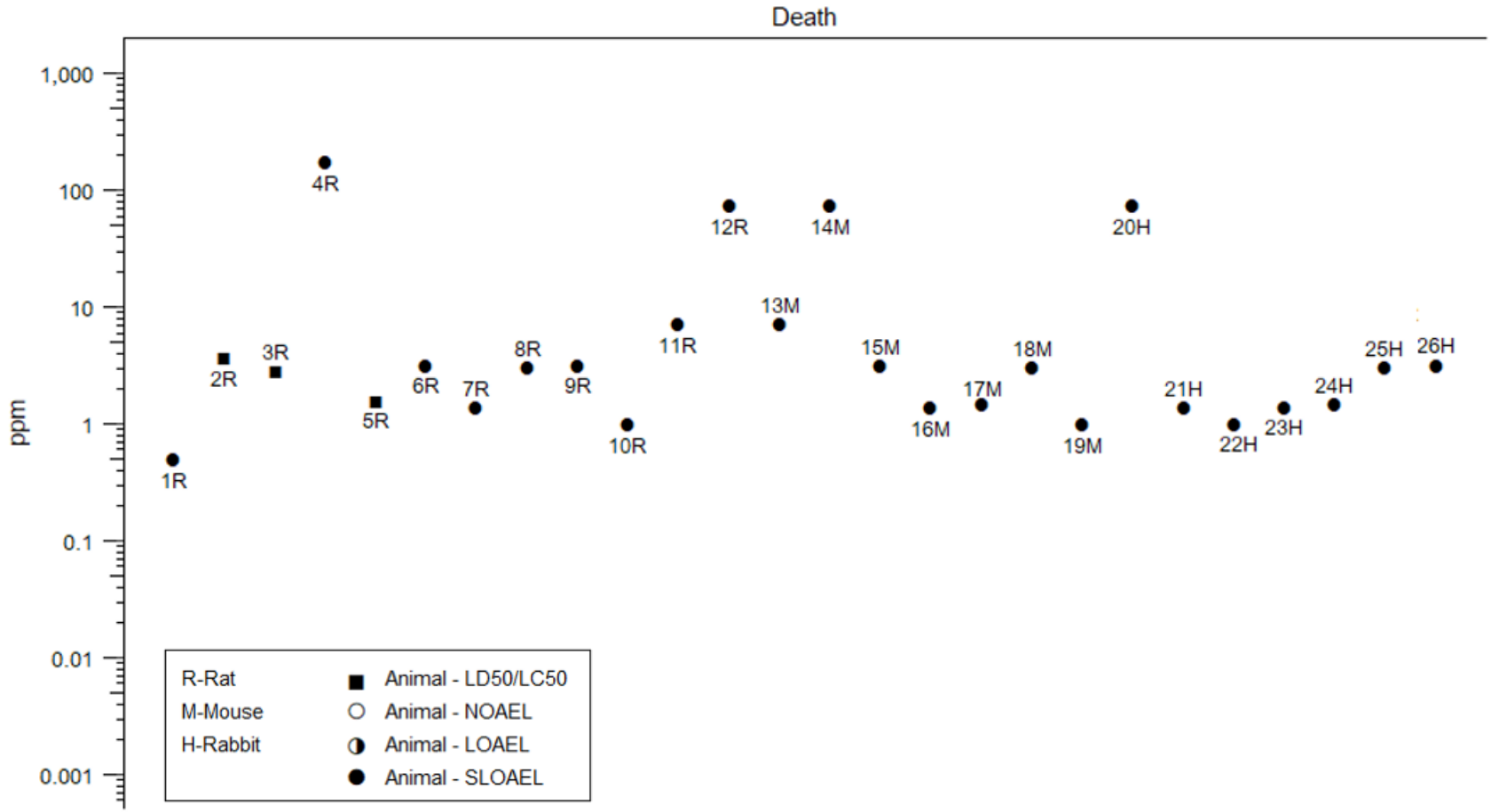


Figure 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Inhalation
Acute (≤14 days)

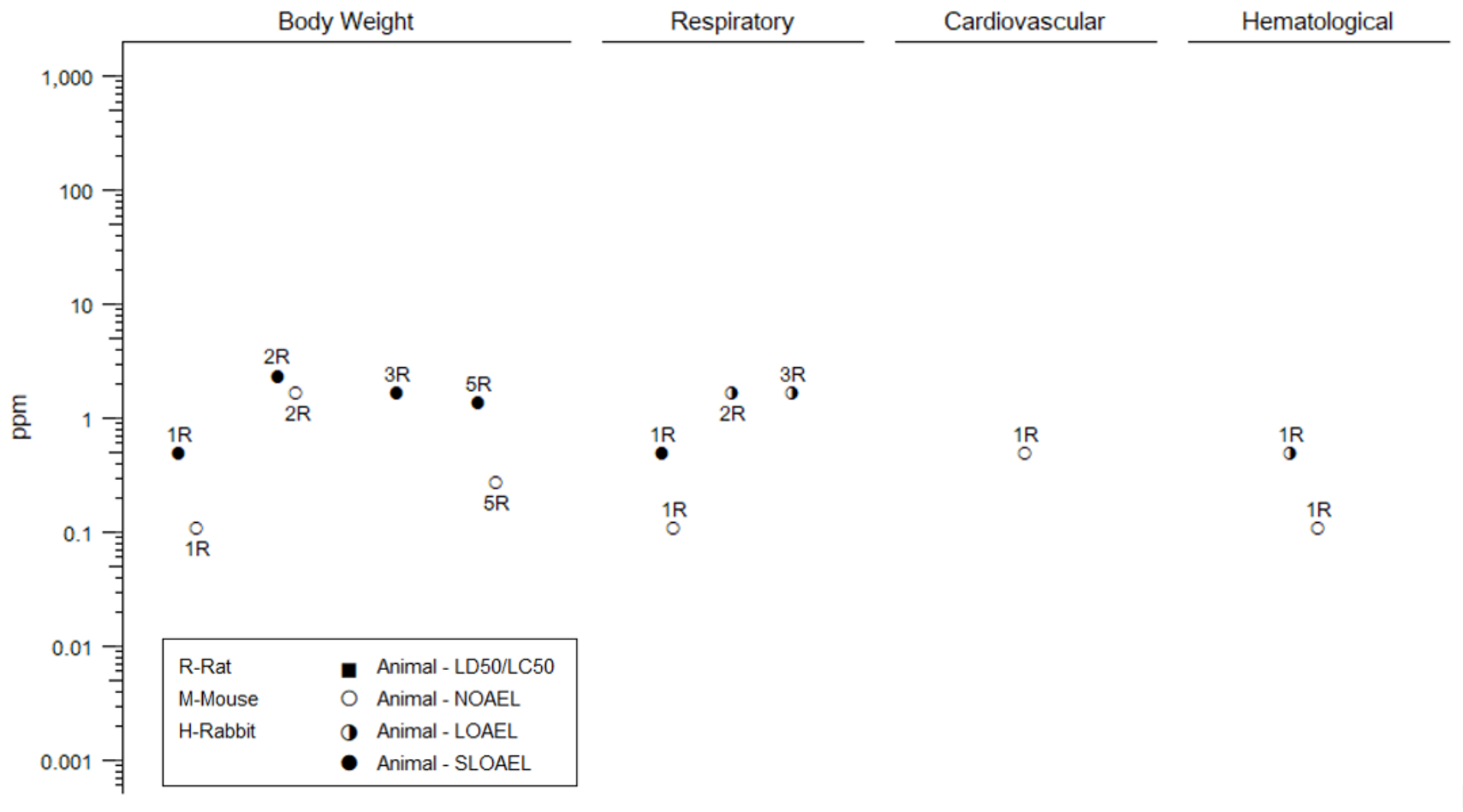


Figure 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Inhalation
Acute (≤14 days)

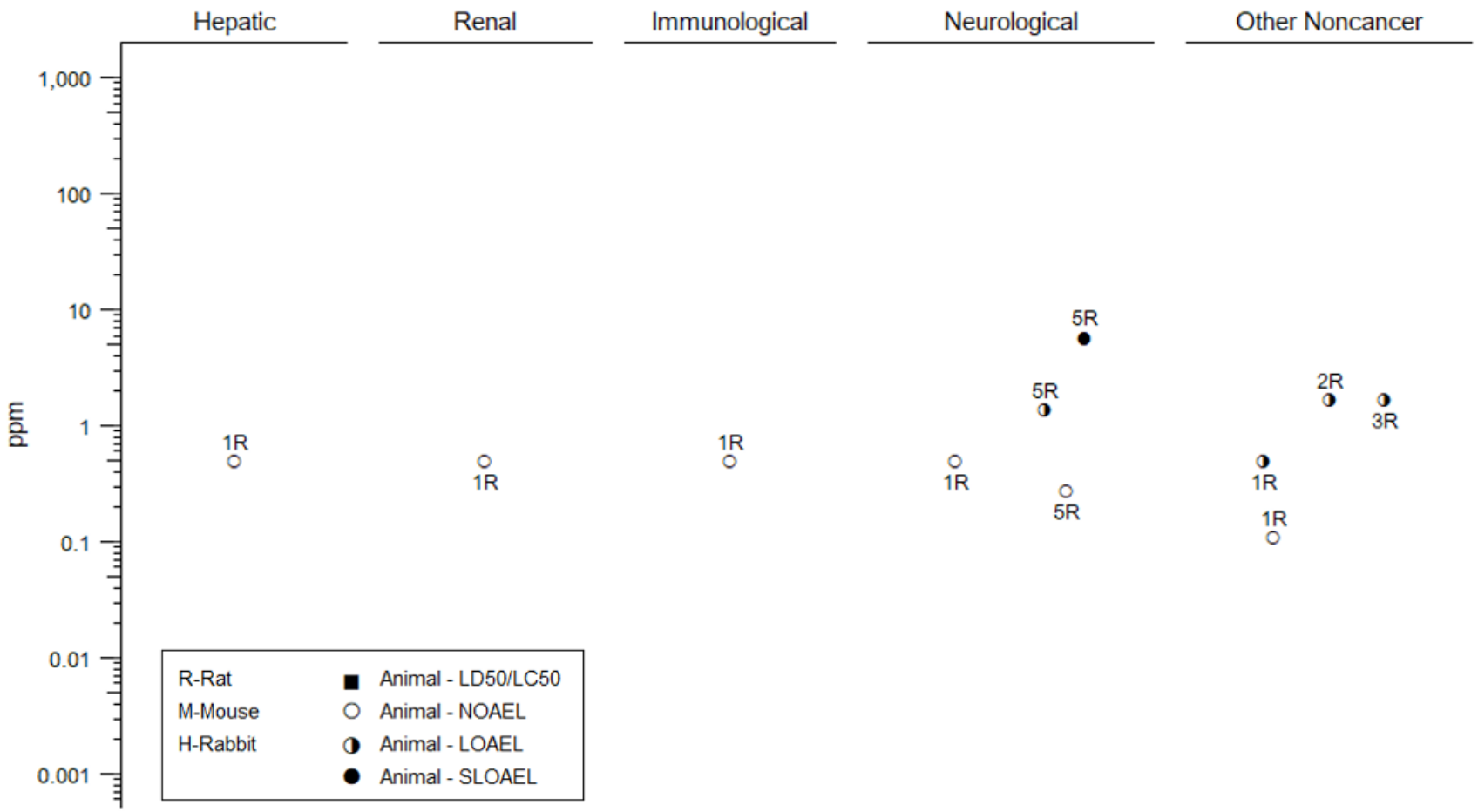


Figure 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Inhalation
Intermediate (15–364 days)

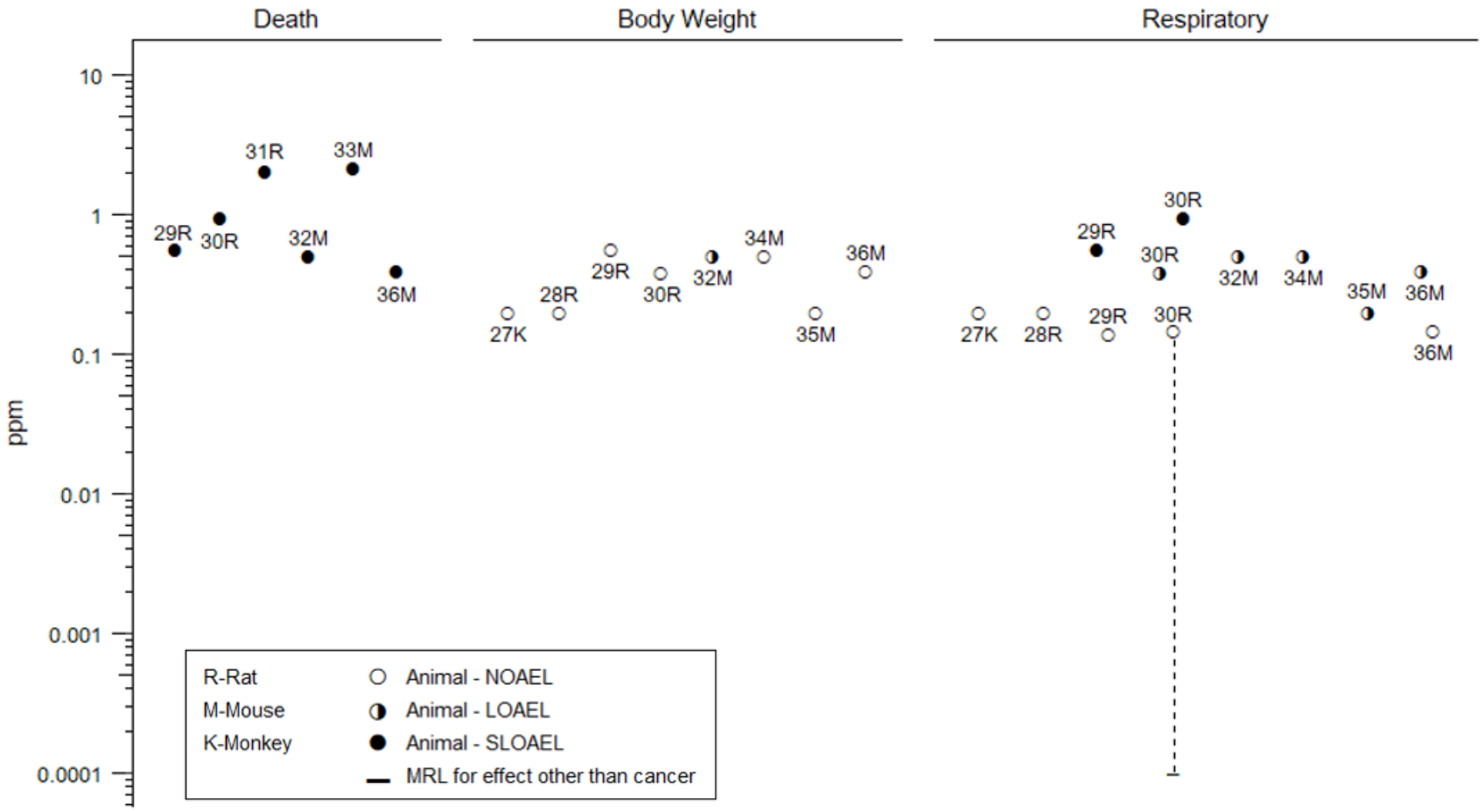


Figure 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Inhalation
Intermediate (15–364 days)

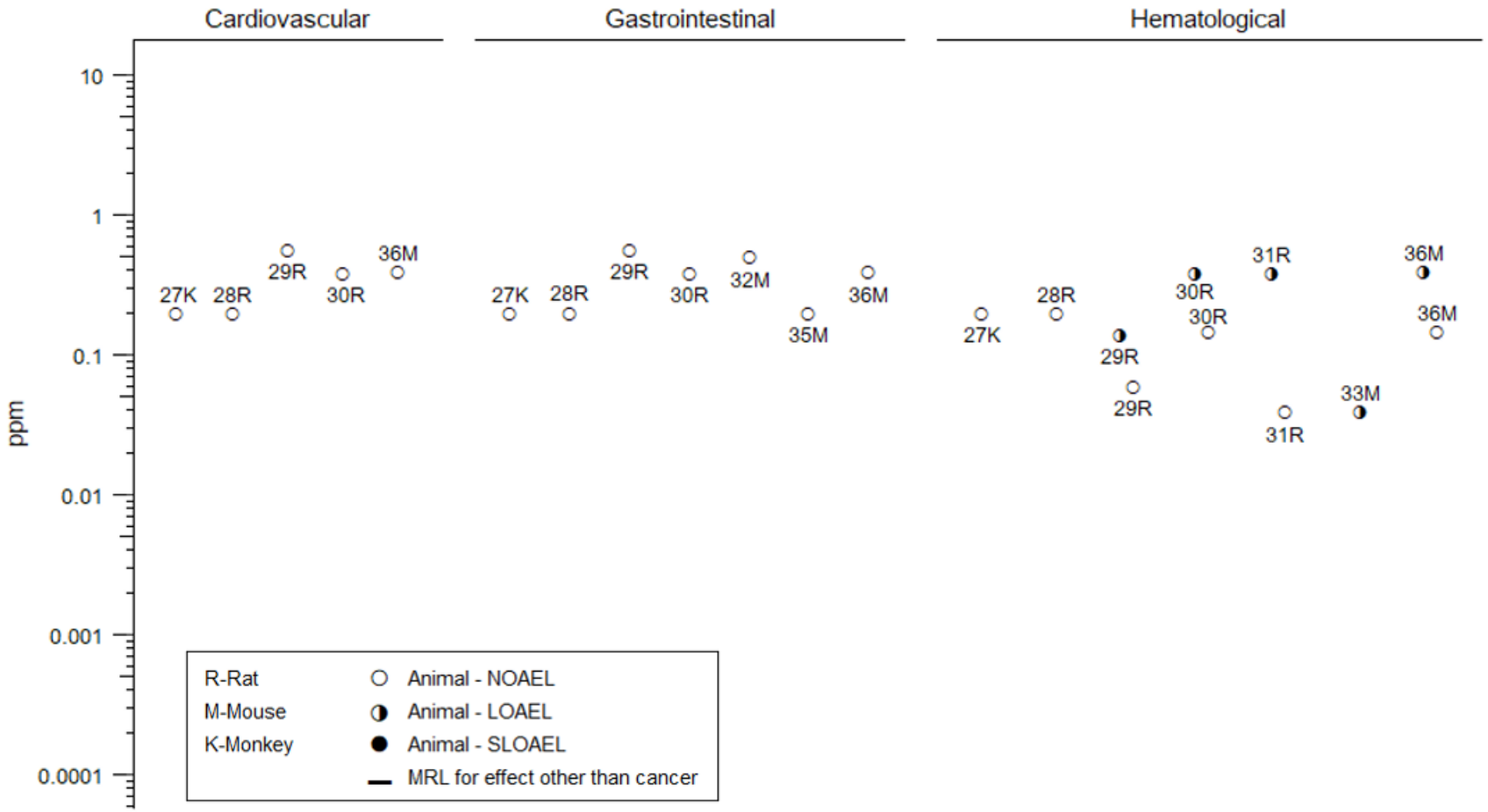


Figure 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Inhalation
Intermediate (15–364 days)

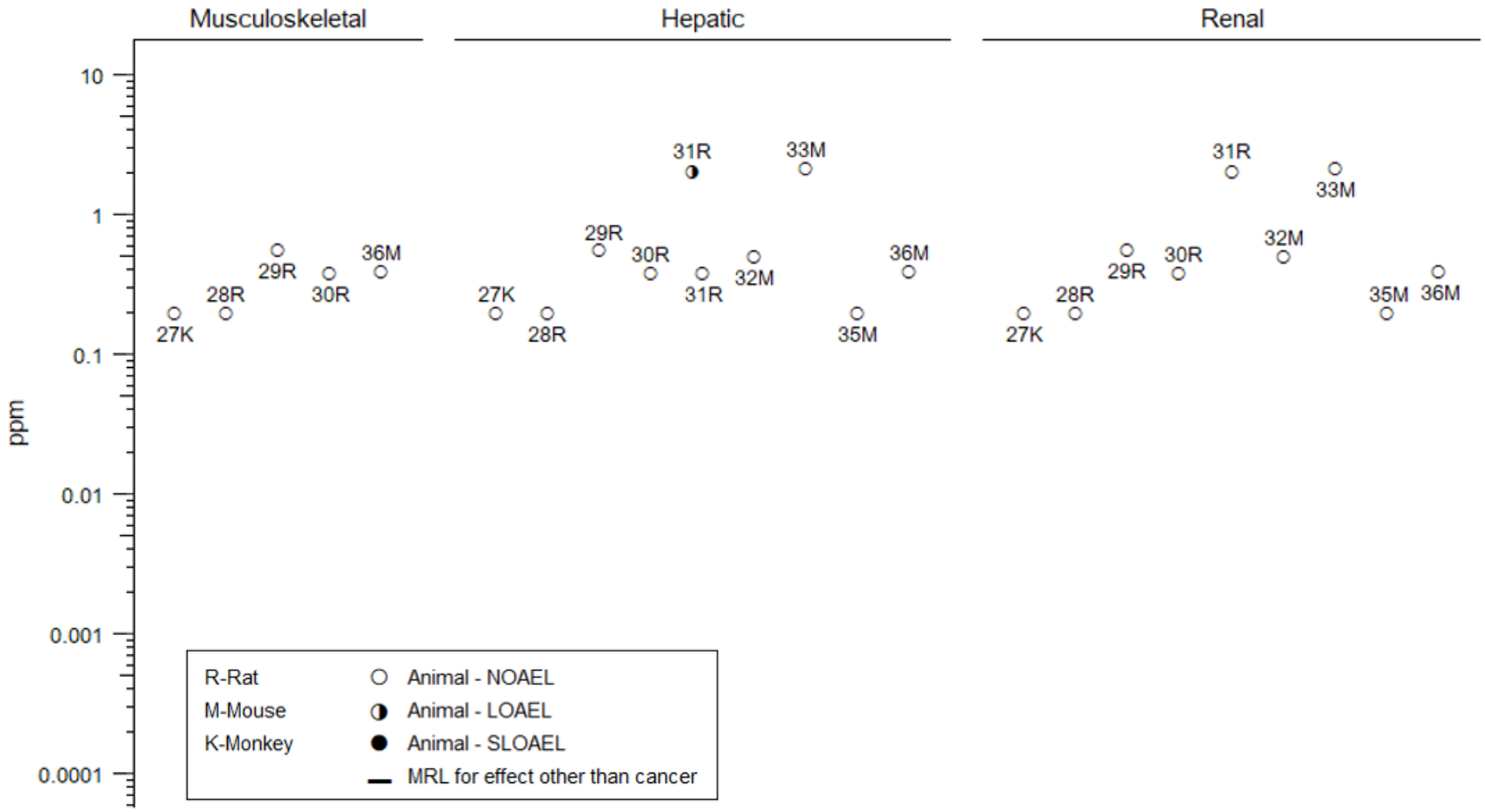


Figure 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Inhalation
Intermediate (15–364 days)

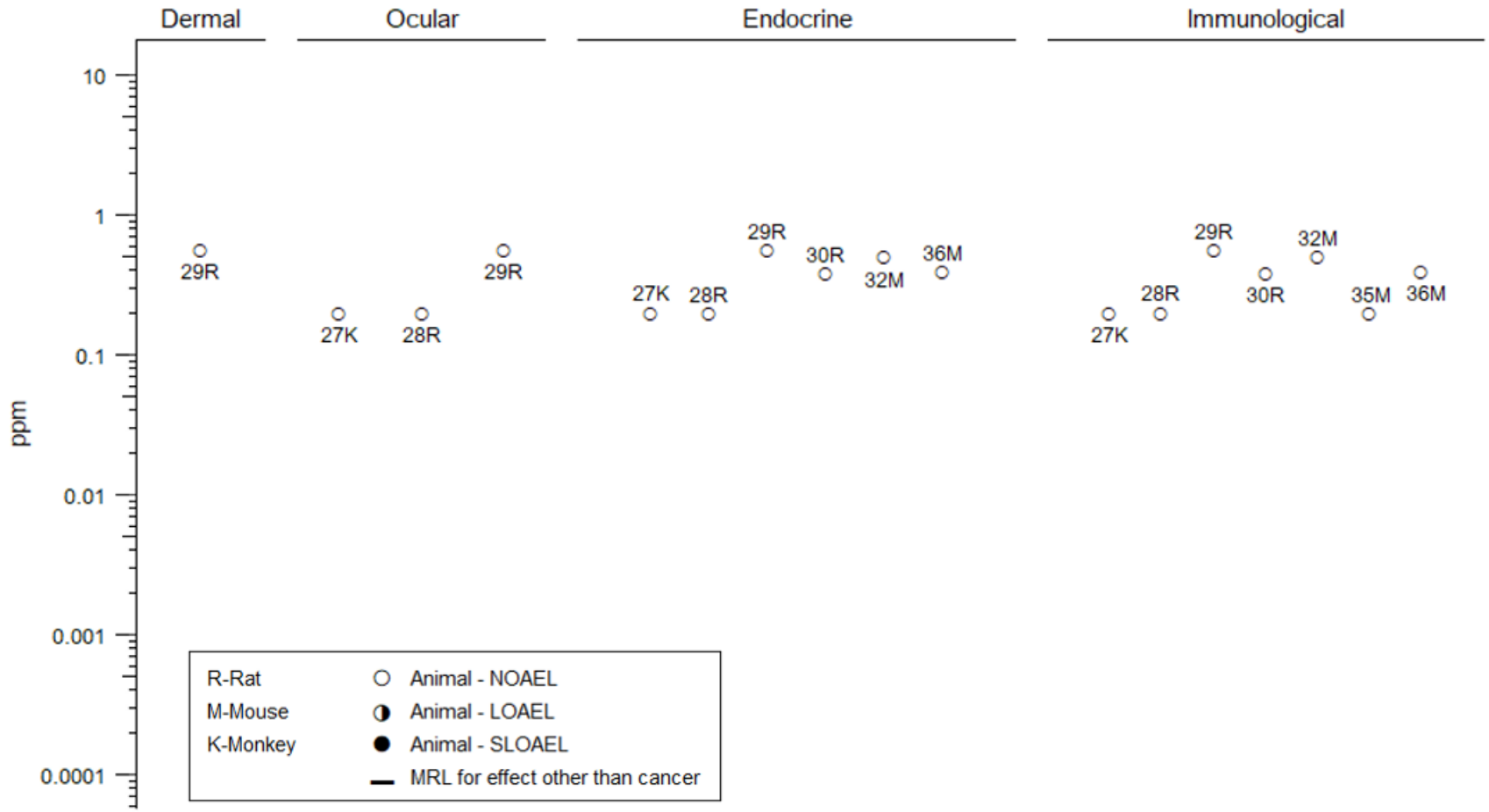


Figure 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Inhalation
Intermediate (15–364 days)

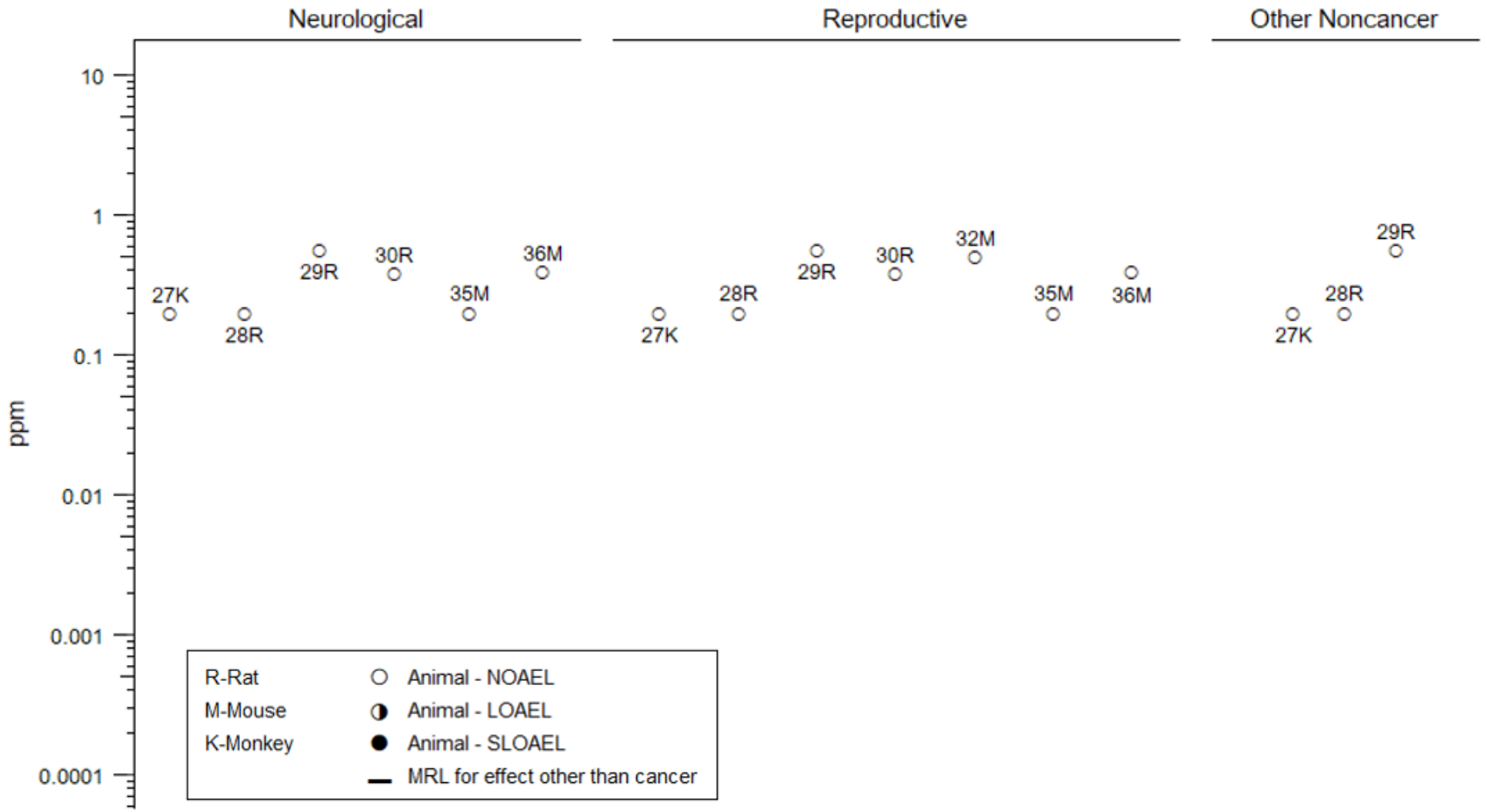


Figure 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Inhalation
Chronic (≥365 days)

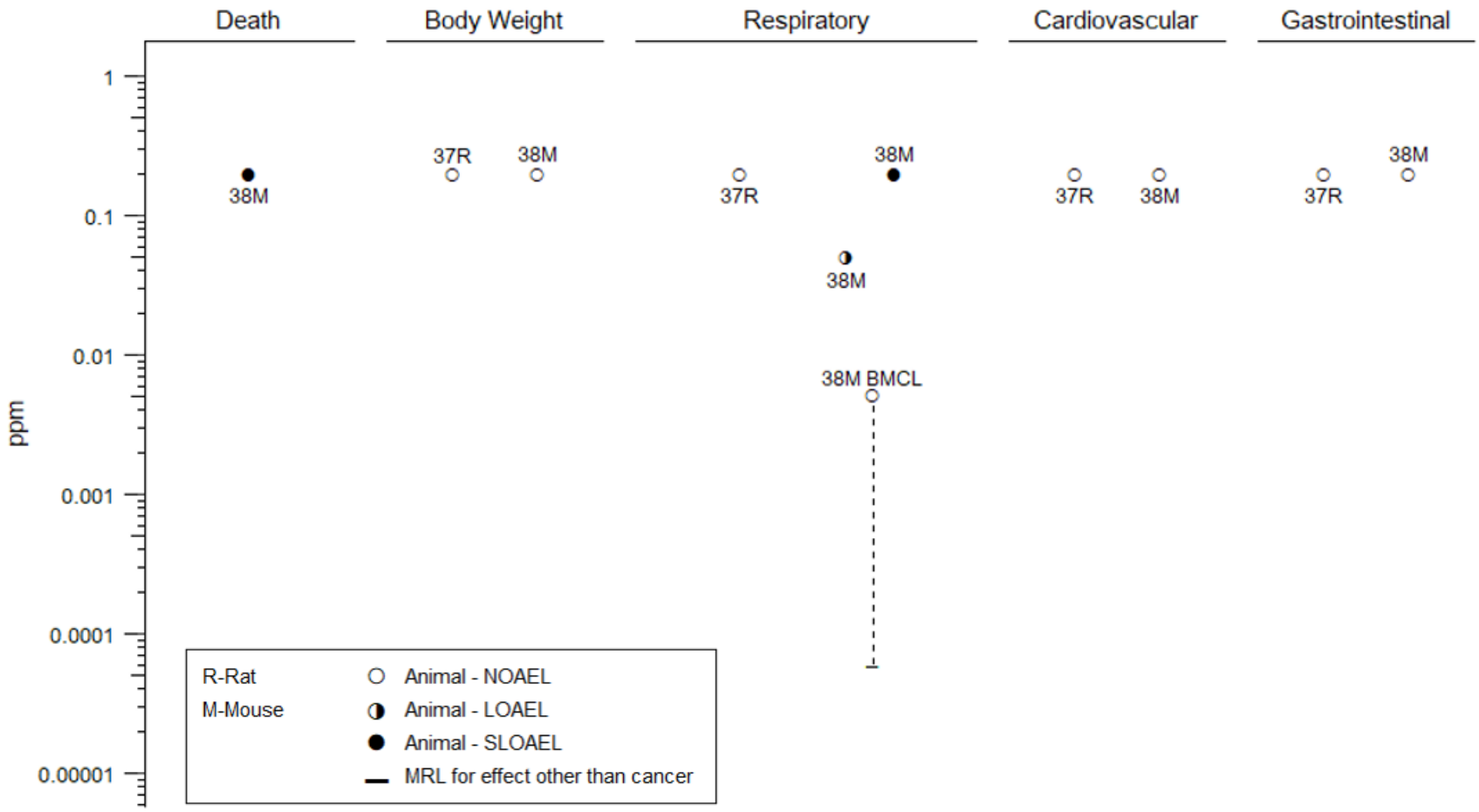


Figure 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Inhalation
Chronic (≥365 days)

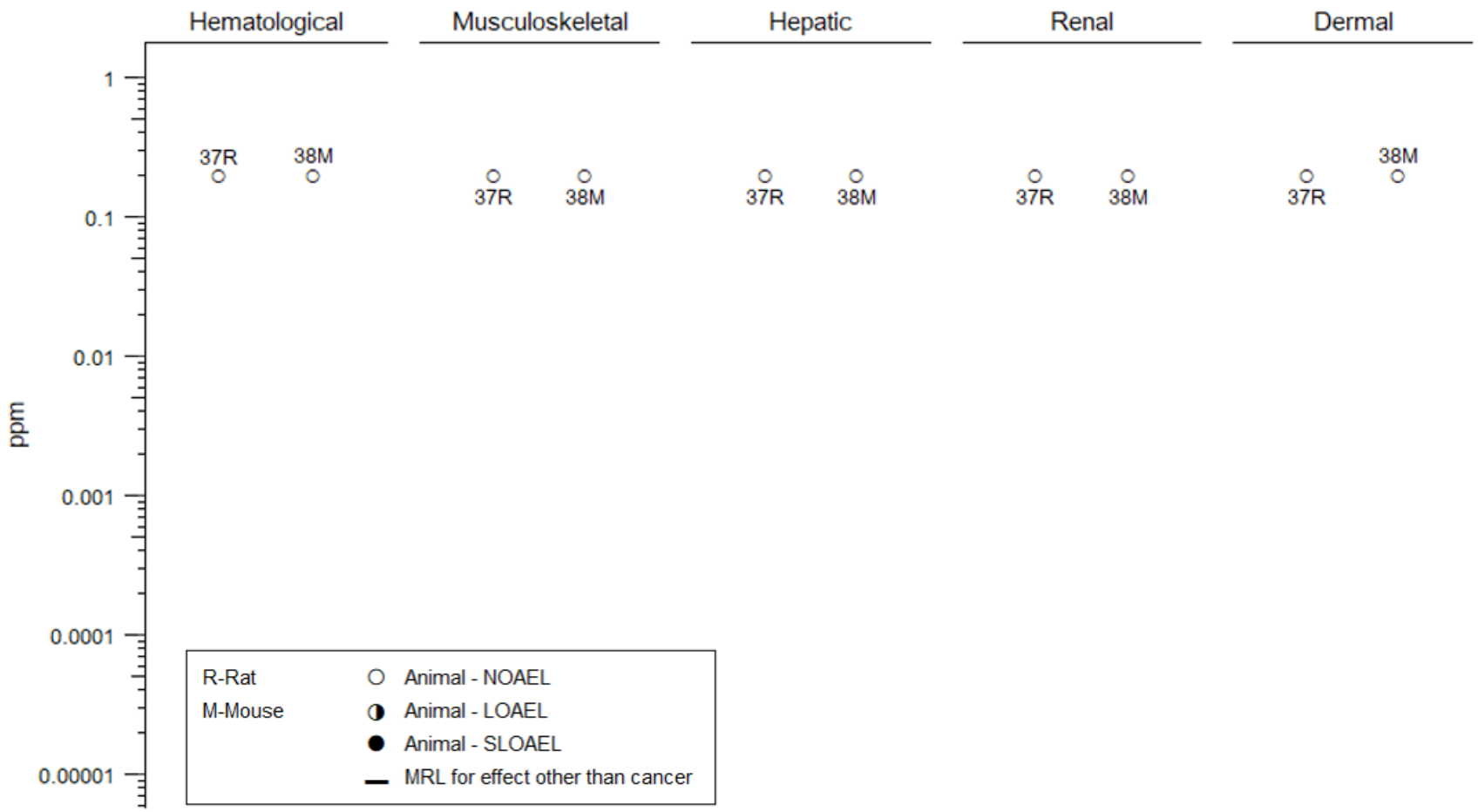


Figure 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Inhalation
Chronic (≥365 days)

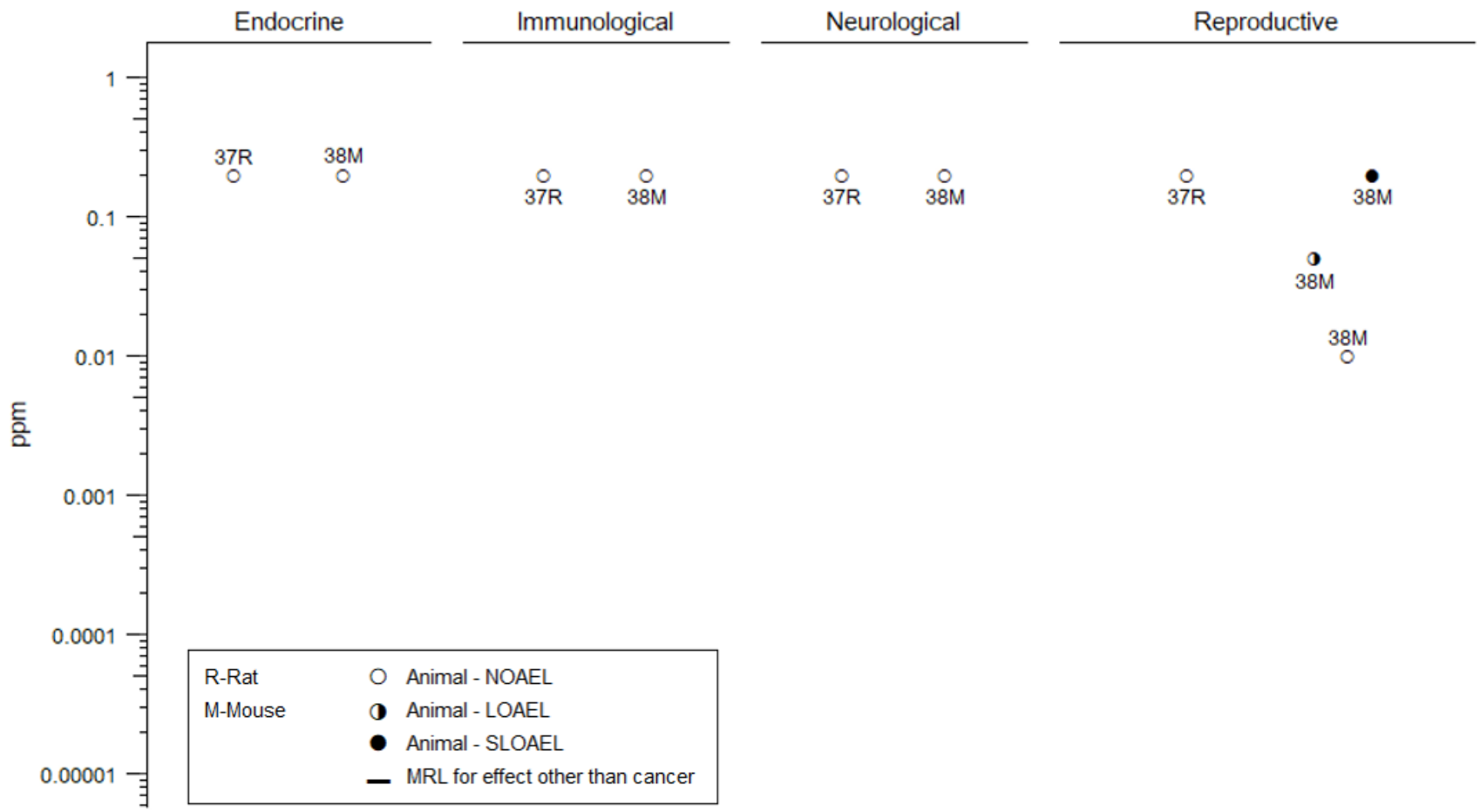


Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Gardner 1986a									
1	Rat (CFY) 5 M, 5 F	Once (GO)	1,260, 1,600, 2,000	LE, CS, BW, GN	Death			1,300 F 1,500 M	LD_{50} LD_{50}
					Resp			1,260	Decreased respiratory rate
					Gastro		1,260		Diarrhea
					Neuro		1,260		Abnormal gait, lethargy
OxyChem 1972									
2	Rat (Spartan) 25 M, 25 F	Once (GO)	315, 500, 794, 1,250, 1,984	LE	Death			530 F 630 M	LD_{50} LD_{50}
Treon et al. 1955									
3	Rat 9–11 M	Once (GO)	280, 340, 420, 520, 620, 940, 1,400	LE, CS, GN	Death			505	LD_{50}
Treon et al. 1955									
4	Rat 10 F	Once (GO)	280, 940, 1,400, 2,100	LE, CS, GN	Death			940	9/10 died
Chernoff and Kavlock 1982, 1983; Gray and Kavlock 1984; Gray et al. 1986									
5	Mouse (CD-1) 16 F	5 days GDs 8–12 (GO)	0, 45	BW, DX	Bd wt Develop	45 45			
Offspring evaluated through PND 250 for postnatal viability, growth, locomotor activity, female sexual development, and reproductive function									

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Dean 1977									
6	Mouse (CD-1) 5 M, 5 F	Once (GO)	21.5, 46.4, 100, 215, 464, 1,000, 2,150	LE, CS, BW	Death			679	LD_{50}
					Resp	1,000		2,150	Decreased respiratory rate
					Gastro	215 F	464 F		Diarrhea
						464 M	1,000 M		Diarrhea
					Musc/skel	464	1,000		Decreased limb tone in animals that died
					Neuro	215	464	1,000	LOAEL: Hypoactivity SLOAEL: Ataxia
Murray et al. 1980									
7	Mouse (CF-1) NS F	10 days GDs 6–15 (GO)	0, 5, 25, 75	LE, CS, BW, FI, WI, RX, DX	Bd wt	75			
					Develop	75			
					Other noncancer	75			
Murray et al. 1980									
8	Mouse (CF-1) 5 F	10 days GDs 6–15 (GO)	0, 25, 75, 250, 500	LE, CS, BW	Death			250	3/5 dams died
Murray et al. 1980									
9	Rabbit (New Zealand) NS F	13 days GDs 6–18 (GO)	0, 5, 25, 75	LE, CS, BW, RX, DX	Death			75	Unspecified increased maternal death during pregnancy
					Develop	25	75		Increased proportion of fetuses with 13 ribs
Murray et al. 1980									
10	Rabbit (New Zealand) 5 F	13 days GDs 6–18 (GO)	0, 25, 75, 250, 500	LE, CS, BW	Death			250	4/5 does died

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Treon et al. 1955									
11	Rabbit 3 F	Once (GO)	180, 280, 420, 620, 940	LE, CS, GN	Death			940	3/3 died
INTERMEDIATE EXPOSURE									
Abdo et al. 1984; Velsicol 1981b									
12	Rat (Fischer-344) 10 M, 10 F	13 weeks 5 days/week (GO)	0, 10, 19, 38, 75, 150	LE, BW, GN, OW, HP	Death			150 M	60% treatment-related mortality
					Bd wt	38 F	75 F		15% decreased terminal body weight
						19 M	38 M	75 M	LOAEL: 13% decreased terminal body weight SLOAEL: 30% decreased terminal body weight
					Resp	150			
					Cardio	150			
					Gastro	19[b]	38		Forestomach epithelial hyperplasia and focal inflammation ($BMDL_{10}$ for combined incidence of forestomach lesions = 7.7 mg/kg/day)[b]
					Hemato	150			
					Musc/skel	150			
					Hepatic	150			
					Renal	19	38		Toxic nephrosis
					Dermal	150			
					Endocr	150			
					Immuno	150			
					Neuro	150			
					Repro	150			

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Abdo et al. 1984; Velsicol 1981a									
13	Mouse (B6C3F1) 10 M, 10 F	13 weeks 5 days/week (GO)	0, 19, 38, 75, 150, 300	LE, BW, GN, OW, HP	Death			300	10/10 males died, 3/10 females died
					Bd wt	75 M	150 F		11% decreased terminal body weight
						150 F	300 F		13% decreased terminal body weight
					Resp	300			
					Cardio	300			
					Gastro	38	75		Focal inflammation and epithelial hyperplasia of the forestomach
					Hemato	300			
					Musc/skel	300			
					Hepatic	300			
					Renal	38 F	75 F		Toxic nephrosis
						150 M	300 M		Acute tubular necrosis
					Dermal	300			
					Endocr	300			
					Immuno	300			

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Neuro	300			
					Repro	300			

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive a provisional intermediate-duration oral MRL of 0.06 mg/kg/day based on a $BMDL_{10}$ of 7.7 mg/kg/day, which was adjusted to continuous duration exposure to a $BMDL_{ADJ}$ of 5.5 mg/kg/day and divided by an uncertainty factor of 100 (10 for human variability and 10 for animal to human extrapolation). See Appendix A for more detailed information regarding the MRL.

Green shading indicates the study selected for derivation of the provisional oral MRL.

ADJ = adjusted; Bd wt or BW = body weight; BMDL = benchmark dose lower confidence limit; $BMDL_{10}$ = 95% benchmark dose lower confidence limit (subscript denotes benchmark response: i.e., 10 = dose associated with 10% extra risk); Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = median lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skeletal = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; RX = reproductive function; SLOAEL = serious lowest-observed-adverse-effect level; WI = water intake

Figure 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene – Oral
Acute (≤14 days)

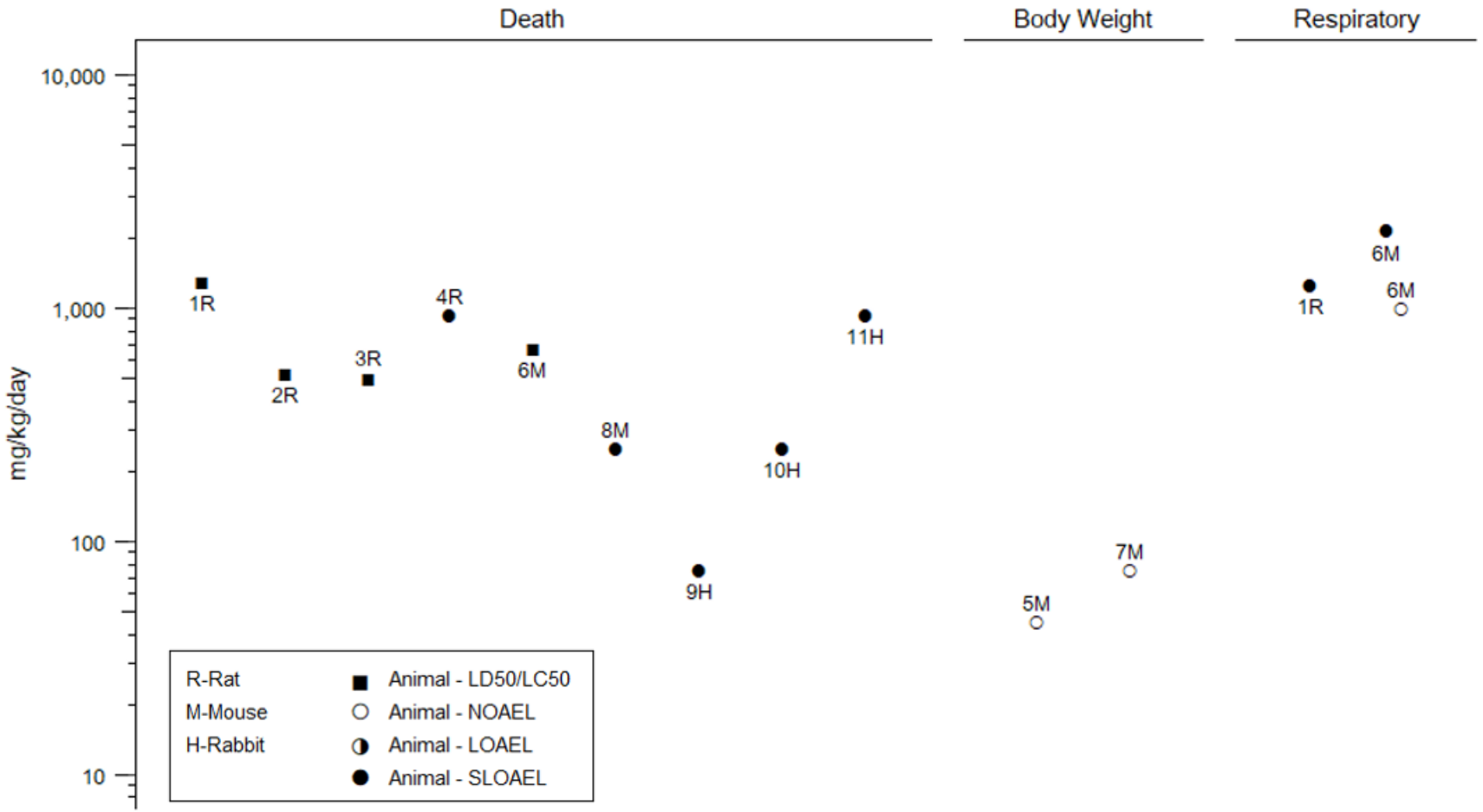


Figure 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene – Oral
Acute (≤14 days)

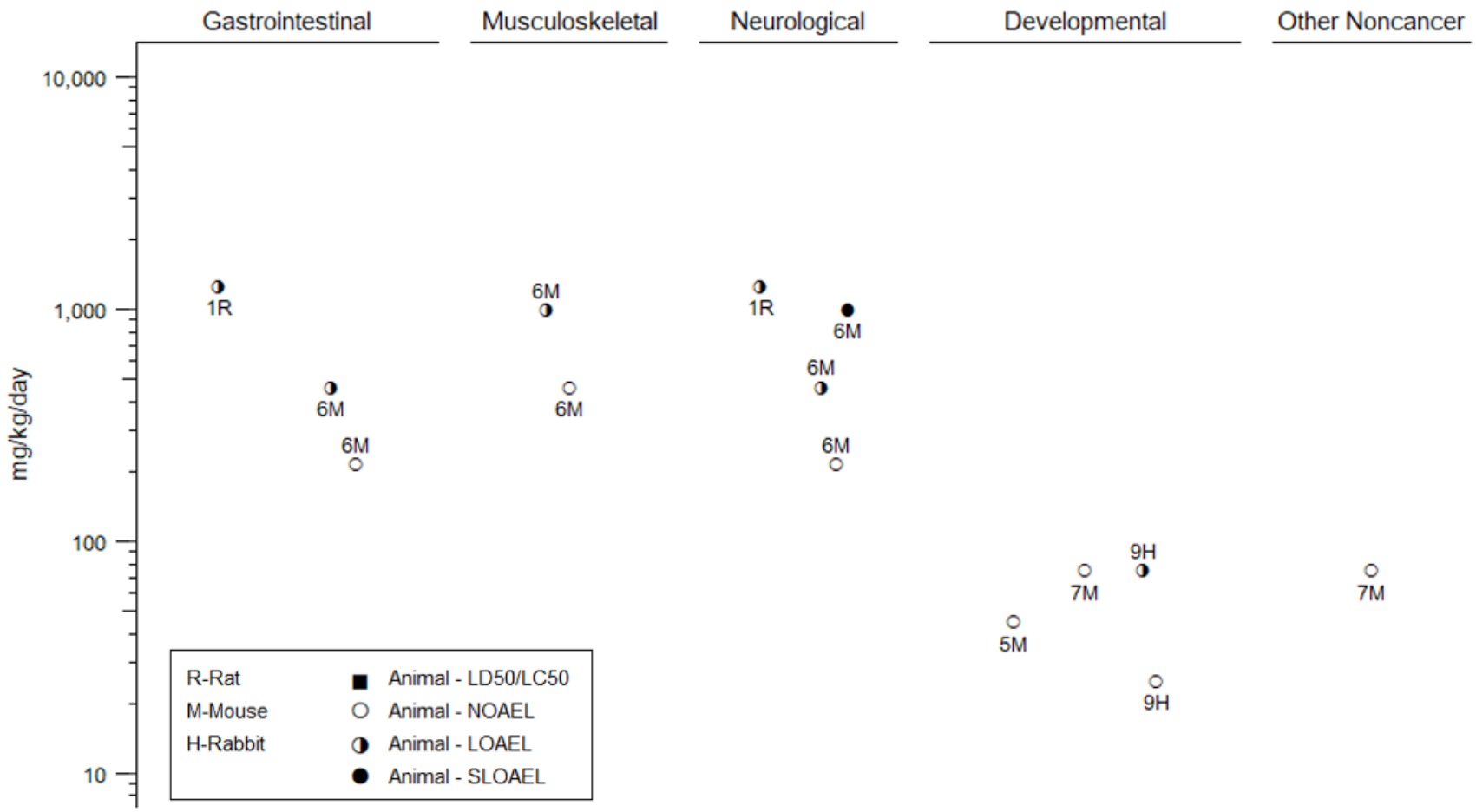


Figure 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene – Oral
Intermediate (15–364 days)

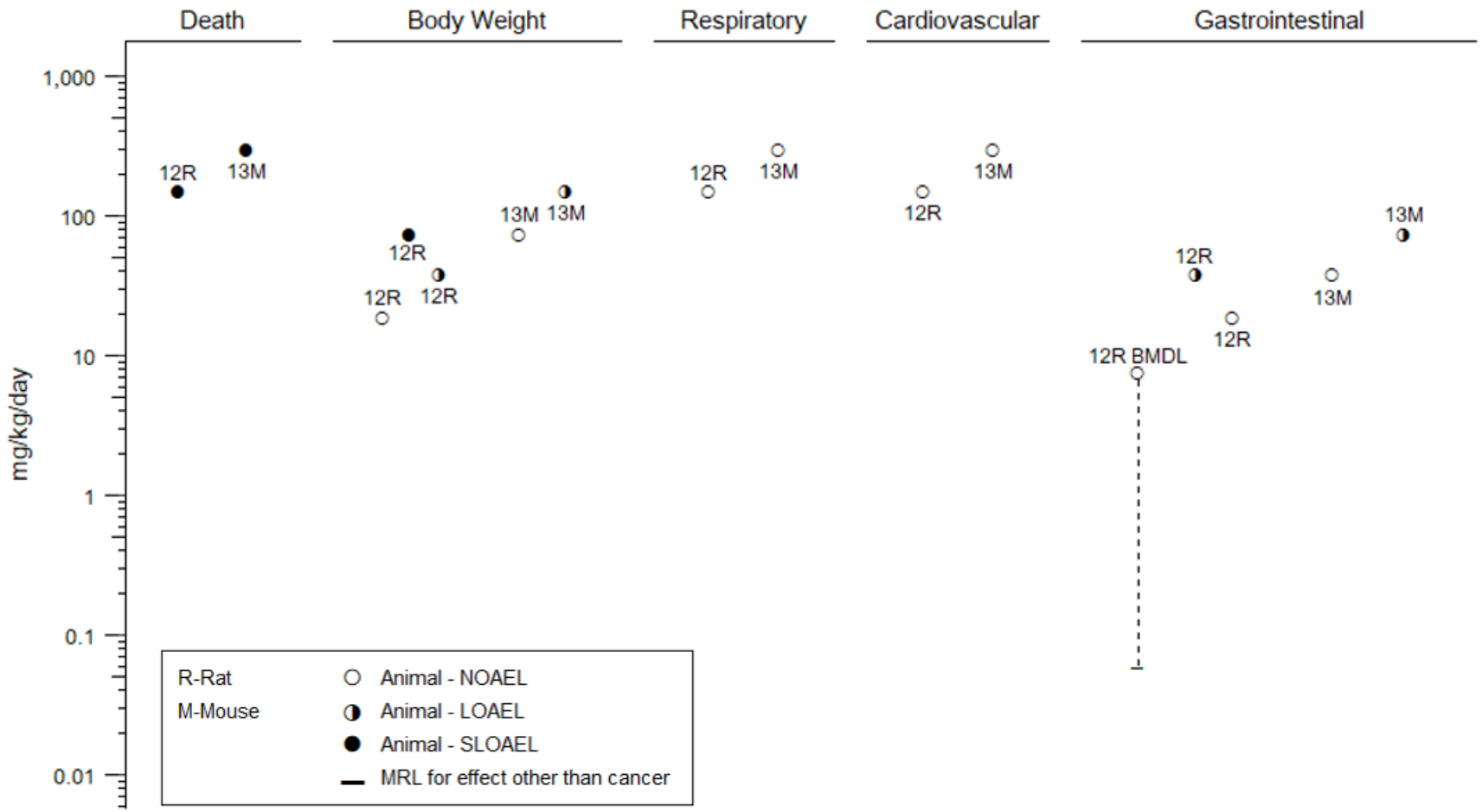


Figure 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene – Oral
Intermediate (15–364 days)

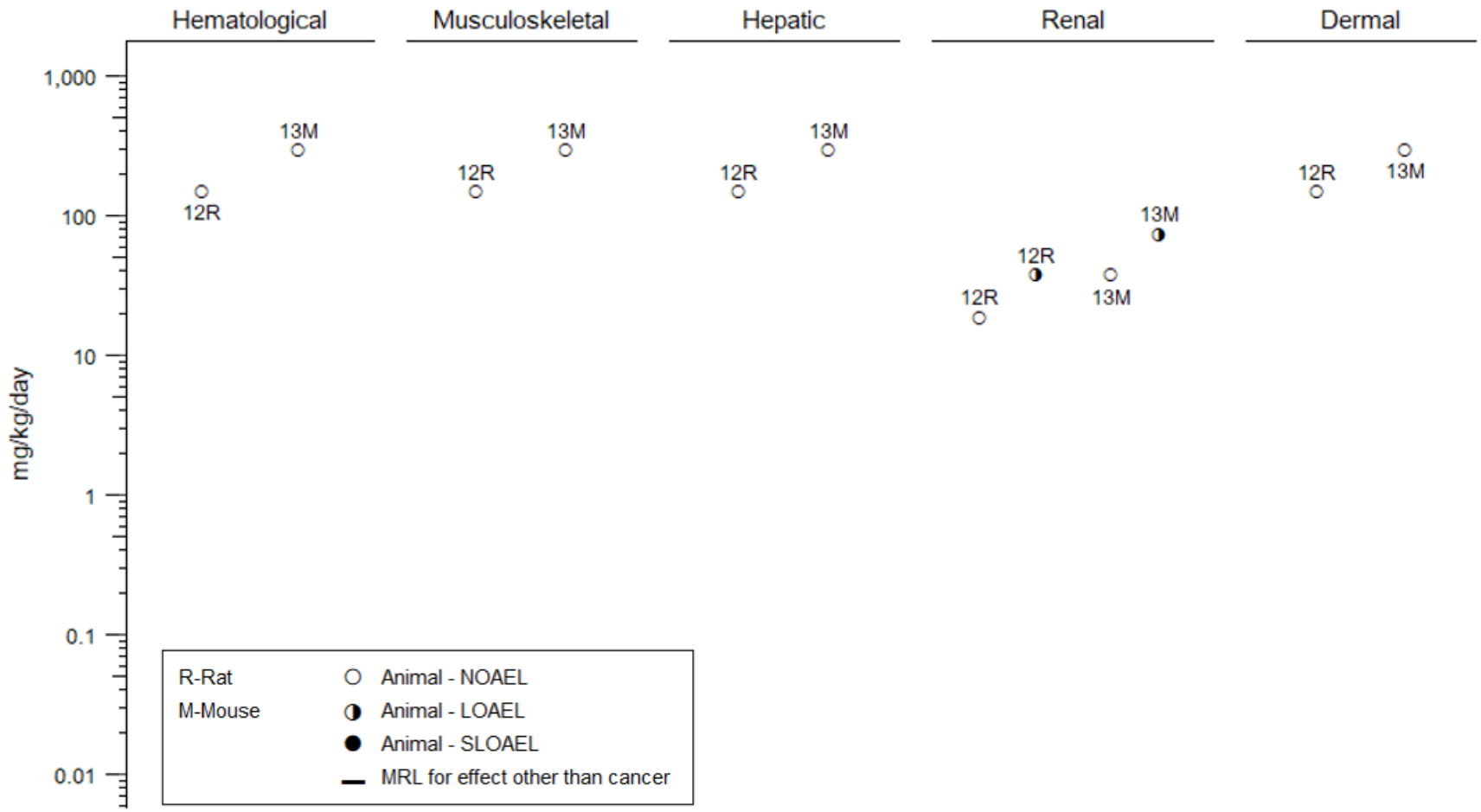


Figure 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene – Oral
Intermediate (15–364 days)

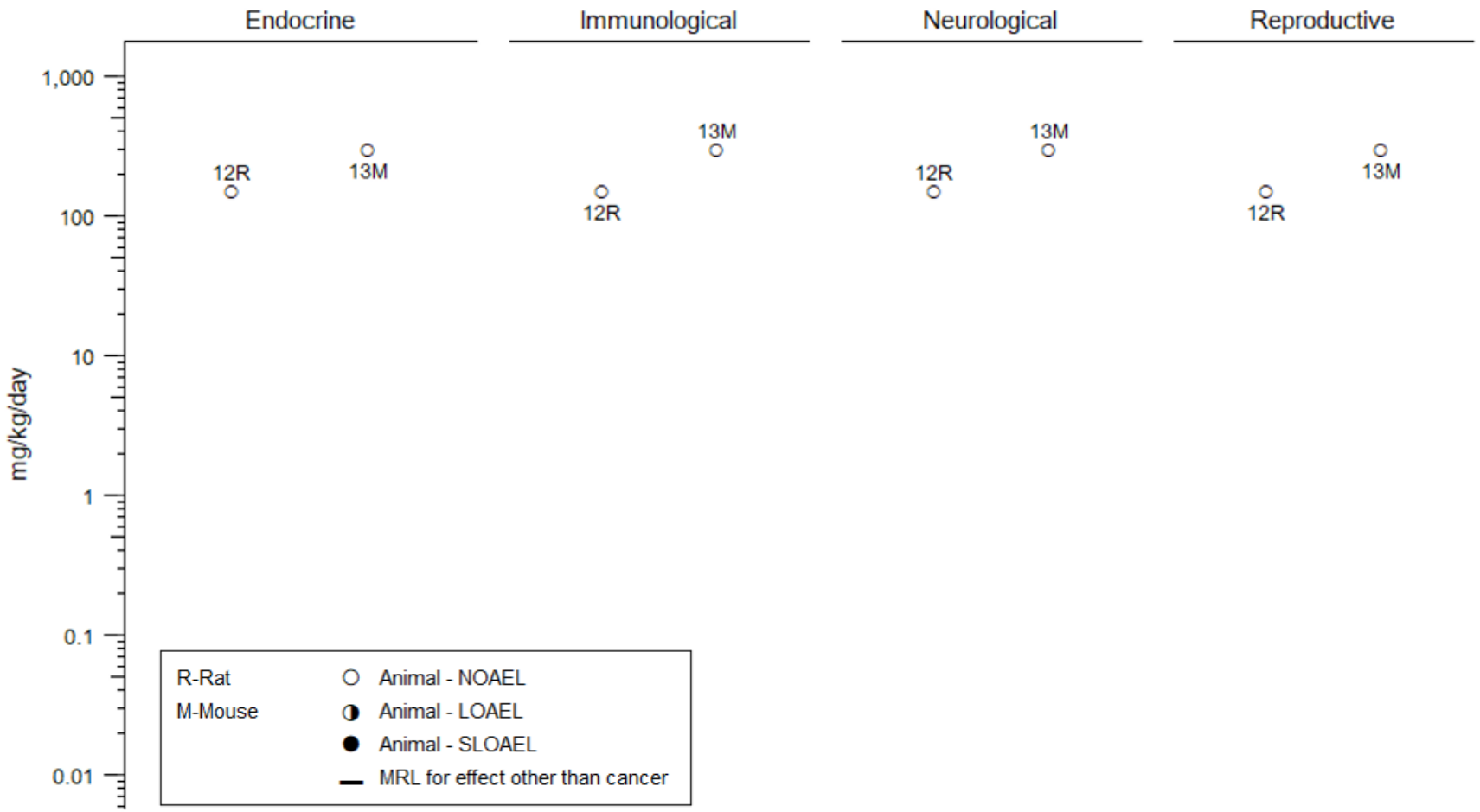


Table 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Kominsky et al. 1980								
Human 154 M, 23 F	3–15 days	≤0.97 ppm	CS, BC	Dermal		0.97		Skin irritation
				Ocular		0.97		Eye irritation
Treon et al. 1955								
Monkey 1 NS	Once	0.001, 0.01, 0.1, 1, 10% (0.01 mL); 20, 40, 60, 90% (0.05 mL)	CS	Dermal	10	20		Skin discoloration and swelling
Treon et al. 1955								
Monkey 1 NS	3 days Once/day	10%	CS	Dermal			10	Skin irritation, necrosis, hemorrhaging
Alexander et al. 1980a; Rand et al. 1982a								
Rat (Sprague-Dawley) 10 M, 10 F	1–2 weeks 5 days/week 6 hours/day	0, 0.022, 0.11, 0.5 ppm	CS	Ocular	0.11	0.5		Dark red eyes
Gardner 1986b								
Rat (CFY) 5 M, 5 F	24 hours	1,600, 2,000, 3,200 mg/kg	LE, CS, BW, GN	Death			3,100 F 2,600 M	LD_{50} LD_{50}
				Dermal		1,600		Moderate to severe edema
Jackson and Hardy 1986								
Rat (Wistar) 5 M, 5 F	1 hour	0, 1.67, 2.38, 3.53, 6.25, 8.30 ppm	CS	Ocular		1.67		Total or partial closing of the eyes
Jackson and Hardy 1987								
Rat (Wistar) 5 M, 5 F	4 hours	0, 1.68, 1.83, 3.31, 3.47 ppm	CS	Ocular		1.68		Total or partial closing of the eyes
Rand et al. 1982a								
Rat (Sprague-Dawley) 10 M, 10 F	4 hours	0.28, 1.4, 2.5, 3.1, 3.3, 3.4, 4, 5.8 ppm	CS	Ocular	4	5.8		Lacrimation

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Treon et al. 1955								
Rat 4 NS	5 days 7 hours/day	0.33, 1, 1.6 ppm	CS	Ocular		0.33		Eye irritation
Treon et al. 1955								
Rat 4 NS	3 days 7 hours/day	1.4 ppm	CS	Ocular		1.4		Eye irritation
Treon et al. 1955								
Rat 4 NS	4 hours	73.6 ppm	CS	Ocular		73.6		Eye irritation
Treon et al. 1955								
Rat 4 NS	7 hours	1.5, 3.2, 6.7 ppm	CS	Ocular		1.5		Eye irritation
Treon et al. 1955								
Rat 4 NS	2.6–3.6 hours	1.4, 3.1, 7.1, 11.1, 12.7, 46.5, 56.9, 70.4 ppm	CS	Ocular		1.4		Eye irritation
Treon et al. 1955								
Rat 3–4 NS	0.25–1.25 hours	1.4, 1.5, 3.1, 7.2. 13.0, 13.8, 19.4, 20.0, 20.2, 69.1, 69.2 ppm	CS	Ocular		1.4		Eye irritation
Treon et al. 1955								
Rat 4 NS	2 days 7 hours/day	3.2 ppm	CS	Ocular		3.2		Eye irritation
Treon et al. 1955								
Mouse 4–5 NS	0.25–1.25 hours	1.4, 1.5, 3.1, 7.2, 13.0, 13.8, 19.4, 20.0, 20.2, 69.1, 69.2 ppm	CS	Ocular		1.4		Eye irritation
Treon et al. 1955								
Mouse 5 NS	7 hours	1.5, 3.2, 6.7 ppm	CS	Ocular		1.5		Eye irritation

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Treon et al. 1955								
Mouse 5 NS	2.6–3.6 hours	1.4, 3.1, 7.1, 12.4, 12.7, 46.5, 56.9, 70.4 ppm	CS	Ocular		1.4		Eye irritation
Treon et al. 1955								
Mouse 5 NS	4 hours	73.6 ppm	CS	Ocular		73.6		Eye irritation
Treon et al. 1955								
Mouse 5 NS	2 days 7 hours/day	3.2 ppm	CS	Ocular		3.2		Eye irritation
Treon et al. 1955								
Mouse 5 NS	3 days 7 hours/day	1.4 ppm	CS	Ocular		1.4		Eye irritation
Treon et al. 1955								
Mouse 5 NS	5 days 7 hours/day	0.33, 1.0, 1.6 ppm	CS	Ocular		0.33		Eye irritation
OxyChem 1972								
Rabbit (New Zealand) 3 M, 3 F	4 hours	0.5 mL	LE, CS	Death			0.5	3/6 died
				Dermal		0.5		Moderate to severe edema
				Neuro			0.5	Ataxia and hypoactivity
OxyChem 1972								
Rabbit (New Zealand) 5 NS	5 minutes	0.1 mL	LE, CS	Death			0.1	5/5 died within 9 days
OxyChem 1972								
Rabbit (New Zealand) 2 M, 2 F	Once	200, 2,000 mg/kg	LE, CS, BW	Death			200 M	2/2 died within 14 days
							2,000 F	2/2 died within 24 hours
				Dermal		200		Dermal irritation and discoloration
				Neuro		200 M		Hypoactivity

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
OxyChem 1972								
Rabbit (New Zealand) 3 NS	24 hours	0.1 mL	LE, CS	Death			0.1	3/3 died within 6 days
				Ocular			0.1	Severe eye irritation and corrosion
OxyChem 1992								
Rabbit (New Zealand) 12 NS	24 hours	200 mg/kg	LE, CS	Death			200	8/12 died
				Dermal			200	Eschar formation
OxyChem 1992								
Rabbit (New Zealand) 6 NS	4 hours	0.5 mL	LE, CS	Dermal			0.5	Erythema, edema, necrosis
Treon et al. 1955								
Rabbit 1–3 F	24 hours	430, 610, 1,020, 2,130, 6,130 mg/kg	LE, CS, GN	Death			1020	2/3 died
				Dermal		430		Skin irritation, discoloration, subcutaneous edema, acanthosis, epilation, hyperkeratosis, chronic inflammation
Treon et al. 1955								
Rabbit 3 NS	4 hours	73.6 ppm	CS	Ocular		73.6		Eye irritation
Treon et al. 1955								
Rabbit 3 NS	2.6–3.6 hours	1.4, 3.1, 7.1, 12.4, 12.7, 46.5, 56.9, 70.4 ppm	CS	Ocular		1.4		Eye irritation
Treon et al. 1955								
Rabbit 3 NS	7 hours	1.5, 3.2, 6.7 ppm	CS	Ocular		1.5		Eye irritation
Treon et al. 1955								
Rabbit 3 NS	0.25–1.25 hours	1.4, 1.5, 3.1, 7.2, 13.0, 13.8, 19.4, 20.0, 20.2, 69.1, 69.2 ppm	CS	Ocular		1.4		Eye irritation

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Treon et al. 1955								
Rabbit 3 NS	2 days 7 hours/day	3.2 ppm	CS	Ocular		3.2		Eye irritation
Treon et al. 1955								
Rabbit 3 NS	3 days 7 hours/day	1.4 ppm	CS	Ocular		1.4		Eye irritation
Treon et al. 1955								
Rabbit 3 NS	5 days 7 hours/day	1, 1.6 ppm	CS	Ocular		1		Eye irritation
Treon et al. 1955								
Guinea pig 2 NS	Once	0.01, 0.1, 1, 40, 60, 90%	CS	Dermal	1	40		Skin discoloration and irritation
INTERMEDIATE EXPOSURE								
Alexander et al. 1980b; Rand et al. 1982a								
Monkey (Cynomolgus) 6 M, 6 F	14 weeks 5 days/week 6 hours/day	0, 0.01, 0.05, 0.2 ppm	CS	Ocular	0.2			
Alexander et al. 1980b; Rand et al. 1982a								
Rat (Sprague-Dawley) 40 M, 40 F	14 weeks 5 days/week 6 hours/day	0, 0.01, 0.05, 0.2 ppm	CS	Ocular	0.01	0.05		Dark red eyes
Treon et al. 1955								
Rat 4 NS	30 weeks 5 days/week 7 hours/day	0.15 ppm	CS	Ocular	0.15			
Treon et al. 1955								
Rat 4 NS	6 weeks 5 days/week 7 hours/day	0.34 ppm	CS	Ocular		0.34		Eye irritation
Treon et al. 1955								
Mouse 5 NS	30 weeks 5 days/week 7 hours/day	0.15 ppm	CS	Ocular	0.15			

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Treon et al. 1955								
Mouse 5 NS	6 weeks 5 days/week 7 hours/day (WB)	0.34 ppm	CS	Ocular		0.34		Eye irritation
Treon et al. 1955								
Rabbit 6 NS	6 weeks 5 days/week 7 hours/day	0.34 ppm	CS	Ocular		0.34		Eye irritation
Treon et al. 1955								
Rabbit 2 NS	30 weeks 5 days/week 7 hours/day	0.15 ppm	CS	Ocular	0.15			

BC = serum (blood) chemistry; BW = body weight; CS = clinical signs; F = female(s); GN = gross necropsy; LD_{50} = median lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; (WB) = whole-body exposure

2.2 DEATH

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

HCCPD induced death in experimental animals via the inhalation, oral, and dermal routes. The lethality of HCCPD following inhalation exposures has been evaluated for acute-, intermediate-, and chronic-duration studies. Acute-duration inhalation exposures to HCCPD at 1.0–73.6 ppm were lethal to rats, mice, guinea pigs, and rabbits in a concentration- and exposure duration-related manner (Treon et al. 1955). For example, the concentrations that produced 50% fatalities in mice after 1-, 3.5-, and 7-hour exposures were 7.2, <3.1, and <1.5 ppm, respectively. Species-specific differences were observed in the mortality data; the concentrations that produced 50% fatalities after 3.5-hour exposures were 7.1 ppm for guinea pigs, 3.1 ppm for rats, <3.1 ppm for mice, and <1.4 ppm for rabbits. All 10 rats exposed to 176 ppm HCCPD for 4 hours died within 48 hours of the exposure period (OxyChem 1972). The 1- and 4-hour inhalation LC_{50} values for rats are 3.69 ppm (Jackson and Hardy 1986) and 2.9 ppm (Jackson and Hardy 1987), respectively. Male rats appear to be more susceptible to HCCPD lethality than female rats; the sex-specific 4-hour inhalation median lethal concentration (LC_{50}) values are 1.6 ppm for males and 3.5 ppm for females (Rand et al. 1982a). With 2-week exposures to 0.5 ppm HCCPD, one rat of each sex died, and nine male rats and one female rat were sacrificed in moribund condition by the end of the exposure period. When the exposure duration was reduced to 5 days, three of five males and none of five females died at 0.5 ppm. All animals exposed to ≤0.11 ppm survived until the scheduled sacrifice (Alexander et al. 1980a; Rand et al. 1982a).

In 13-week studies, all rats and mice exposed to ≥0.941 ppm HCCPD died during the exposure periods (NTP 1994). As was observed after acute-duration inhalation exposures, mice appeared to be more sensitive to HCCPD-induced lethality; all mice exposed to 2.142 ppm died during the first week while rats exposed to 2.065 ppm survived for up to 3 weeks. Additionally, no rat mortalities were observed at ≤0.385 ppm, while 5 of 10 male mice died at 0.389 ppm. 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 mouse air passages. No treatment-related deaths were reported for rats or monkeys exposed to ≤0.2 ppm for 14 weeks (Alexander et al. 1980b; Rand et al. 1982a) and overall survival was not statistically significantly affected by HCCPD treatment in male mice exposed to 0.2 ppm for 33 weeks or 0.5 ppm for 26 weeks (NTP 1994). Although overall survival of male rats was not affected after exposure to 0.5 ppm for 42 weeks, survival in this group decreased 14% 3 weeks after exposure cessation (NTP 1994). In a 30-week study, 22% of male rats exposed to 0.56 ppm died during

the exposure period (Clark 1981). No mortality attributed to HCCPD was observed in rats exposed to 0.06 or 0.14 ppm.

Survival of male and female rats and male mice chronically exposed to 0.01–0.2 ppm HCCPD for 2 years was similar to controls. Decreased survival was observed for female mice exposed to 0.2 ppm, but not at lower concentrations (NTP 1994). Ovarian inflammation, possibly resulting from an infection, appeared to be the cause of premature deaths in female mice exposed to 0.2 ppm HCCPD.

The lethality of HCCPD in laboratory animals has been evaluated for acute- and intermediate-duration oral exposures. The oral median lethal dose (LD_{50}) values were 505 mg/kg in male rats of an unspecified strain (Treon et al. 1955), 630 and 530 mg/kg in male and female Spartan rats, respectively (OxyChem 1972), and 1,500 and 1,300 mg/kg in male and female CFY rats, respectively (Gardner 1986a). An oral dose of 940 mg/kg was lethal to ≥90% of the male and female rats (Treon et al. 1955). Acute-duration oral lethality data for species other than rats are more limited. The oral LD_{50} value for male and female mice is 679 mg/kg (Dean 1977). In rabbits, doses of 420, 620, and 940 mg/kg killed 0/3, 1/3, and 3/3 animals, respectively (Treon et al. 1955). In pregnant animals, several rabbits (exact number not identified) did not survive 13 days of treatment with 75 mg/kg/day HCCPD on gestational days (GDs) 6–18 (Murray et al. 1980). With intermediate-duration oral exposure, rats appeared to be more sensitive to HCCPD lethality than mice, a reverse of the sensitivity observed for inhalation exposures. There were no mouse deaths following 13-week exposures to ≤150 mg/kg/day, but 6 of 10 male rat deaths at 150 mg/kg/day were attributed to HCCPD treatment following 13 weeks of exposure (Abdo et al. 1984: Velsicol 1981a, 1981b). All 10 male mice and 3 of 10 female mice died during the first 2 weeks of exposure to 300 mg/kg/day (Abdo et al. 1984; Velsicol 1981a).

For the dermal route, lethality of HCCPD in laboratory animals has only been evaluated for acute-duration exposures. In rabbits administered topical applications of 200 mg/kg for 24 hours, deaths were reported in 2/2 males and 0/2 females (OxyChem 1972) and 8/12 rabbits of unspecified sex (OxyChem 1992). Dermal exposure to 2,000 mg/kg resulted in 100% mortality in male and female rabbits within 24 hours (OxyChem 1972). At lower doses, single dermal doses applied for 24 hours caused mortality in 0/3, 1/3, and 2/3 rabbits at 430, 610, and 1,020 mg/kg, respectively (Treon et al. 1955). In the multi-dose study by Treon et al. (1955), survival time was inversely proportional to the dose; rabbits survived 72, 24–48, 20, and 17 hours after dermal dosing with 610, 1,020, 2,130, and 6,130 mg/kg, respectively. None of the animals died with a dermal application of 430 mg/kg, although one rabbit was in poor condition and likely would have died had it not been sacrificed at 21 days. In rats, the dermal LD_{50} values were

2,600 mg/kg in males and 3,100 mg/kg in females (Gardner 1986b). These results suggest that rabbits are more sensitive to HCCPD toxicity via the dermal route relative to rats.

When 0.1 mL of HCCPD was instilled into the conjunctival sac of five rabbits for 5 minutes and then rinsed with water, the quantity of material absorbed was lethal to all the animals within 9 days (OxyChem 1972). When ocular rinsing was delayed until 24 hours post-instillation, all three rabbits administered 0.1 mL of HCCPD died within 6 days.

2.3 BODY WEIGHT

No reports of body weight effects in humans after exposure to HCCPD were found. The available data in laboratory animals indicate that HCCPD produces body weight effects at sufficiently high inhalation and oral exposure levels; no body weight data are available via the dermal route. In several of these studies, body weight changes were associated with decreased food and/or water intake (see Section 2.18, Other Noncancer, for additional details).

Body weight effects resulting from inhalation exposures to HCCPD have been assessed in acute-, intermediate-, and chronic-duration studies. Inhalation exposures to sufficient HCCPD concentrations over acute and intermediate periods decrease body weights and/or suppress body weight gains. A single 1-hour exposure to HCCPD resulted in decreased body weights in rats during the 3-week post-exposure observation period at concentrations ≥2.38 ppm; when animals that died prematurely and those sacrificed at the end of the observation period are combined, body weight decreases compared to control were 41% in males and 26% in females (Jackson and Hardy 1986). A 4-hour exposure resulted in >20% decreases in body weight in male and female rats at ≥1.68 and 1.83 ppm, respectively, during the 4-week observation period (Jackson and Hardy 1987). In both studies by Jackson and Hardy (1986, 1987), body weight effects were associated with decreased food intake. Similarly, after a 4-hour exposure to HCCPD, body weight decreases of at least 25 and 17% relative to pre-exposure weights were observed for male and female rats, respectively, after exposures to 1.4–5.8 ppm; no food intake data were provided (Rand et al. 1982a). With significantly decreased food intake, male and female rats exposed to 0.5 ppm HCCPD for 1–2 weeks lost body weight; male body weights decreased 32% on day 10 and terminal female body weight decreased 29% (Alexander et al. 1980a; Rand et al. 1982a).

In 13-week inhalation studies, terminal body weights remained within 10% of control values following exposure to HCCPD at concentrations up to 0.385 ppm in rats and 0.389 ppm in mice (NTP 1994).

Similarly, no effects on body weight were observed in rats and monkeys exposed to ≤0.2 ppm HCCPD for 14 weeks (Alexander et al. 1980b; Rand et al. 1982a). Body weight decreased 19% and body weight gain decreased 42% in male mice exposed to 0.5 ppm for 42 weeks (NTP 1994). No body weight deficits were identified after exposure of male mice to 0.2 ppm for 33 weeks or to 0.5 ppm for 26 weeks (NTP 1994). Body weights remained within 10% of control values for male and female rats exposed to ≤0.56 ppm for 30 weeks (Clark 1981), and in male and female mice and rats exposed to ≤0.2 ppm for 2 years (NTP 1994).

Body weight effects after oral exposure to HCCPD in experimental animals have been evaluated in acute- and intermediate-duration studies. In intermediate-duration studies, sufficient oral dosing with HCCPD decreased body weights and suppressed body weight gains. Male and female rats and mice experienced dose-related decreased body weights and body weight gains when compared to controls after oral exposure to HCCPD for 13 weeks (Abdo et al. 1984; Velsicol 1981a, 1981b). Male rats were affected more than females, and rats were affected more than mice. Terminal body weights in male rats decreased 13–35% and overall body weight gains were reduced 21–58% at dose levels of ≥38 mg/kg/day. In female rats exposed to 75–150 mg/kg/day, terminal body weights were reduced 15–17% and overall body weight gains decreased 28–36%. Terminal body weights in male mice were reduced 11% and overall body weight gains decreased 39% at 150 mg/kg/day. In female mice, terminal body weights decreased 13% at 300 mg/kg/day and overall body weight gains were reduced 22–44% at ≥150 mg/kg/day. Differences in terminal body weights and overall body weight gains were within 10% of control values for male rats at ≤19 mg/kg/day, female rats at ≤38 mg/kg/day, and male and female mice at ≤75 mg/kg/day. Maternal weight loss was observed in rabbits administered 75 mg/kg/day on GDs 6–18; the magnitude of weight loss was not reported (Murray et al. 1980). No body weight effects were reported for rabbits dosed with ≤25 mg/kg/day on GDs 6–18 or for mice dosed with ≤75 mg/kg/day on GDs 6–15.

2.4 RESPIRATORY

The data provide strong evidence that HCCPD produces portal-of-entry effects in the respiratory system following inhalation exposures; no effects on the respiratory tract were observed following oral or dermal exposures to HCCPD. Based upon systematic review (Appendix C), the respiratory system is a presumed hazard of HCCPD toxicity following inhalation exposure based on inadequate evidence in humans and a high level of evidence from laboratory animal studies.

The available data on respiratory effects of HCCPD in humans are limited to reports of WWTP workers and cleanup crew members exposed to HCCPD for 3–15 days after an inadvertent industrial release of this material into the sewage system (Kominsky et al. 1980; Morse et al. 1979). Maximum atmospheric concentrations for the treatment plant workers were unknown but were most likely >0.97 ppm, the maximum concentration measured 4 days after compound identification (Morse et al. 1979). The maximum concentration recorded during cleanup was 19.2 ppm (Kominsky et al. 1980). Symptoms of tracheobronchial irritation were reported by the treatment plant workers early in the exposure period. These symptoms were recounted by 39 of 145 (27%) employees who responded to a questionnaire shortly after the exposure incident and by 16 of 177 (9%) employees who responded to a follow-up questionnaire 6 weeks later (Morse et al. 1979). Chest x-rays of 28 exposed workers were normal and tests of pulmonary function were normal in a subset of 22 workers from this group (Kominsky et al. 1980). Minor respiratory complaints included sore throat, cough, chest discomfort, and difficulty breathing. These effects were likely a consequence of the direct action of the HCCPD vapor on the mucous membranes of the respiratory tract, rather than systemic effects due to exposure to HCCPD through the lungs. 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.

Respiratory effects induced by HCCPD in laboratory animals have been evaluated in acute-, intermediate-, and chronic-duration inhalation exposure studies. Inhalation exposures to HCCPD produced clinical signs of respiratory toxicity and/or irritation including abnormal respiratory pattern (irregular or exaggerated respiratory movements, fast or irregular respiration rate or pattern, rales and/or noisy respiration, and/or gasping), labored respiration, sneezing, increased respiration rate, and/or mouth breathing in rats exposed to 1.67 ppm for 1 hour (Jackson and Hardy 1986), 1.68 ppm for 4 hours (Jackson and Hardy 1987), 0.5 ppm for 1–2 weeks (Alexander et al. 1980a; Rand et al. 1982a), 0.56 ppm for 30 weeks (Clark 1981), and ≥0.941 ppm for 13 weeks (NTP 1994). No respiratory clinical signs were observed in rats or monkeys exposed to 0.2 ppm for 14 weeks (Alexander et al. 1980b; Rand et al. 1982a), mice exposed to ≤2.142 ppm for 13 weeks (NTP 1994), male mice exposed to 0.2 ppm for 33 weeks or 0.5 ppm for 26 or 42 weeks (NTP 1994), or rats and mice exposed to ≤0.2 ppm for 2 years (NTP 1994). Based on these data, it appears that rats are more susceptible to HCCPD-induced respiratory irritation effects than mice. Blood gas analysis, pulmonary ventilation, and lung mechanics were within normal ranges in pulmonary function tests of monkeys exposed to ≤0.2 ppm HCCPD for 7 and 13 weeks (Alexander et al. 1980b; Rand et al. 1982a).

Inhalation exposures to HCCPD vapor caused histopathological changes in the respiratory tracts of experimental animals. At nonlethal concentrations, these alterations were largely inflammatory or hyperplastic in nature, consistent with repetitive irritation at the portal of entry. Inflammation of the tissues was followed by necrosis, exfoliation, and/or hemorrhage. No histopathological examination was conducted, but gross necropsy of the lungs showed pale and swollen lungs in rats exposed to ≥1.68 ppm for 4 hours; findings were associated with increased absolute and relative lung weights at ≥3.31 and 1.83 ppm in male and female rats, respectively (Jackson and Hardy 1987). Inflammation, hyperplasia, and epithelial erosion were identified in the lungs of rats exposed to HCCPD vapor at 0.5 ppm for 1–2 weeks; recovery was apparent 2 weeks after exposure ceased in surviving animals (Alexander et al. 1980a; Rand et al. 1982a). No histopathological changes were identified in respiratory tissues of rats exposed to ≤0.11 ppm in the same manner (Alexander et al. 1980a; Rand et al. 1982a) or in rats and monkeys exposed to ≤0.2 ppm for 14 weeks (Alexander et al. 1980b; Rand et al. 1982a). Using electron microscopy, exposure-related increases in electron-lucent inclusions in club cells, formerly called Clara cells, were observed in rats exposed to 0.01–0.2 ppm for 14 weeks (Huntingdon Research Centre 1980; Rand et al. 1982b); however, this findings is considered a biomarker of exposure rather than evidence of toxicity due to the absence of histopathological findings or any other ultrastructural changes. No exposure-related ultrastructural changes were observed in monkeys exposed to ≤0.2 ppm for 14 weeks (Rand et al. 1982b). In a 30-week inhalation exposure study in rats, increased incidences of perivascular/peribronchiolar inflammatory cell infiltration were observed in males and females exposed to 0.56 ppm; males exposed to this concentration also exhibited an increased incidence of bronchiolar epithelial thinning/ulceration (Clark 1981). The incidences of bronchiolar epithelial hyperplasia, sloughing/loss, and edema also increased in male and female rats exposed to 0.56 ppm but did not reach statistical significance. Following a 14-week recovery period, no histopathological differences were identified in the lungs of control and treated rats, indicating reversibility of these lesions.

In 13-week studies, microscopic effects in the respiratory system produced by lethal HCCPD concentrations included necrotizing inflammation of the nose, larynx, trachea, and bronchus/bronchiole and hemorrhaging of the alveolus in male and female rats exposed to 0.941–2.065 ppm; suppurative inflammation of the alveolus in male and female rats at 0.941 ppm; acute necrosis of the nose, larynx, trachea, and lung epithelium and lung congestion in male and female mice at 2.142 ppm; tracheal squamous metaplasia in male and female mice at 0.949 ppm; and suppurative inflammation of the nasal epithelium of male and female mice exposed to 0.949–2.142 ppm (NTP 1994). Increased incidences of suppurative inflammation and squamous metaplasia in the nose and necrotizing and suppurative inflammation of the bronchus/bronchiole were identified in male rats exposed to 0.385 ppm, increased

incidences of nasal suppurative inflammation and tracheal squamous metaplasia were observed in male mice exposed to 0.389 ppm, and an increased incidence of nasal serous inflammation was present in female mice exposed to 0.389 ppm. No statistically significant increases were identified for non-neoplastic lesions in the respiratory tract tissues of female rats exposed to ≤0.385 ppm, male rats exposed to 0.146 ppm, or male or female mice exposed to ≤0.146 ppm (NTP 1994).

Histopathological findings in male and female mice exposed to 0.2 ppm for 2 years included nasal suppurative inflammation characterized by accumulation of cellular debris, mucus, neutrophils, and fibrin in the nasal lumen and infiltration of mononuclear cells and neutrophils into the lamina propria (NTP 1994). After 2-year exposures, an increased incidence of squamous metaplasia of the larynx (minimal severity) was identified in female rats at 0.01 and 0.2 ppm; the incidence at 0.05 ppm was also elevated but was not statistically significantly different from the concurrent control incidence. No treatment-related respiratory tract lesions were identified in male rats. The toxicological relevance of the squamous metaplasia was not clear to the NTP (1994) authors due to difficulties in obtaining consistent sections for analysis and determination of the boundary between squamous and columnar epithelium. Due to this, as well as the lack of clear dose-response, a LOAEL determination for squamous metaplasia was not included in Table 2-1.

To examine the progression and permanence of non-neoplastic lesions in the respiratory tract, NTP (1994) conducted additional studies in male mice with the intent of evaluating the relative effects of concentration and duration on development of these lesions. In these studies, concentrations were 0 or 0.2 ppm for 33 weeks and 0 or 0.5 ppm for 26 or 42 weeks. Animals were sacrificed at interim evaluations after 27, 34, or 43 weeks or 15 months of exposure or were sacrificed after 2 years. At the end of the exposure periods, the incidence of nasal suppurative inflammation increased in all treatment groups and suppurative inflammation of the trachea and lungs and alveolar epithelial hyperplasia increased in animals exposed to 0.5 ppm for 42 weeks. The incidence of alveolar epithelial hyperplasia also increased in male mice exposed to 0.5 ppm for 42 weeks. An evaluation of the data indicated that both concentration and duration of exposure influenced the development of these respiratory tract lesions; the inflammation of the trachea and lungs was not observed unless the product of the concentration and duration was >20 or 21 ppm-weeks.

In the chronic-duration studies of rats and mice exposed to HCCPD for 2 years, accumulation of a granular yellow-brown pigment was observed in the nasal epithelium in male and female rats and mice at ≥0.01 ppm, tracheal epithelium of male and female mice at ≥0.01 ppm, bronchiole epithelium of female

rats at ≥0.01 ppm, and lung epithelium of male and female mice ≥0.05 ppm (NTP 1994). At 0.2 ppm, minimal-to-mild tracheal, bronchiole, and peribronchiole pigmentation was observed in male rats and peribronchiole pigmentation was identified in female rats (NTP 1994). The pigmentation incidence and severity generally increased with concentration for each sex-species combination. In male mice exposed to 0.2 ppm for 33 weeks or 0.5 ppm for 26 or 42 weeks and then maintained for up to 2 years, pigmentation of the respiratory tract (nose, trachea, and/or lungs) was seen in the majority of exposed animals and did not disappear following exposure cessation and evaluation at 2 years, indicating a lack of recovery and physiological turnover of the pigment material. The incidence and severity were similar after 33, 66, and 104 weeks of exposure to 0.2 ppm HCCPD. In the chronic-duration and additional studies in male mice exposed to 0.2 ppm for 33 weeks and 0.5 ppm for 26 or 42 weeks, the pigmentation did not co-occur with respiratory lesions and did not appear to be a precursor to more significant effects (i.e., did not indicate an initial phase in the progression of a disease state). Results of several staining procedures applied to the pigmented lung sections of rats and mice indicated the presence of reducing substances, but no further analytical identification was performed. NTP (1994) indicated that the pigmentation may be a unique response to HCCPD and could be due to lipid peroxidation. Based on these data, ATSDR concludes that it is more appropriate to characterize the pigmentation as a marker of exposure to HCCPD rather than an adverse effect attributable to HCCPD exposure.

The potential for oral exposure to HCCPD to induce respiratory effects has been evaluated in acute- and intermediate-duration studies. In rats and mice administered lethal gavage doses of HCCPD, decreased respiratory rates were observed prior to death (Dean 1977; Gardner 1986a); this clinical sign was likely a consequence of significant morbidity prior to death rather than an effect of HCCPD on the respiratory system. No gross or histopathological changes were identified in the nasal cavity, trachea, larynx, bronchi, or lungs of rats at doses ≤150 mg/kg/day or in mice at doses ≤300 mg/kg/day for 13 weeks (Abdo et al. 1984; Velsicol 1981a, 1981b).

The potential toxicological effects of HCCPD on the respiratory tract following dermal exposure were evaluated in one acute-duration dermal toxicity study. A decreased rate of respiration was observed in rats administered topical doses ≥2,000 mg/kg for 24 hours (Gardner 1986b). The animals appeared normal 5–9 days after dosing and no gross pathological changes were identified in the lungs of animals that survived to the scheduled sacrifice.

2.5 CARDIOVASCULAR

No studies were located regarding cardiovascular effects in humans after exposure to HCCPD. Available data from laboratory animals indicate that the cardiovascular system is not a sensitive toxicity target following inhalation or oral exposure to HCCPD.

The cardiovascular system has been evaluated in experimental animals exposed to HCCPD via inhalation in acute-, intermediate-, and chronic-duration studies. Diffuse degenerative changes were observed in the hearts of rats, mice, and rabbits that died following acute exposure to lethal concentrations of HCCPD ranging from 0.3 to 66 ppm for 15 minutes to 2 weeks; incidence data were not provided, and findings were potentially attributable to autolysis (Treon et al. 1955). In another acute-duration study, there were no histopathological changes in the heart in rats exposed to concentrations up to 0.5 ppm after either 1 or 2 weeks (Alexander et al. 1980a; Rand et al. 1982a). In longer-term inhalation studies, there was no evidence for histopathological changes in the heart at intermediate-duration concentrations up to 0.56 ppm in rats, 0.389 ppm in mice, or 0.2 ppm in monkeys (Alexander et al. 1980b; Clark 1981; NTP 1994; Rand et al. 1982a) or chronic-duration concentrations up to 0.2 ppm in rats or mice (NTP 1994).

Potential cardiovascular effects of HCCPD oral exposures in experimental animals were evaluated in acute- and intermediate-duration studies. Single oral doses of 280–2,100 mg/kg caused degenerative changes in the hearts of rats and rabbits, possibly due to tissue autolysis; incidence data were not provided (Treon et al. 1955). In contrast, there were no gross or histopathological changes in the hearts of rats exposed to doses ≤150 mg/kg/day or mice exposed to doses ≤300 mg/kg/day for 13 weeks (Abdo et al. 1984; Velsicol 1981a, 1981b).

Rabbits that died following single dermal doses of 610–6,130 mg/kg displayed degenerative changes in the heart, possibly because of tissue autolysis; incidence data were not provided (Treon et al. 1955).

2.6 GASTROINTESTINAL

The data provide evidence that HCCPD produces portal-of-entry effects in the gastrointestinal system, specifically the stomach, following oral exposures. Data on adverse gastrointestinal effects following inhalation exposure are limited to clinical signs following accidental occupational exposure; no effects on the gastrointestinal system were observed following dermal exposure to HCCPD. Based upon systematic review (Appendix C), the gastrointestinal system is a presumed hazard of HCCPD toxicity following oral

exposure based on no route-specific data in humans and a high level of evidence from laboratory animal studies.

WWTP workers exposed to HCCPD for 3–15 days due to an inadvertent industrial release complained of nausea (22% of 177 workers) and abdominal cramps (prevalence not specified) (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). While classified as gastrointestinal in this profile, it is possible that nausea may be neurological in origin.

Gastrointestinal effects of HCCPD have been evaluated in laboratory animals following intermediate- and chronic-duration inhalation exposures. No microscopic changes were seen in the stomach, esophagus, or intestines of monkeys, rats, or mice exposed to concentrations up to 0.2, 0.56, or 0.5 ppm, respectively, in intermediate-duration studies (Alexander et al. 1980b; Clark 1981; NTP 1994; Rand et al. 1982a), or rats or mice following chronic-duration exposure to concentrations up to 0.2 ppm (NTP 1994). The gastrointestinal tract does not appear to be a sensitive target for HCCPD in animals following inhalation exposures.

The potential impact of HCCPD exposure on gastrointestinal tissues has been evaluated in acute- and intermediate-duration oral exposure studies in experimental animals. Increased incidences of diarrhea were observed in rats dosed with ≥1,260 mg/kg (Gardner 1986a) and female and male mice dosed with 464 and 1,000 mg/kg, respectively (Dean 1977). Acute necrotic lesions of the forestomach were noted in some rats administered an oral dose of 280–2,100 mg/kg; incidence data were not provided (Treon et al. 1955). After 13-week exposures to HCCPD, increased incidences of forestomach epithelial hyperplasia were observed in male and female rats at 38 mg/kg/day and male and female mice at 75 mg/kg/day (Abdo et al. 1984; Velsicol 1981a, 1981b). Increased incidences of focal inflammation in the forestomach were identified in male and female rats at 38 mg/kg/day and male and female mice at 75 mg/kg/day. The incidences and ranges of lesion severities were directly related to the dose. No histopathological changes were identified in the esophagus, duodenum, jejunum, ileum, or colon of males and females of either species. These data suggest that rats are more sensitive to HCCPD-induced effects to the forestomach than mice. The presence of the forestomach lesions and lack of histopathological changes in other regions of the gastrointestinal tract suggests that the forestomach effects result from direct contact of these tissues with HCCPD.

2.7 HEMATOLOGICAL

The data indicate HCCPD may alter red blood cell hematology parameters following inhalation exposure without causing histopathological changes to bone marrow; no consistent effects were noted in white blood cell parameters following inhalation exposure and no effects on the hematological system were observed in animals following oral exposures to HCCPD. Data are not available via the dermal route. Based upon systematic review (Appendix C), the hematological system, specifically red blood cell parameters, is a suspected hazard of HCCPD toxicity following inhalation exposure based on inadequate data in humans and a moderate level of evidence from laboratory animal studies. White blood cell effects are not classifiable as to the hazard to humans based on inadequate data in humans and animals.

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

The potential hematological effects of HCCPD were evaluated in experimental animals exposed via inhalation after acute-, intermediate-, and chronic-duration exposures. No effects on bone marrow histopathology were reported in rats exposed to 0.5 ppm for 1–2 weeks (Alexander et al. 1980a; Rand et al. 1982a), rats and mice exposed to ≤0.385 and ≤0.389 ppm, respectively, for 13 weeks, or rats and mice exposed to ≤0.2 ppm for 2 years (Alexander et al. 1980b; NTP 1994; Rand et al. 1982a). Across acute- and intermediate-duration multiple exposure studies, altered red blood cell hematology parameters were identified in rats, particularly males, as seen in Table 2-4.

Table 2-4. LOAEL Values for Red Blood Cell Hematological Effects of Rats Exposed to HCCPD Vapor in Acute- and Intermediate-Duration Inhalation Studies

Hematology parameter	Rand et al. 1982a[a]: 1–2 weeks	Rand et al. 1982a[a]: 1–2 weeks (recovery group)	NTP 1994: 13 weeks	NTP 1994: 13-week special hematology study	Clark 1981: 30 weeks
Males					
PCV	↑ (0.5[b])	↔	↑ (0.385)	↔	–
Hb	↑ (0.5)	↑ (0.5)	↑ (0.385)	↔	↑ (0.14)
RBC	↑ (0.5)	↔	↑ (0.385)	↔	↑ (0.14)
MCV	↔	↔	↔	↑ (0.385)	↔
MCH	–	–	↑ (0.385)	↔	↔
MCHC	↔	↑ (0.5)	↔	↔	↔

Table 2-4. LOAEL Values for Red Blood Cell Hematological Effects of Rats Exposed to HCCPD Vapor in Acute- and Intermediate-Duration Inhalation Studies

Hematology parameter	Rand et al. 1982a[a]: 1–2 weeks	Rand et al. 1982a[a]: 1–2 weeks (recovery group)	NTP 1994: 13 weeks	NTP 1994: 13-week special hematology study	Clark 1981: 30 weeks
HCT	–	–	–	–	↑ (0.14)
Females					
PCV	↑ (0.5)	↔	↔	↑ (0.385)	–
Hb	↑ (0.5)	↔	↔	↑ (0.385)	↔
RBC	↑ (0.5)	↔	↓ (0.385)	↑ (0.385)	↔
MCV	↔	↔	↑ (0.385)	↑ (0.385)	↔
MCH	–	–	↔	↑ (0.385)	↔
MCHC	↔	↔	↔	↔	↔
HCT	–	–	–	–	↔

[a]Data are also available in the unpublished industry report by Alexander et al. (1980a).
[b]LOAEL concentrations are in ppm.

↑ = increased mean value; ↓ = decreased mean value; ↔ = no significant, dose-related change in mean value; – = not assessed; Hb = hemoglobin; HCT =hematocrit; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration; MCV = mean cell volume; PCV = packed cell volume; RBC = red blood cell count

The most consistently observed effects were increased hemoglobin levels in male and female rats and increased red blood cell counts in male rats. Generally, effects were observed at concentrations ≥0.14 ppm and had magnitudes of effect that were <10% of control values. The exceptions are for the 1–2-week range-finding study (Alexander et al. 1980a; Rand et al. 1982a), where 20–30% increases in red blood cell parameters were identified at 0.5 ppm, a concentration that co-occurred with significantly decreased water intake and produced significant mortality and morbidity (see Section 2.2). Drinking water intakes were not assessed in the NTP (1994) studies and were not affected by HCCPD exposure in the Clark (1981) study (see Section 2.18). While statistically significant altered hemoglobin, mean cell volume (MCV), and mean cell hemoglobin concentration (MCHC) values were reported in rats following a 14-week exposure at concentrations as low as 0.01 ppm, these changes were sporadically observed and were not dose-responsive, and the magnitudes of effect were generally low (≤5%) (Alexander et al. 1980b; Rand et al. 1982a). Therefore, they were not considered to be biologically significant in this assessment and are not presented in Table 2-4. For intermediate-duration exposures in rats, the NOAEL values were 0.039–0.146 ppm for the NTP (1994) 13-week studies and 0.06 ppm for the Clark (1981) 30-week study.

Rand et al. (1982a) postulated that these minor variances in hematological parameters were a consequence of hemorrhagic lesions in the lungs and not a direct influence of HCCPD on hematopoiesis or red cell turnover. Since the red blood cell hematology parameters were more consistently altered in male rats than in female rats, this hypothesis correlates with the increased absolute and relative lung weights and more severe histopathological effects observed in the lungs of male rats in the 1–2-week Rand et al. (1982a) study. NTP (1994) suggested that the red blood cell hematology alterations were not attributable to HCCPD treatment due to the inconsistent dose-response and lack of correlation in the results across sexes and between the core and special 13-week hematology studies. While there are inconsistencies in the red blood cell parameter results obtained from the NTP (1994) studies, common alterations in hemoglobin levels and red blood cell counts across repeated inhalation exposure studies suggest a consistent biological response to HCCPD. In the absence of additional data and based on the lack of histopathological effects to bone marrow, ATSDR considers the altered red blood cell parameters to be plausibly related to respiratory tract damage resulting in compromised gas exchange.

In mice, the only consistent HCCPD treatment-related effect on red blood cell hematology parameters across studies was decreased MCV in female mice after exposure to 0.389 ppm for 13 weeks in the core and special hematology studies (NTP 1994). Other red blood cell effects were limited to increased MCHC in male mice at 0.389 ppm and in female mice at 0.039–0.389 ppm in the special 13-week hematology study. The magnitudes of effect were within 5% of control values. HCCPD treatment-related effects on other hematological parameters following inhalation exposures were limited to decreased reticulocytes (40%) in female rats exposed to 0.385 ppm in the special hematology study (NTP 1994); decreased total white blood cells (46%) and lymphocyte count (53%) in male rats, and increased neutrophil count (114%) in female rats exposed to 0.5 ppm for 1–2 weeks (Alexander et al. 1980a; Rand et al. 1982a); and decreased percent lymphocytes (8–10%) and increased neutrophil count (27–36%) in male rats exposed to ≥0.14 ppm and decreased lymphocyte count (16%) in female rats exposed to 0.56 ppm for 30 weeks (Clark 1981). No clear biological basis can be identified for these effects based on the lack of consistency across studies.

In intermediate-duration oral exposure studies, no histopathological changes were identified in the bone marrow of rats dosed with ≤150 mg/kg/day or mice dosed with ≤300 mg/kg/day for 13 weeks (Abdo et al. 1984; Velsicol 1981a, 1981b). Hematology parameters were not evaluated in this study.

2.8 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans after exposure to HCCPD. Available inhalation and oral data in laboratory animals indicate the musculoskeletal system is not a sensitive target of toxicity following exposure to HCCPD; no dermal studies were identified.

The potential effect of HCCPD on musculoskeletal tissues has been evaluated in laboratory animals following intermediate- and chronic-duration inhalation exposures and acute- and intermediate-duration oral exposures. HCCPD did not affect skeletal muscle of rats or monkeys exposed to up to 0.2 ppm for 14 weeks (Alexander et al. 1980b; Rand et al. 1982a); femoral muscle, knee joint, or femur of male and female rats exposed to ≤0.56 ppm for 30 weeks (Clark 1981); bone histopathology of mice or rats exposed to ≤0.389 ppm for 13 weeks or ≤0.2 ppm for 2 years (NTP 1994). Similarly, no histopathological changes were identified in thigh muscle, rib (costochondral junction), or femur of rats exposed to ≤150 mg/kg/day or mice exposed to ≤300 mg/kg/day via gavage for 13 weeks (Abdo et al. 1984; Velsicol 1981a, 1981b). In animals that died, decreased limb tone was observed in mice (prior to death) after a single exposure to 1,000 mg/kg via gavage (Dean 1977).

2.9 HEPATIC

The data indicate that the hepatic system is not a sensitive target of HCCPD toxicity.

Serum markers of hepatotoxicity were evaluated in 97 cleanup workers exposed to HCCPD vapors at a WWTP because of an inadvertent industrial release (Kominsky et al. 1980). Abnormal serum marker ranges were identified for 18 of the 97 workers (19%); aspartate aminotransferase (AST) values were elevated for 12 workers, alkaline phosphatase (ALP) was elevated for 5 workers, and total bilirubin was elevated for 1 worker (Kominsky et al. 1980). For 8 of the 97 cleanup crew members, these biochemical parameters were abnormal on more than one occasion, and 7 workers had values that were temporally-related to exposure conditions. It should be noted that evaluations were not performed on unexposed workers, and it is not known if the abnormal values observed in exposed workers differ from the unexposed local general population.

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). Clinical tests included measurement of alanine aminotransferase

(ALT), AST, ALP, total bilirubin, γ-glutamyltransferase (GGT), lactate dehydrogenase (LDH), and total bile acids. Personal air sampling for HCCPD was performed on a subset of study participants but was not used to evaluate associations between HCCPD exposure and liver function values.

The hepatotoxic potential of HCCPD has been evaluated in laboratory animals following acute-, intermediate-, and chronic-duration inhalation exposures. Mild-to-moderate hepatic tissue degeneration was observed following acute-duration inhalation exposures to 0.34–73.6 ppm for 15 minutes to 5 days, and to intermediate-duration exposures to 0.34 ppm for 6 weeks or 0.15 ppm for 30 weeks; incidence data were not provided (Treon et al. 1955). 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 in moribund or dying animals. An apparent dose-related increase in perivascular/peribiliary inflammatory cell infiltrates in the liver was observed in female rats exposed to 0.06–0.56 ppm; however, incidences did not differ significantly from control and no hepatic lesions were observed in similarly exposed male rats (Clark 1981). In other inhalation studies, no exposure-related hepatic lesions were seen following acute-duration exposure in rats to concentrations up to 0.5 ppm (Alexander et al. 1980a; Rand et al. 1982a); intermediate-duration exposure in monkeys, rats, or mice to concentrations up to 0.2, 0.385, or 0.5 ppm, respectively (Alexander et al. 1980b; NTP 1994; Rand et al. 1982a); or chronic-duration exposure in rats or mice to concentrations up to 0.2 ppm (NTP 1994).

No consistent evidence of exposure-related changes in hepatic serum biochemistry or liver weight was observed following inhalation exposure to HCCPD. Serum concentrations of the biochemical parameters LDH, AST, ALP, and ALT in rats and mice were not influenced by inhalation exposure to HCCPD concentrations ≤0.389 ppm for 13–14 weeks (Alexander et al. 1980b; NTP 1994; Rand et al. 1982a). During the 13-week special hematology, clinical chemistry, and urinalysis study conducted in rats by NTP (1994), the highest concentration of 2.065 ppm caused elevated serum AST concentrations (1.7–7.6-fold) in male and female rats on days 4–16; however, this concentration was lethal to all the animals prior to the day 46 clinical evaluation, and a comparable increase was not observed in mice (NTP 1994). Relative liver weights of rats were significantly reduced by 3–15% in males and females exposed to 0.01–0.2 ppm for 13 weeks, but the decreases were not dose-related (Alexander et al. 1980b; Rand et al. 1982a). No changes in liver weights were observed in rats or mice exposed to concentrations ≤0.389 ppm for 13 weeks or ≤0.2 ppm for 2 years (NTP 1994).

Acute- and intermediate-duration oral toxicity studies have evaluated the potential effects of HCCPD exposure on the liver. High, acute-duration oral doses of HCCPD were associated with liver necrosis and

tissue degeneration in rats (261–1,959 mg/kg) and rabbits (579–877 mg/kg); incidence data were not provided (Treon et al. 1955). HCCPD did not induce histopathological changes in hepatic tissues of rats and mice exposed to doses up to 150 and 300 mg/kg/day, respectively, via gavage for 13 weeks (Abdo et al. 1984; Velsicol 1981a, 1981b).

The potential for HCCPD to cause hepatotoxicity following dermal exposure was evaluated only for acute-duration exposures. Rabbits exposed to single dermal doses of 401–5,719 mg/kg displayed necrosis of the liver; incidence data were not provided (Treon et al. 1955). The study authors stated that degenerative changes persisted even 21 days after the exposure period in surviving animals.

2.10 RENAL

The data indicate that the renal system is a potential target for HCCPD via the oral route; it does not appear to be a sensitive target for HCCPD via the inhalation or dermal routes. Based upon systematic review (Appendix C), the kidney is a presumed hazard of HCCPD toxicity following oral exposure based on no data in humans and a high level of evidence from laboratory animal studies.

Urine samples were collected from 41 workers exposed for 3–15 days to HCCPD at a WWTP as the result of an inadvertent industrial release into the sewage system (Morse et al. 1979). Proteinuria was identified in 6 of 41 workers immediately after exposure but no abnormalities were detected 3 weeks later. Urinalysis parameters were normal in all 97 cleanup crew workers evaluated (Kominsky et al. 1980). It should be noted that urinalysis was not performed on unexposed workers, and it is not known if proteinuria values observed in exposed workers differ from the local general population.

Relative to a group of 35 controls, 73 male operators employed for an average of 8.2 years in a plant producing chlorinated hydrocarbons, including HCCPD, showed no evidence of damage to the renal tubules (Boogaard et al. 1993). The investigations 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. Personal air sampling for HCCPD

was performed on a subset of study participants but was not used to evaluate associations with renal function values.

The potential renal effects following inhalation exposure to HCCPD have been evaluated in laboratory animals following acute, intermediate, and chronic durations. Inhalation exposure of HCCPD caused renal tubular necrosis in rats, mice, guinea pigs, and rabbits at 0.34–73.6 ppm for 15 minutes to 7 days, 0.34 ppm for 6 weeks, and 0.15 ppm for 30 weeks; incidence data were not provided (Treon et al. 1955). In other inhalation studies, no significant, exposure-related renal lesions were seen following acute-duration exposure in rats to concentrations up to 0.5 ppm (Alexander et al. 1980a; Rand et al. 1982a); intermediate-duration exposure in monkeys, rats, or mice to concentrations up to 0.2, 0.56, or 0.5 ppm, respectively (Alexander et al. 1980b; Clark 1981; NTP 1994; Rand et al. 1982a); or chronic-duration exposure in rats or mice to concentrations up to 0.2 ppm (NTP 1994).

The potential toxicological effects of HCCPD on the kidneys have been evaluated in laboratory animals in acute-and intermediate-duration oral studies. Degenerative lesions in the kidney tubules resulted from single gavage doses of 261–1,959 mg/kg in rats and 579–877 mg/kg in rabbits; incidence data were not provided (Treon et al. 1955). Toxic nephrosis was observed in male and female rats exposed to ≥38 mg/kg/day and female mice exposed to ≥75 mg/kg/day via gavage for 13 weeks (Abdo et al. 1984; Velsicol 1981a, 1981b). These lesions were located in the terminal sections of the proximal tubules of the renal cortex and were characterized by mild dilation of the tubules and karyomegaly, cytomegaly, and anisokaryosis accompanied by cytoplasmic and nuclear vacuolization. Additionally, brown granular pigment debris protruded into the lumen. In male mice, tubular necrosis was present in 70% of the male mice receiving the 300 mg/kg/day dose but not at lower doses; this lesion was morphologically distinct from the toxic nephrosis seen in the other animals and may have contributed to the early deaths observed at this dose level. No renal histopathological effects were identified in male and female rats at ≤19 mg/kg/day, female mice at ≤38 mg/kg/day, or male mice at ≤150 mg/kg/day (Abdo et al. 1984; Velsicol 1981a, 1981b).

Rabbits exposed to single dermal doses of 401–5,719 mg/kg displayed degeneration and necrosis of the kidney tubules; incidence data were not provided (Treon et al. 1955). The study authors stated that renal effects were still apparent 21 days after dosing in surviving animals.

2.11 DERMAL

Human and animal data indicate HCCPD causes skin irritation following direct dermal contact with HCCPD liquid or vapor.

An unspecified percentage of 145 workers exposed to HCCPD vapors for 3–15 days at a WWTP as a result of an inadvertent industrial release reported skin irritation, with five employees verified to exhibit visible signs of skin irritation (Morse et al. 1979). In a subsequent publication, 21% of 177 employees with usable medical questionnaire responses reported skin irritation following HCCPD release and prior to plant closure; 10% of the 177 employees reported experiencing skin irritation approximately 6 weeks later (Kominsky et al. 1980).

In acute-duration dermal toxicity studies, topical application of HCCPD in either its pure form or in solution appears to have a pronounced effect upon the epidermis of experimental animals. Generally, HCCPD initially causes edema that progressed to hardening or encrustation at the application site (Gardner 1986b; OxyChem 1972; Treon et al. 1955). In a series of studies, severe irritation and skin necrosis were observed in a monkey administered 0.05 mL of a 10% (v/v) solution for 3 days; necrotic, hardened, encrusted, and discolored skin was identified following application of Ultrasene solutions containing ≥40% HCCPD to guinea pigs; and subcutaneous edema and local discoloration that progressed to encrustation and fissuring were observed after a dermal dose of ≥430 mg/kg was applied to rabbit skin; incidence data were not provided (Treon et al. 1955). The lesions generally healed with time in the surviving animals. Thirteen months after exposure, the monkey's treated skin was scarred and hairless. No evidence of dermal effects was identified in a monkey administered 0.01 mL of Ultrasene solutions containing up to 10% HCCPD, but application of 0.05 mL of solutions containing ≥20% HCCPD caused the skin to become discolored and swell. No evidence of skin irritation was observed in guinea pigs after dermal doses of 0.05 mL of Ultrasene solutions containing ≤1% HCCPD (Treon et al. 1955). Eschar formation was noted after dermal application of 200 mg/kg HCCPD to rabbits (OxyChem 1992). Results of standard dermal irritation tests indicated that 0.5 mL HCCPD produced slight to severe edema and necrosis at the application sites (OxyChem 1972, 1992).

The potential effects of systemic HCCPD exposure on skin histopathology of laboratory animals were evaluated in intermediate- and chronic-duration inhalation studies and intermediate-duration oral studies. No histopathological changes were identified in the skin (specific location not identified) of male or female rats exposed to concentrations ≤0.56 ppm for 30 weeks (Clark 1981) or in male or female rats and

mice exposed to concentrations ≤0.2 ppm for 2 years (NTP 1994). Additionally, no histopathological changes were identified in skin (specific location not identified) of rats and mice at gavage doses up to 150 or 300 mg/kg/day, respectively, for 13 weeks (Abdo et al. 1984; Velsicol 1981a, 1981b).

2.12 OCULAR

Human and animal data indicate that direct ocular contact with HCCPD vapor may produce ocular irritation at sufficiently high concentrations.

Eye irritation was one of the major symptoms reported by sewage treatment plant workers exposed to HCCPD vapors for 3–15 days at a WWTP because 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, 85 (59%) complained of eye irritation (Morse et al. 1979). In a follow-up questionnaire 6 weeks later, 9% of 177 respondents were still experiencing ocular irritation (Kominsky et al. 1980; Morse et al. 1979). Tearing and redness of the eyes were present in five individuals on the day of exposure.

Eye irritation, as evidenced by lacrimation, was also observed in animals exposed to HCCPD vapors for up to 7 hours (Jackson and Hardy 1986, 1987; OxyChem 1972; Rand et al. 1982a; Treon et al. 1955). Partially or completely closed eyes were identified in rats exposed to ≥1.67 ppm for 1 hour (Jackson and Hardy 1986) and ≥1.68 ppm for 4 hours (Jackson and Hardy 1987). Direct ocular exposure to HCCPD vapors most likely contributed to these effects. Irritation of the eyes or eyelids was observed for rats, mice, guinea pigs, and rabbits following single exposures to HCCPD concentrations as low as 1.0 ppm and multiple exposures to concentrations as low as 0.33 ppm for up to 6 weeks; ocular irritation was not observed in any species exposed to 0.15 ppm for up to 30 weeks (Treon et al. 1955). Lacrimation was evident in rats exposed to 5.8 ppm HCCPD for 4 hours and dark red eyes were observed in rats exposed to 0.5 ppm for 5–10 days and ≥0.05 ppm for 14 weeks (Alexander et al. 1980a, 1980b; Rand et al. 1982a). No clinical signs of eye irritation were noted in monkeys exposed to HCCPD vapor at concentrations up to 0.2 ppm for 14 weeks (Alexander et al. 1980b; Rand et al. 1982a). No ophthalmological or histopathological changes were identified in the ocular tissues of rats or monkeys exposed to concentrations up to 0.2 ppm for 14 weeks (Alexander et al. 1980b; Rand et al. 1982a). HCCPD exposure did not cause histopathological changes in the eyes of rats exposed to concentrations up to 0.56 ppm for 30 weeks (Clark 1981).

Severe eye irritation was produced when 0.1 mL of HCCPD was placed in the conjunctival eye sac for 5 minutes and then rinsed with water (OxyChem 1972). Corrosion of the ocular tissues occurred when the material was left in place for 24 hours prior to rinsing (OxyChem 1972).

2.13 ENDOCRINE

No reports of changes in human endocrine parameters or organs after exposure to HCCPD were found. Based on available data in laboratory animals, HCCPD does not produce histopathological changes to endocrine organs. Insufficient data are available to assess the potential effects of HCCPD exposure on endocrine function, including endocrine hormone levels.

Potential histopathological and organ weight effects in endocrine organs have been evaluated in laboratory animals following acute-, intermediate-, and chronic-duration inhalation exposure to HCCPD. Degenerative changes in the adrenal glands of rats, mice, guinea pigs, and rabbits were observed after exposures to concentrations of 0.34–73.6 ppm for periods of 15 minutes to 1 week, 0.34 ppm for 6 weeks, and 0.15 ppm for 30 weeks; incidence data were not provided (Treon et al. 1955). Due to the high mortality observed at these concentrations, these changes may have been the result of tissue autolysis in moribund or dying animals. Effects on the adrenal, thyroid, parathyroid, pancreas, and pituitary glands following inhalation exposure of male mice to 0.039–0.389 ppm HCCPD for 13 weeks were limited to increased relative adrenal weights; no histopathological changes were noted in these organs in treated male mice and no effects on adrenal, thyroid, parathyroid, pancreas, or pituitary gland weights or histopathology were observed in female mice exposed to ≤0.389 and male and female rats exposed to ≤0.385 ppm for 13 weeks (NTP 1994). The biological significance of these adrenal weight changes cannot be assessed quantitatively in the absence of hormone product measurements or concurrent histopathological findings. There were no organ weight or histopathological changes in the adrenal glands, pancreas, thyroid, parathyroid gland, and/or pituitary gland identified in male and female rats and monkeys exposed for 14 weeks at ≤0.2 ppm (Alexander et al. 1980b; Rand et al. 1982a), in male and female rats after 30-week exposures to ≤0.56 ppm (Clark 1981), or in rats and mice following 2-year exposures to ≤0.2 ppm (NTP 1994). Additionally, no effects on the adrenal glands were identified in male mice exposed to 0.5 ppm for 26–42 weeks (NTP 1994).

Potential effects of HCCPD on endocrine organ weight and histology have also been evaluated in laboratory animals following acute- and intermediate-duration oral exposures and acute-duration dermal exposures. Degenerative changes in the adrenal tissues resulted from exposure to single oral doses of

280–2,100 mg/kg in rats and 620–940 mg/kg in rabbits; these changes may have resulted from tissue autolysis in moribund or dying animals, but no incidence data were reported (Treon et al. 1955). There were no histopathological changes in the adrenals, thyroid, parathyroid, or pituitary glands in 13-week studies at gavage doses up to 150 mg/kg/day in rats and 300 mg/kg/day in mice (Abdo et al. 1984; Velsicol 1981a, 1981b). Rabbits that were dermally exposed to HCCPD (430–6,130 mg/kg) had degenerative changes of the adrenal glands that were still apparent in survivors 21 days after exposure; incidence data were not provided (Treon et al. 1955).

No data were identified evaluating endocrine function following *in vivo* exposure to HCCPD; however, limited *in vitro* screening data are available. HCCPD exhibited statistically significant radioactive iodide uptake inhibition in a ToxCast high-throughput screening assay (Wang et al. 2019). Iodide uptake is the first step in thyroid hormone biosynthesis.

2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects in humans after exposure to HCCPD. Based on available data in laboratory animals, HCCPD does not cause histopathological alterations to immunological organs. However, no studies evaluating immune function following exposure to HCCPD were identified.

Potential effects of HCCPD on immune organ weight and histology have also been evaluated in acute-, intermediate-, and chronic-duration inhalation exposure studies and intermediate-duration oral exposure studies in laboratory animals. No exposure-related changes were identified in these studies. There were no histopathological changes in the spleen of rats exposed to ≤0.5 ppm for 1–2 weeks (Alexander et al. 1980a; Rand et al. 1982a). In intermediate-duration studies, no histopathological changes were identified in immune organs (spleen, thymus, and/or lymph nodes) of monkeys, rats, or mice to concentrations up to 0.2, 0.56, or 0.5 ppm, respectively (Alexander et al. 1980b; Clark 1981; NTP 1994; Rand et al. 1982a). Similarly, no histopathological effects were observed in immune organs of rats or mice exposed to ≤0.2 ppm for 2 years (NTP 1994). In a 13-week oral study, no treatment-related histopathological findings were identified in the mandibular and mesenteric lymph nodes, thymus, or spleen at gavage doses up to 150 mg/kg/day in rats or 300 mg/kg/day in mice (Abdo et al. 1984; Velsicol 1981a, 1981b).

2.15 NEUROLOGICAL

Based on available data, HCCPD does not cause histopathological alterations in the nervous system. Evaluation of neurological function is limited to clinical signs of toxicity; therefore, insufficient data are available to assess the potential effect of HCCPD exposure on neurological function, including behavior.

Among sewage treatment plant workers exposed to HCCPD at a WWTP because of an inadvertent industrial release, headaches were self-reported by 65 of 145 workers (45%) after exposure for 3–15 days (Morse et al. 1979). Six weeks later, 32 of 177 workers (18%) responding to a questionnaire were still experiencing headaches (Kominsky et al. 1980). No studies were located regarding neurological effects in humans after oral or dermal exposure to HCCPD.

Neurological clinical signs of toxicity and nervous system histopathology were evaluated in acute-, intermediate-, and chronic-duration inhalation exposure studies. Rats and mice exposed to concentrations of 0.385–2.142 ppm HCCPD were described as listless after 1–3 weeks of exposure (NTP 1994). Incidence data for clinical signs were not provided, so it is unclear how many animals exhibited this effect or how frequently; however, the study authors did note that listlessness was observed earlier during the exposure period with higher HCCPD concentrations. Some rats, mice, guinea pigs, and rabbits exposed to high lethal concentrations of HCCPD (≥46.5 ppm) by acute-duration inhalation experienced tremors; incidence data were not provided (Treon et al. 1955). At necropsy, diffuse degenerative changes in the brain were observed in all rats, mice, guinea pigs, and rabbits after exposures to 0.34–73.6 ppm for periods of 15 minutes to 1 week, 0.34 ppm for 6 weeks, and 0.15 ppm for 30 weeks; incidence data were not provided (Treon et al. 1955). These degenerative changes may have been the result of tissue autolysis. In contrast, there were no histopathological changes in the brains of rats exposed to 0.5 ppm for 1–2 weeks (Alexander et al. 1980a; Rand et al. 1982a), male mice exposed to 0.2 ppm for 33 weeks (NTP 1994), or rats and mice exposed to ≤0.389 ppm for 13 weeks or ≤0.2 ppm for 2 years (NTP 1994). Similarly, no histopathological changes were observed in the brains or sciatic nerve of rats or monkeys exposed to ≤0.2 ppm for 14 weeks (Alexander et al. 1980b; Rand et al. 1982a) or in brain, spinal cord, or sciatic or posterior tibial nerves of rats exposed to ≤0.56 ppm for 30 weeks (Clark 1981).

The potential neurotoxicity of HCCPD has been evaluated in acute- and intermediate-duration oral exposure studies. Clinical signs of neurotoxicity were observed following acute-duration gavage exposure in mice, including hypoactivity at 464 mg/kg and ataxia at 1,000 mg/kg, a dose associated with lethality (Dean 1977). Similarly, all rats exposed once to ≥1,260 mg/kg via gavage exhibited abnormal

gait (high stepping, waddling) and lethargy (Gardner 1986a). Single oral doses ≥180 mg/kg caused lethargy in rats and rabbits 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 in the rats that survived to the scheduled sacrifice; incidence data were not provided. No histopathological lesions of the brain, sciatic nerve, or spinal cord were noted in rats or mice exposed to gavage doses up to 150 or 300 mg/kg/day, respectively, for 13 weeks (Abdo et al. 1984; Velsicol 1981a, 1981b). These data suggest that brain lesions occur only with exposures to high oral doses of HCCPD.

Rabbits exposed to single dermal doses of HCCPD (430–6,130 mg/kg) displayed degenerative changes in the brain at necropsy; incidence data were not provided (Treon et al. 1955). These changes were still apparent 21 days after exposure in surviving animals. Ataxia, hypoactivity, and a depressed breathing pattern have been observed in rabbits at lethal dermal doses of HCCPD (OxyChem 1972).

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans after exposure to HCCPD. The available animal data do not indicate that HCCPD causes histopathological alterations to reproductive organs. However, insufficient data are available to thoroughly assess the potential for toxicity to the reproductive system, as no studies evaluating reproductive function following inhalation, oral, or dermal exposure to HCCPD were identified.

The potential effects of HCCPD on reproductive organ weight and histology have been evaluated in experimental animals exposed by inhalation for intermediate and chronic durations. The sole effect on reproductive organs identified with HCCPD treatment is an increased incidence of ovarian suppurative inflammation in female mice exposed to HCCPD at 0.05–0.2 ppm for 2 years; no histopathological changes were identified in the uterus (NTP 1994). While this lesion is clearly adverse, as it was the suspected cause of increased mortality at 0.2 ppm, the causal relationship between HCCPD exposure and lesion development is unclear. The study authors noted that lesions were similar to those observed in other NTP studies attributed to stress-related susceptibility to utero-ovarian infection by *Klebsiella* species (NTP 1994). In contrast, no treatment-related histopathological lesions of the female (ovaries and uterus) or male (testes, prostate, and/or seminal vesicle) reproductive organs were identified in monkeys, rats, or mice exposed to concentrations up to 0.2, 0.385, or 0.389 ppm for 13–14 weeks (Alexander et al. 1980b; NTP 1994; Rand et al. 1982a); male mice exposed to 0.2 ppm for 33 weeks or 0.5 ppm for

42 weeks (NTP 1994); rats exposed to ≤0.56 ppm for 30 weeks (Clark 1981); or rats or male mice exposed to ≤0.2 ppm for 2 years (NTP 1994).

The potential effects of HCCPD on reproductive organ weight and histology have also been evaluated in laboratory animals following intermediate-duration oral exposure. HCCPD did not cause treatment-related effects on the testes, seminal vesicles, prostate, ovaries, or uterus in rats or mice exposed to doses up to 150 or 300 mg/kg/day, respectively, via gavage for 13 weeks (Abdo et al. 1984; Velsicol 1981a, 1981b).

No data were identified evaluating reproductive function following inhalation, oral, or dermal exposure to HCCPD; however, limited screening data are available. Although it exhibited some estrogen receptor binding affinity in a recombinant human estrogen receptor α (hERα) binding assay, HCCPD did not exhibit estrogenic or anti-estrogenic activity in an immature uterotrophic assay in female rats following subcutaneous injection (Akahori et al. 2008). No anti-androgenic activity was detected for HCCPD in Chinese hamster ovary (CHO) cells transfected with human androgen receptor (hAR) in an androgen-responsive luciferase reporter assay (Roy et al. 2004).

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans after exposure to HCCPD. Animal data are available only via the oral route and are too limited to assess whether or not the developing organism is a target of HCCPD toxicity at doses below those associated with maternal toxicity.

HCCPD was not embryotoxic, fetotoxic, or teratogenic in mice following maternal exposure to gavage doses up to 75 mg/kg/day during GDs 6–15 (Murray et al. 1980). In rabbits, a dose-dependent increase in the incidence of 13 ribs was identified in the offspring of does exposed to 75 mg/kg/day via gavage during GDs 6–18; nonstatistically significant increases were also identified at 5 and 25 mg/kg/day. No other evidence of embryotoxicity, fetotoxicity, or teratogenicity was identified in rabbits (Murray et al. 1980). The natural variation in the number of ribs for rabbits is 12–13. It should be noted that the compound was not maternally toxic in mice, but maternal mortalities and weight loss were observed in rabbits at 75 mg/kg/day (numbers affected and magnitude of effect not specified).

A screening study was performed to evaluate prenatal and postnatal development of mice exposed to HCCPD during gestation. Mice born to dams administered 45 mg/kg/day HCCPD via gavage during

GDs 8–12 did not exhibit evidence of developmental toxicity when evaluated on postnatal days (PNDs) 1 and 3 (Chernoff and Kavlock 1982, 1983). When the offspring were evaluated over a 250-day postnatal period (including through puberty and breeding), there were no adverse effects on postnatal viability, growth, locomotor activity, sexual development (percent vaginal patency at day 30), or reproductive function (Gray and Kavlock 1984; Gray et al. 1986).

2.18 OTHER NONCANCER

No studies were located regarding other noncancer effects in humans after exposure to HCCPD.

Other noncancer effects of HCCPD identified in experimental animals are limited to food and water intake. During the first few days of the post-exposure observation periods, decreased food and water intake were observed in rats exposed for 1 hour to ≥1.67 ppm (Jackson and Hardy 1986) and rats exposed for 4 hours to ≥1.68 ppm (Jackson and Hardy 1987); these concentrations were associated with overt signs of toxicity during exposure (e.g., abnormal respiratory pattern). After a 1–2-week exposure to HCCPD, male and female rats exposed to 0.5 ppm had decreased food and water intake (Alexander et al. 1980a; Rand et al. 1982a). All males exposed to 0.5 ppm died or were sacrificed in moribund condition by the end of the exposure period. Minor decreases in food intake were also observed for male rats exposed to 0.11 ppm without meaningful changes to body weight; the biological significance of this finding is uncertain. Food intake was not affected in rats or monkeys and water intake was not affected in rats exposed to ≤0.2 ppm for 14 weeks (Alexander et al. 1980b; Rand et al. 1982a). In a 30-week study, no treatment-related deficits were identified for male or female rats regarding food or water intake following exposure to ≤0.56 ppm (Clark 1981). No treatment-related effects were observed for food and water intake of pregnant mice administered gavage doses of HCCPD at ≤75 mg/kg/day on GDs 6–15 (Murray et al. 1980). Where deficits in food and/or water intake were observed after exposure to HCCPD, these effects were likely the result of nonspecific toxicity following exposures to high concentrations of an irritating/corrosive chemical.

2.19 CANCER

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

The carcinogenicity of HCCPD has been evaluated in 2-year rodent bioassays in which male and female rats and mice were exposed to concentrations up to 0.2 ppm for 104 weeks (NTP 1994). There were no

statistically significant increases in tumor incidence in rats or mice. There was a slight increase in the incidence of adenomas of the pituitary pars distalis in male rats at 0.2 ppm and in thyroid follicle cell adenomas in female mice at 0.05 ppm, but, since the incidences were similar to the historical control means, were within the historical control range, or did not exhibit a dose-dependency, NTP (1994) did not consider these tumors to be related to HCCPD exposure. In male mice exposed to 0.5 ppm for 26 or 42 weeks, then evaluated at 105 weeks, the incidence of alveolar/bronchiolar carcinomas was significantly increased but was within the historical range for the laboratory (NTP 1994). Thus, alveolar/bronchiolar carcinomas may not have been exposure-related. No exposure-related tumors were observed in male mice exposed to 0.2 ppm for 33 weeks when evaluated at 105 weeks (NTP 1994). Overall, NTP (1994) concluded that there was no evidence of carcinogenic activity for HCCPD in these studies. On the basis of these data, the EPA determined that HCCPD is not likely to be a human carcinogen by the inhalation route (IRIS 2003). IARC has not evaluated the carcinogenicity of HCCPD (IARC 2025). HHS has not evaluated a cancer classification category for HCCPD (NTP 2021).

2.20 GENOTOXICITY

The data indicate that HCCPD is not likely to be a potent genotoxic compound in humans. It is not mutagenic or clastogenic *in vivo*. *In vitro,* HCCPD does not induce deoxyribonucleic acid (DNA) damage or repair in mammalian cells, and findings regarding clastogenicity are mixed.

In vivo genotoxicity studies of HCCPD do not show evidence of clastogenicity or mutagenicity; these studies are summarized in Table 2-5. No studies were located regarding genotoxic effects in humans after exposure to HCCPD. The incidence of micronucleated peripheral red blood cells did not increase in male or female mice exposed to ≤0.2 ppm HCCPD for 13 weeks (NTP 1994; Witt et al. 2000), indicating a lack of clastogenicity. In *Drosophila melanogaster*, HCCPD did not induce sex-linked recessive lethal mutations following feeding with ≤40 ppm or injection with ≤3,000 ppm (Mason et al. 1992; NTP 1994; Zimmering et al. 1985). In a dominant lethality study, HCCPD did not induce genetic damage in germ cells of male mice administered oral doses ≤1 mg/kg for 5 days (Litton Bionetics 1978b).

Table 2-5. Genotoxicity of Hexachlorocyclopentadiene *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mammalian cells			
Mouse (inhalation)	Micronucleus in peripheral red blood cells	–	NTP 1994; Witt et al. 2000
Mouse (oral)	Dominant lethal mutations	–	Litton Bionetics 1978b
Eukaryotic organisms			
Insects			
Drosophila melanogaster (feed)	Sex-linked recessive lethals	–	Mason et al. 1992; NTP 1994; Zimmering et al. 1985
D. melanogaster (injection)	Sex-linked recessive lethals	–	Mason et al. 1992; NTP 1994; Zimmering et al. 1985

– = negative result

In vitro findings in bacteria and mammalian cells showed no evidence for mutagenicity and DNA repair, evidence for clastogenicity, and mixed results for DNA damage; these studies are summarized in Table 2-6. No evidence of mutagenicity by HCCPD was obtained in a series of bacterial mutagenicity assays in *Salmonella typhimurium* and *Escherichia coli* (Goggelman et al. 1978; Greim et al. 1977; NTP 1994) or mouse lymphoma cells (Litton Bionetics 1978a). HCCPD did not induce DNA repair in primary rat hepatocytes at nontoxic concentrations (Brat 1983). HCCPD induced DNA damage in a bacterial assay (Matsui et al. 1989). In contrast, DNA damage was not observed in a GreenScreen HC assay, which utilizes a green fluorescent protein (GFP) reporter assay to evaluate the gene expression of *GADD45a* (growth arrest and DNA damage) in a human lymphoblastoid cell line (p53 wild-type Tk6) (Tate and Walmsley 2017). In assays that evaluated chromosomal effects in CHO cells, HCCPD caused sister chromatid exchanges (SCEs) 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.

Table 2-6. Genotoxicity of Hexachlorocyclopentadiene *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Prokaryotic organisms				
Salmonella typhimurium TA1535, TA1538	Gene mutation	–	No data	Greim et al. 1977
S. typhimurium TA100, TA1535, TA1537, TA998	Gene mutation	–	–	Haworth et al. 1983; NTP 1994

Table 2-6. Genotoxicity of Hexachlorocyclopentadiene *In Vitro*

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
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 lymphoma L5178Y cells	Gene mutation	–	–	Litton Bionetics 1978a
Primary rat hepatocytes	DNA repair	–	–	Brat 1983
p53 wild-type Tk6 cells	DNA damage	–	–	Tate and Walmsley 2017
Chinese hamster ovary cells	Sister chromatid exchange	+	+	NTP 1994
Chinese hamster ovary cells	Chromosomal aberrations	+	+	NTP 1994

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

2.21 MECHANISM 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 1991; 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 cytochrome-P450 mixed function oxidase system (Rand et al. 1982b).

The attack of HCCPD on tissues can be regarded as a two-phase phenomenon. Primary lesions are formed by direct contact of the material with exposed tissues (nasal passages, lungs, forestomach, and skin) (Alexander et al. 1980a; Abdo et al. 1984; Clark 1981; NTP 1994; Rand et al. 1982a; Velsicol 1981a, 1981b). These lesions can be hypothesized to result from reactions of HCCPD or one of its metabolites with epithelial cells impairing function and, potentially, resulting in cell death. Once exposure ceases, new cells replace the damaged ones, and slow recovery begins (Alexander et al. 1980a;

Clark 1981; Rand et al. 1982a). Secondary lesions form at sites distant from the point of contact when reaction sites at the portal of entry become saturated and systemic circulation carries unreacted HCCPD or a metabolite to the liver, kidneys, heart, brain, and adrenals. These tissues may become targets for HCCPD by virtue of their physiological function and large blood supply (liver and kidney) or the tendency for their cell products or membrane components to react with HCCPD or an HCCPD metabolite (brain and adrenal).

There are minor changes (electron-lucent inclusions) in club cells, formerly called Clara cells, of the lung epithelium in rats when exposure occurs by the inhalation route (Huntingdon Research Centre 1980; Rand et al. 1982b). These 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). Club cells have particularly rich concentrations of microsomes and enzymes of the cytochrome-P450 mixed function oxidase system (Huntingdon Research Centre 1980; Rand et al. 1982b).

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 observed in rats exposed to inhalation concentrations ≤0.389 ppm for 13–14 weeks (Alexander et al. 1980b; NTP 1994; Rand et al. 1982a) or ≤0.56 ppm for 30 weeks (Clark 1981), but they were seen with acute-duration exposure to higher concentrations (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 sufficiently high 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 could be possible.

The effects of HCCPD on the adrenal glands (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.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- HCCPD is readily absorbed via the inhalation route (80.7–86% of administered dose) but is poorly absorbed following oral exposure (25–40% of administered dose). No estimate of dermal absorption is available.

- Absorbed HCCPD distributes throughout the body rapidly, although route and species differences have been observed. HCCPD distributes to the lungs, trachea, kidneys, liver, and fat following inhalation exposures. It distributes to the kidneys, liver, fat, and female gonads after oral exposures, but concentrations are highest in the kidneys of rats and livers of mice.

- Metabolites of HCCPD have been measured in the liver, kidneys, urine, and feces of rats following oral exposure, but these have not been fully characterized, only identified as polar. Results of *in vitro* studies indicate that microbial degradation of HCCPD occurs in the digestive tract. Only a minimal amount of HCCPD is completely metabolized to carbon dioxide (CO_2).

- HCCPD and its metabolites are excreted in the urine and bile regardless of exposure route. Higher ^{14}C-radiolabel fecal content following oral dosing is a reflection of the poor absorption from the gastrointestinal tract.

3.1.1 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. Low ^{14}C-HCCPD radiolabel concentrations in the blood after oral dosing, as compared to that observed for equal intravenous and inhalation doses, indicate poor gastrointestinal absorption (Lawrence and Dorough 1982).

HCCPD was absorbed across the respiratory tract in rats exposed via inhalation as evidenced by the detection of the ^{14}C-radiolabel in blood and internal organs (El Dareer et al. 1983; Lawrence and Dorough 1981, 1982). Female rats absorbed and retained an average of 83.9% (range of 80.7–86%) of the radioactivity following inhalation of 0.0014–0.0374 mg ^{14}C-HCCPD/kg during a 1-hour, nose-only exposure period (Lawrence and Dorough 1981, 1982). No significant difference in retention was observed with varying administered doses. Although these studies utilized a nose-only exposure method, some dermal absorption of the administered HCCPD dose is likely to have occurred through the exposed skin.

HCCPD was absorbed from the gastrointestinal tracts of rats and mice following oral exposure based on the detection of ^{14}C-radiolabel in blood and internal organs (Dorough and Ranieri 1984; El Dareer et al. 1983; Lawrence and Dorough 1981, 1982; Mehendale 1977; Yu and Atallah 1981). Following single gavage doses of female rats with 25 mg ^{14}C-HCCPD/kg, peak blood concentrations of HCCPD equivalents reached 2.25 ppm at 4 hours and then declined until the last measurement at 24 hours post-dosing (Yu and Atallah 1981). High ^{14}C-radiolabel content in the feces of orally dosed rats relative to urine and bile indicates a low gastrointestinal absorption; based on the sum of urinary and biliary excretion, estimates of oral absorption ranged from 25 to 42% of the administered dose (Dorough and Ranieri 1984; Lawrence and Dorough 1982; Mehendale 1977). A significant proportion of the orally administered HCCPD binds to the stomach mucosa or contents, precluding its gastrointestinal absorption; when HCCPD was extracted with hexane immediately after being added to rat stomach contents, only 50% of the HCCPD could be recovered, with the remainder associated with the solid and aqueous phases (Lawrence and Dorough 1982).

Results of studies comparing HCCPD absorption across routes indicate that it is more readily absorbed via inhalation than oral exposure. When female rats were administered equivalent doses of 0.010 mg/kg via gavage, inhalation exposure, or intravenous injection, the ^{14}C-HCCPD equivalents measured in the blood 1–6 hours after treatment were ≤2.5 ng/mL for the oral route, 5–10 ng/mL for the inhalation route, and 50–100 ng/mL for the intravenous route (Lawrence and Dorough 1982). When tissue distributions of ^{14}C-HCCPD were evaluated via oral, inhalation, and/or intravenous exposures, a significantly higher oral dose (6 mg/kg) was required to produce detectable tissue residues compared to inhalation exposure (0.024 mg/kg) or intravenous injection (0.010 mg/kg) (Lawrence and Dorough 1981, 1982). In female rats orally dosed with 25 mg ^{14}C-HCCPD/kg or injected intravenously with 0.74 mg ^{14}C-HCCPD/kg, the area under the curve (AUC) for the radiolabel measured in the blood was 70 times greater in the intravenous dosed animals than the value for orally dosed animals up to 48 hours after dosing (Yu and Atallah 1981). Additionally, the ^{14}C-radiolabel body burden was 37.98% for the intravenously administered dose compared to 2.788% for the orally administered dose. These results indicate poor oral absorption of HCCPD.

No studies were located regarding absorption of HCCPD in experimental 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 death at sufficient doses (Gardner 1986b; OxyChem 1972, 1992; Treon et al. 1955).

3.1.2 Distribution

No studies were located regarding the distribution of HCCPD in human tissue after any route of exposure. In experimental animals, the distribution of ^{14}C-HCCPD is dependent on the route of exposure. Additionally, species differences exist in the principal site of ^{14}C-HCCPD deposition following oral exposure.

In rats exposed to ^{14}C-HCCPD at 0.024–1.8 mg/kg via inhalation for up to 2 hours, the greatest percentage of the administered radioactivity measured 72 hours after exposure was in the carcass (5.6–7.8%) followed by the lungs (1.6–2.0%) and kidneys (<1–1.7%); the liver, skin, brain, and trachea contained <1% of the administered dose (El Dareer et al. 1983; Lawrence and Dorough 1981, 1982). This distribution was similar to that measured 6 hours post-exposure in rats exposed via inhalation to 1.3 mg/kg; the carcass contained 15.1% of the administered dose while the lungs and kidneys had 4.5 and 3.6% of the administered dose, respectively (El Dareer et al. 1983). When expressed as ^{14}C-HCCPD concentration equivalents in tissue (ng/g tissue), the trachea had the highest concentration of ^{14}C-radiolabel (107 ng/g) followed by the lungs (71.5 ng/g) and kidneys (29.5 ng/g); the liver, fat, and remaining carcass contained <5 ng/g tissue (Lawrence and Dorough 1981, 1982). The total body burden of radioactivity 72 hours after exposure was 12.9% of the administered dose. Based on unextractable ^{14}C-radiolabel at 6 and 72 hours in the kidneys (16.1 and 19.6%, respectively) and lungs (44.7 and 46.7%, respectively), some tissue binding occurred. The remainder of the radioactivity was present in the water-soluble fractions (El Dareer et al. 1983).

Differences in the relative organ content of HCCPD and its metabolites have been identified for rats and mice after oral dosing. Single oral dose studies in rats identified the kidney as the site of greatest distribution for absorbed ^{14}C-HCCPD. In male and female rats sacrificed 48 hours to 7 days after single oral dose administration, the kidneys contained the greatest amount of radiolabeled HCCPD or metabolite when expressed as a percentage of the administered dose or as HCCPD concentration equivalents (El Dareer et al. 1983; Lawrence and Dorough 1981, 1982; Mehendale 1977; Yu and Atallah 1981). Significant but lower radiolabel concentrations were measured in the liver, lungs, and fat tissues of these animals. A comparison of male and female rats and mice administered single or 30-day dietary oral exposures to ^{14}C-HCCPD identified the kidney as the organ with the highest radiolabel concentrations in rats and the liver as the organ with the highest radiolabel concentration in mice following either exposure condition (Dorough and Ranieri 1984). Substantial radioactivity levels were also measured in the gonads of female rats and mice and in the adipose tissues of all animals after single or repeated oral dosing. At

the end of the 30-day exposure period, rapid decreases of 80–90% radioactivity were measured in kidney, liver, and ovaries when the animals were placed on a clean diet for 30 days. Adipose tissue radioactivity remained high until the end of the 30-day period on the clean diet. These results suggest male and female animals of the same species are not likely to differ significantly in the distribution of HCCPD in organs other than the gonads. While similar overall elimination patterns and rates were observed for rats and mice administered oral doses of HCCPD (Dorough and Ranieri 1984; Logan and Croucher 1983), it is not clear if the differences in major organ distribution of HCCPD in rats and mice result from variable metabolism rates as no metabolism data are available for mice.

The distribution of ^{14}C-HCCPD has also been evaluated in rats administered intravenous doses. In male rats injected with 0.59 mg ^{14}C-HCCPD/kg, 18.4, 13.9, 2.9, and 1.2% of the administered dose was measured in the carcass, liver, blood, and kidneys, respectively, 72 hours after dosing (El Dareer et al. 1983). Less than 1% of the administered dose was measured in each of the brain, intestines, lungs, and skin. Radiolabel content was not provided in ^{14}C-HCCPD concentration equivalents for this study. The highest ^{14}C-HCCPD concentration equivalents (ng/g tissue) in female rats administered intravenous injections of 0.010 mg ^{14}C-HCCPD/kg were identified in the kidneys (22.3 ng/g) followed by lungs (14.9 ng/g), liver (9.6 ng/g), trachea (3.3 ng/g), fat (2.3 ng/g), and the remaining carcass (0.5 ng/g) 72 hours after dosing (Lawrence and Dorough 1982). The total body burden of radioactivity was 31% of the administered dose 72 hours after dosing. After intravenous injection of 0.72 or 0.74 mg ^{14}C-HCCPD/kg in female rats, the blood had the highest percentage of the administered radioactivity (15.34% at 24 hours and 26.15% at 48 hours); the next highest percentages were measured in the digestive system (9%), liver (4.68%), and kidneys (2.92%) at 24 hours and liver (4.85%), kidneys (1.81%), and digestive system (1.32%) at 48 hours (Yu and Atallah 1981). When expressed as ^{14}C-HCCPD concentration equivalents (ppm), the kidneys (2.64 ppm) had the highest radiolabel concentration 24 hours after dose, while the spleen (2.95 ppm) and blood (2.94 ppm) had the highest radiolabel concentrations 48 hours after dosing. Oral preexposure of rats to HCCPD at 0.05 mg/kg/day for 3 days increased the concentration of HCCPD in the kidneys following intravenous administration of 5 µmol ^{14}C-HCCPD (Mehendale 1977). The hepatic concentration, biliary excretion, and blood decay curves appeared to be unaltered by oral preexposure to HCCPD.

Studies have been conducted to evaluate tissue binding and subcellular distribution of HCCPD. In *in vitro* incubation studies, HCCPD was found to bind to liver, plasma, and whole blood; as incubation time increased, decreasing amounts of HCCPD was measured in organic extractions while increasing amounts were detected in the aqueous phase and pellet, indicating HCCPD exists in both free and bound forms in

these tissues (El Dareer et al. 1983). In the kidneys of female rats administered single gavage doses of ^{14}C-HCCPD and sacrificed 8 hours later, 52.96% of the radioactivity was present in a free form, 8.07% was water-soluble, and 13.47% was not extractable (Yu and Atallah 1981). Similar results were obtained for the liver, which had 57.5% of the radioactivity as free, 14.38% as water-soluble, and 19.19% as unextractable. When the livers and kidneys of male rats sacrificed 6 hours after intravenous injection with 5 µmole ^{14}C-HCCPD were homogenized and fractionated, 93.8 and 67.5% of the radioactivity was detected in the kidney and liver cytosols, respectively (Mehendale 1977).

No studies were located regarding distribution of HCCPD or its metabolites in experimental animals after dermal exposure.

3.1.3 Metabolism

Insufficient data are available to fully characterize HCCPD metabolism. No studies were located concerning the metabolism of HCCPD in humans. In experimental animals, complete oxidation of HCCPD is limited based on the small amount of radiolabel that is eliminated as exhaled CO_2 (≤1.4%) after exposure of rats to ^{14}C-HCCPD via the oral, inhalation, or intravenous routes (El Dareer et al. 1983; Lawrence and Dorough 1981, 1982). No studies were located regarding metabolism of HCCPD in experimental animals after dermal exposure.

Evaluations of HCCPD metabolites have been performed in internal organs and feces. Thin-layer chromatography (TLC) analysis of livers and kidneys collected from female rats administered single oral doses of 25 mg ^{14}C-HCCPD/kg identified five and four polar metabolites, respectively (Yu and Atallah 1981). In the feces collected from the same animals, TLC analysis of free (non-acid released) metabolites present in the ethyl acetate extractions identified eight metabolites constituting 10.56% of the fecal radioactivity. An additional 31.81, 25.28 and 20.88% of the fecal radioactivity was present as acid-released ethyl acetate extractables, water-soluble, and unextractable solids, respectively. Unmetabolized HCCPD was not detected in the fecal samples of these animals, reflecting microbial metabolism of HCCPD in the gastrointestinal tract. Based on their low retention factors, the metabolites identified in the feces, liver, and kidneys were considered polar (Yu and Atallah 1981). Radiolabels in fecal samples from rats and mice provided diets containing 1, 5, or 25 ppm ^{14}C-HCCPD for 30 days consisted largely of polar metabolites, with unmetabolized HCCPD composing up to 21%, but typically 5–10%, of the fecal radioactivity (Dorough and Ranieri 1984). No further chemical characterization was performed for any of these hepatic, renal, or fecal metabolites.

Evaluations of HCCPD metabolites have also been performed in urine. Organic extraction (hexane:isopropanol, 9:1) of urine obtained from male rats orally dosed with 6 mg ^{14}C-HCCPD/kg indicated the presence of at least four nonpolar metabolites following TLC separation (Mehendale 1977). In urine collected from female rats administered single oral doses of 25 mg ^{14}C-HCCPD/kg, TLC analysis of free and acid-released metabolites present in the ethyl acetate extractions identified six metabolites constituting 33.39 and 9.67% of the urine radioactivity, respectively (Yu and Atallah 1981). An additional 35.99% of the urinary radioactivity was present as water-soluble compounds. High-performance liquid chromatography (HPLC) analysis of the urine identified one major peak that did not correspond to speculated HCCPD metabolites (hexachloro-2-cyclopentanone; hexachloro-3-cyclopentanone; hexachloro-indone; or octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione). As observed in organs and feces, the metabolites identified in the urine were considered polar based on their low retention factors (Yu and Atallah 1981). Urine collected from rats, rabbits, and mice orally dosed with 20 mg ^{14}C-HCCPD/kg also contained polar metabolites, but these compounds were too unstable for further identification (Logan and Croucher 1983). In urine collected from rats and mice provided diets containing 1, 5, or 25 ppm ^{14}C-HCCPD for 30 days, extraction characteristics of the radioactive material present indicated that HCCPD was extensively metabolized in these animals (Dorough and Ranieri 1984). No further chemical characterization was performed.

Results of *in vitro* studies indicate that HCCPD is metabolized or degraded in various biological tissues or by microbes present in the body. Extractions of rat liver, feces, and intestinal contents incubated with ^{14}C-HCCPD for up to 60 minutes indicated that the fraction of HCCPD decreased with incubation time (El Dareer et al. 1983). Microbial degradation of ^{14}C-HCCPD was demonstrated following incubation with rat feces and gut contents; addition of mercuric chloride, which inhibits microbial activity, reduced, but did not eliminate, HCCPD degradation (Yu and Atallah 1981). The half-lives for gut content degradation of HCCPD were 10.1 and 17.2 hours without and with mercuric chloride, respectively, and the half-lives for fecal degradation of HCCPD were 1.6 and 6.2 hours without and with mercuric chloride, respectively. Crude and denatured crude liver homogenates also degraded HCCPD when incubated for up to 24 hours; the half-lives were 14.2 hours for the crude liver homogenate and 12.4 hours for the denatured crude liver homogenate (Yu and Atallah 1981). The low degree of biliary excretion for HCCPD and its metabolites (Dorough and Ranieri 1984; Lawrence and Dorough 1982; Mehendale 1977) and the small amount of unmetabolized HCCPD content in feces (Dorough and Ranieri 1984; Yu and Atallah 1981) support microbial degradation of HCCPD in the gastrointestinal tract following oral exposures.

The affinity that HCCPD, or its metabolites or reaction products, has for the club cells in the lungs and the production of electron-lucent granules in these cells after inhalation exposure of rats to 0.01–0.2 ppm (Huntingdon Research Centre 1980; Rand et al. 1982b) suggests that HCCPD may interact with the microsomes in rats 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 found in the lungs and nasal passages of rats and mice after long-term inhalation exposure to HCCPD were stained with reagents to detect mucopolysaccharides, 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). However, these results do not confirm the presence of either of these complexes as further analytical identification was not performed.

It is also possible that HCCPD, rather than a metabolite, could react directly with cellular alkenes in a spontaneous Diels-Alder cycloaddition reaction (EPA 1991). The occurrence of such a non-enzymatic reaction could explain why HCCPD causes effects at the point of contact for all exposure routes. It could also account for the tissue-binding properties of HCCPD.

3.1.4 Excretion

No data were identified for excretion of HCCPD by humans after any route of exposure. Based on animal data, HCCPD and its metabolites are eliminated primarily in the urine and, to a lesser extent in the bile, following oral, inhalation, and intravenous dosing. A greater ^{14}C-radiolabel content in the feces following oral dosing relative to inhalation and intravenous exposures reflects the poor absorption of HCCPD from the gastrointestinal tract. No studies were located regarding excretion of HCCPD or its metabolites in experimental animals after dermal exposure.

HCCPD absorbed after inhalation exposures in rats is principally eliminated via the urine. Following inhalation of 0.005–0.024 mg ^{14}C-HCCPD/kg for 30–120 minutes, rats primarily excreted the radiolabel via the urine (29.7–33.1%), with a smaller percentage eliminated in the feces (17–23.1%) by 72 hours after dosing; approximately 70% of the radiolabel was recovered by the end of the 72-hour period (Lawrence and Dorough 1981, 1982). Most of the radiolabel was eliminated in the urine and feces during the first 24 hours and approximately 9% of the administered radiolabel was excreted via bile within 28 hours of exposure (Lawrence and Dorough 1982). Higher urinary and fecal elimination of the

radiolabel was observed following inhalation exposures that resulted in absorbed doses of 1.3 or 1.8 mg/kg ^{14}C-HCCPD; the urine and feces contained 41.0 and 28.7% of the label, respectively, after 6 hours and 40.0 and 47.5%, respectively, after 72 hours (El Dareer et al. 1983). According to these studies, ≤1.4% of the administered dose was eliminated as exhaled ^{14}C-HCCPD or ^{14}C-CO_2 (El Dareer et al. 1983; Lawrence and Dorough 1981, 1982).

HCCPD absorbed after oral exposures in rats is eliminated via the urine and bile. The amount of ^{14}C-radiolabel found in rat urine in a 72-hour period after single oral doses of 2.5–61 mg/kg ranged from 12.9 to 35.5% of the administered dose, and the amount in feces, accounting for the unabsorbed ^{14}C-radiolabel content as well as ^{14}C-radiolabel excreted in the bile, ranged from 64 to 80% of the administered dose (Dorough and Ranieri 1984; El Dareer et al. 1983; Lawrence and Dorough 1982; Yu and Atallah 1981). In each case, most of the radiolabel was excreted within the first 24 hours after dosing. Total radiolabel recovery in the urine and feces was >80% across these studies. About 9–18% of the administered radiolabel entered the fecal matter via biliary excretion (Dorough and Ranieri 1984; Lawrence and Dorough 1981; Mehendale 1977), with the remainder of the fecal ^{14}C-radiolabel content likely representing unabsorbed HCCPD or metabolites. Less than 1% of the administered radioactivity was eliminated as exhaled CO_2; there were trace amounts that were exhaled as volatiles other than CO_2 (≤0.3%) (El Dareer et al. 1983). When rats were provided diets containing ^{14}C-HCCPD at 1, 4, or 25 ppm for 30 days, urinary ^{14}C-radiolabel content ranged from 5.4 to 9% of the administered dose and fecal ^{14}C-radiolabel content ranged from 61.5 to 69.9% of the administered dose at the end of the exposure period (Dorough and Ranieri 1984).

Results for additional species also indicate urinary elimination of absorbed HCCPD following oral dosing. In mice, the urine and feces contained 14.9 and 73.9%, respectively, of the administered radiolabeled dose 72 hours after a single administration of 25 mg ^{14}C-HCCPD/kg (Dorough and Ranieri 1984). When mice were fed ^{14}C-HCCPD-containing diets at 1, 5, or 25 ppm for 30 days, urinary ^{14}C-radiolabel content ranged from 6.8 to 12.2% of the administered dose and fecal ^{14}C-radiolabel content ranged from 54 to 68.5% of the administered dose at the end of the 30-day exposure period (Dorough and Ranieri 1984). A comparison of radiolabel elimination in male rats, rabbits, and mice administered single oral doses of 20 mg ^{14}C-HCCPD/kg identified 19.6, 34.9, and 23% urinary excretion, respectively, and 67.6, 50.8, and 69.2% fecal excretion, respectively, by 3 days after dosing; 85.7–92.2% of the administered radiolabel was recovered across the species (Logan and Croucher 1983). These results indicate that rats and mice have similar HCCPD excretion patterns and that rabbits may excrete a greater proportion of the administered HCCPD dose in the urine compared to rats and mice. It is unclear from

the available data if the increased urinary excretion in rabbits is due to a higher oral absorption of HCCPD or its metabolites in this species.

Data are available from two studies that evaluated the excretion of radiolabel in rats after intravenous dosing with 0.005–0.59 mg ^{14}C-HCCPD/kg (El Dareer et al. 1983; Lawrence and Dorough 1982). Over 72 hours, 31–34% of the administered radiolabel was measured in the feces compared to 15.8–22% measured in the urine. Approximately 14% of a 0.005 mg/kg intravenous dose was excreted into the bile within 28 hours of dosing (Lawrence and Dorough 1982). A small amount of radiolabel (<1%) was eliminated as exhaled CO_2 and other volatiles (El Dareer et al. 1983; Lawrence and Dorough 1982). Total radiolabel recovery was 85–89% in these studies. These results indicate that slightly more excretion occurs in the feces than in the urine following intravenous dosing.

A comparison of biliary excretion across exposure routes in rats given 0.005 mg ^{14}C-HCCPD/kg indicated a greater degree of ^{14}C-radiolabel in the bile via the oral route; after 28 hours, approximately 18, 14, and 8% of the administered dose was identified in the bile of female rats administered oral, intravenous, and inhalation exposures, respectively (Lawrence and Dorough 1982). These results likely reflect the initial distribution of HCCPD or its metabolites to the liver following absorption from the gastrointestinal tract compared to inhalation and intravenous exposures.

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

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and 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 (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical

descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

No PBPK models for HCCPD via the oral or inhalation routes were found in the literature. A two-compartment model was established to describe the fate of intravenously injected HCCPD (Yu and Atallah 1981). The existing kinetic data are insufficient for developing a model for experimental animals or humans exposed via the oral or inhalation routes.

3.1.6 Animal-to-Human Extrapolations

Insufficient toxicokinetic data are available for HCCPD in humans. Additionally, no nonhuman primate data were identified that could be used to estimate the toxicokinetic properties of HCCPD in humans.

Species differences exist in the distribution and excretion of HCCPD following oral dosing. When comparing several organs, relatively high ^{14}C-radiolabel content was identified in the kidneys of rats and livers of mice following single and repeated oral dosing with ^{14}C-HCCPD (Dorough and Ranieri 1984). Following single oral dosing, rabbits excreted a higher percentage of HCCPD and its metabolites via the urine (34.9%) compared to rats and mice (19.6–23%) (Logan and Croucher 1983). A comparable decrease was observed in the fecal excretion for rabbits (50.8%) relative to rats and mice (67.6–69.2%). It is not clear from the available data which experimental animal species is most appropriate to predict the toxicokinetic behavior of HCCPD in humans.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic

makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to HCCPD are discussed in Section 5.7, Populations with Potentially High Exposures.

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. In animals, data describing the health effects of HCCPD in immature animals are limited to oral prenatal developmental studies. HCCPD was not embryotoxic, fetotoxic, or teratogenic in mice exposed to the compound at oral doses of ≤75 mg/kg/day during GDs 6–15 (Murray et al. 1980). An HCCPD dose of 75 mg/kg/day administered to pregnant rabbits on GDs 6–18 increased the incidence of 13 ribs in the offspring; maternal mortality and maternal weight loss were also observed at this dose level. No other signs of embryotoxicity, fetotoxicity, or teratogenicity were observed at this dose. Mice that received oral doses of HCCPD (45 mg/kg/day) during GDs 8–12 did not exhibit signs of developmental toxicity when evaluated on PNDs 1 and 3 (Chernoff and Kavlock 1982, 1983). When the offspring of these mice 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, sexual development, or 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 in experimental animals. HCCPD has been detected in human cord blood (Yalçin et al. 2024), suggesting placental transfer of HCCPD, but no data are available for HCCPD levels in human breast milk.

People with preexisting lung, kidney, or liver damage or conditions that compromise the function of these organs may be more at risk than the general population in the event of HCCPD exposure. Asthmatics are probably also likely to be more affected. In two studies of human exposure to HCCPD in the workplace, the most common complaints associated with exposure were eye irritation, headache, and respiratory symptoms, including respiratory tract irritation (Kominsky et al. 1980; Morse et al. 1979). There was also transient elevation of serum liver markers (e.g., AST, ALP, and total bilirubin) 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-induced mortality than females (Abdo et al. 1984; NTP 1994; Rand et al. 1982a; Velsicol 1981a, 1981b). Additionally, toxicokinetic studies indicate that

HCCPD accumulates preferentially in the female gonads compared to male reproductive organs (Dorough and Ranieri 1984), suggesting that female reproduction could be impacted by HCCPD exposures.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 2006).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 2006). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to HCCPD are discussed in Section 3.3.1.

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 2006). 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 effect caused by HCCPD are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

There are no specific biomarkers of exposure for HCCPD except the compound itself. Studies with radiolabeled compound indicate that unmetabolized 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 been fully identified to date and have only been classified as polar. HCCPD can also be measured in blood.

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 provided the pigment chemical is unique to HCCPD; a complete analytical characterization of the pigment has not been performed to date.

3.3.2 Biomarkers of Effect

Evaluation of humans exposed to HCCPD following an inadvertent industrial release did not identify any unique adverse health effects (Kominsky et al. 1980; Morse et al. 1979). Minimal-to-mild abnormalities in liver function tests (AST, ALP, and total bilirubin) were observed in a small percentage of WWTP workers exposed to sewage contaminated with HCCPD (Kominsky et al. 1980; Morse et al. 1979). However, many other reports of xenobiotic 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 experimental animals, HCCPD toxicity includes irritative effects shared with other irritating chemicals and alterations of internal organs that are not suitable for use as biomarkers of effect.

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.

3.4 INTERACTIONS WITH OTHER CHEMICALS

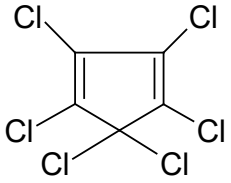
No data were located pertaining to interactions of HCCPD with other compounds. Based on the chemical properties of this material, interactions with other chemicals that provide reactive alkene functional groups, especially those with an electron withdrawing substituent on the carbons adjacent to the double bond, are expected (EPA 1991). For example, a Diels-Alder addition reaction could occur between HCCPD and other dienophiles present in the same environmental media of a waste site. Interactions with these materials preceding exposure would be expected to reduce HCCPD concentrations.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

HCCPD is an organochlorine compound with six chlorine atoms attached to a five-carbon ring containing two double bonds. Information regarding the chemical identity of HCCPD is presented in Table 4-1.

Table 4-1. Chemical Identity of Hexachlorocyclopentadiene

Characteristic	Information	Reference
Chemical name	Hexachlorocyclopentadiene	NLM 2025
Synonym(s) and registered trade name(s)	HCCPD; HEX; hexachloro-1,3-cyclopentadiene; 1,2,3,4,5,5-hexachlorocyclopenta-1,3-diene; perchlorocyclopentadiene; C-56; Graphlox; HRS 1655	NLM 2025; WHO 1991
Chemical formula	C_5Cl_6	NLM 2025
SMILES	C1(=C(C(C(=C1Cl)Cl)(Cl)Cl)Cl)Cl	NLM 2025
Chemical structure		NLM 2025
CAS Registry Number	77-47-4	NLM 2025

CAS = Chemical Abstracts Service; SMILES = simplified molecular-input line-entry system

4.2 PHYSICAL AND CHEMICAL PROPERTIES

HCCPD is a volatile liquid with a pungent, unpleasant odor. It is a relatively hydrophobic compound with low solubility in water and a tendency to adsorb to soils and sediments. Information regarding physical and chemical properties of HCCPD is presented in Table 4-2.

Table 4-2. Physical and Chemical Properties of Hexachlorocyclopentadiene

Property	Information	Reference
Molecular weight	272.772	Rumble 2018
Color	Lemon-yellow/yellow green	Rumble 2018; WHO 1991
Physical state	Liquid	Rumble 2018
Melting point	-9°C	Rumble 2018
Boiling point	239°C	Rumble 2018
Density at 25°C	1.7019 g/mL	Rumble 2018

Table 4-2. Physical and Chemical Properties of Hexachlorocyclopentadiene

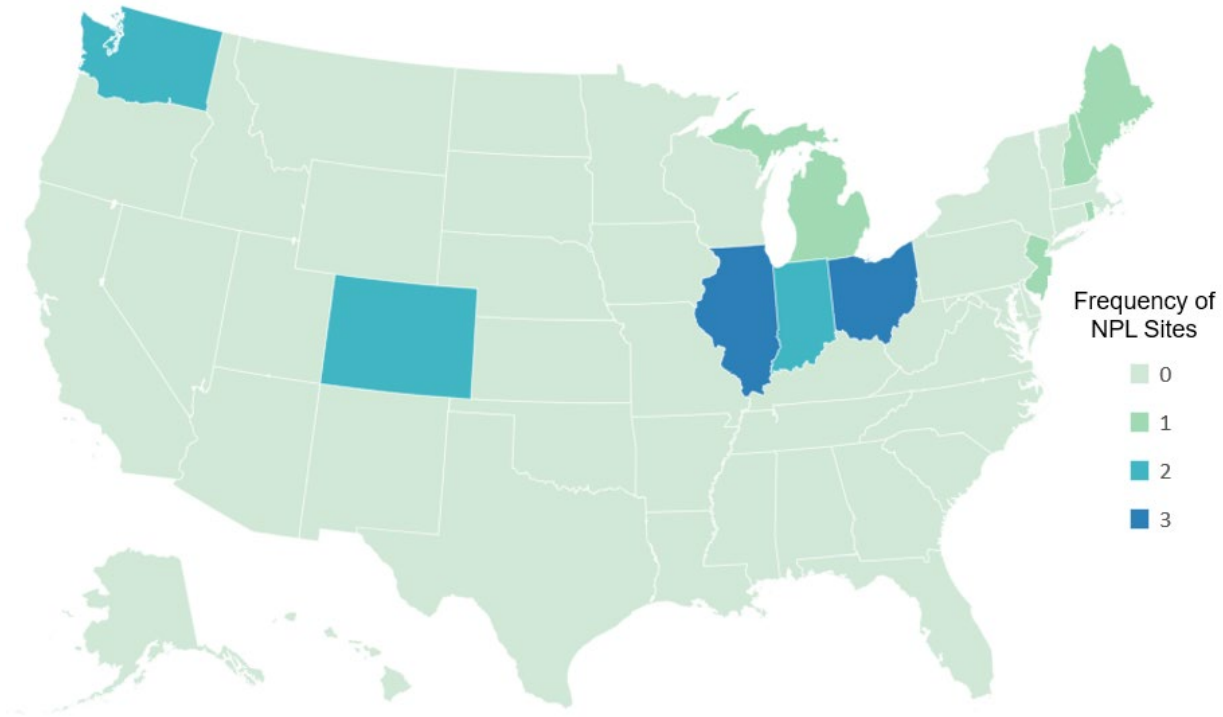
Odor	Pungent, unpleasant; musty	WHO 1991; NLM 2025
Odor threshold:		
Water	0.0077 ppm	Amoore and Hautala 1983
Air	0.00019 mg/m^3; 0.03 ppm (0.34 mg/m^3) 1.5–3.3 mg/m^3	Amoore and Hautala 1983; Ruth 1986; WHO 1991
Taste threshold	No data	
Solubility:		
Water at 25°C	1.8, 2.1, 1.03–1.25 mg/L	EPA 1979, 1991; WHO 1991
Organic solvent(s)	Soluble in all proportions in acetone, carbon tetrachloride, methanol, and hexane	NLM 2025
Partition coefficients:		
Log K_{ow}	4.0–5.04	EPA 1982; NLM 2025; Wolfe et al. 1982
Log K_{oc}	3.68–4.08	EPA 1982; Wolfe et al. 1982
Vapor pressure at 25°C	0.06 mmHg	NLM 2025
Henry's law constant at 24.8°C	2.7x10^{-2} atm-m^3/mol	Wolfe et al. 1982
Autoignition temperature	No data	
Flashpoint	109°C (predicted)	EPA 2025b
Flammability limits	No data	
Conversion factors	1 ppm=11.3 mg/m^3; 1 mg/m^3=0.088 ppm	WHO 1991
Explosive limits	No data	

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

HCCPD has been identified in at least 17 of the 1,379 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2025). However, the number of sites in which HCCPD has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

Figure 5-1. Number of NPL Sites with Hexachlorocyclopentadiene Contamination



Source: ATSDR 2025

- The primary route of exposure to HCCPD is inhalation of contaminated air.
- Occupational exposure is most likely to occur via inhalation and dermal routes.
- General population exposure is most likely to occur via inhalation of contaminated air and ingestion of drinking water contaminated with this chemical.
- The major sources of HCCPD in the environment are from its production, processing, and use as a chemical intermediate.

- HCCPD is not expected to persist in the environment. Major removal processes include volatilization, photolysis, hydrolysis, and biodegradation.

HCCPD is an anthropogenic chemical that is released to the atmosphere primarily by emissions from industrial manufacturing and processing facilities and, to a lesser extent, from the use of products such as chlorinated cyclodiene pesticides that may contain small amounts of HCCPD. Treatment and disposal of HCCPD-containing waste also contribute to environmental concentrations. HCCPD tends to volatilize readily to the atmosphere from other media and to adsorb strongly to soils and sediments. HCCPD reacts readily with hydroxyl and nitrate radicals and can be rapidly degraded by photolysis (EPA 1984; Grosjean and Williams 1992). The atmospheric residence time for this chemical is <1 day (EPA 1984; Grosjean and Williams 1992). Bioconcentration of HCCPD occurs to a very small extent (EPA 1989; Spehar et al. 1979). HCCPD degrades rapidly by photolysis in <1 day (Butz et al. 1982; Chou et al. 1987; Podowski and Khan 1996; Wolfe et al. 1982) and by hydrolysis; half-life values of ≤5 days have been reported for aquatic environments (Podowski and Khan 1996; Wolfe et al. 1982). Photolysis and hydrolysis are the most important environmental fate processes; however, biodegradation also occurs in water, soil, and sediment. Due to low potential for bioconcentration, biomagnification through the food chain is unlikely to occur.

Exposure of the general population, including children, to HCCPD is insignificant (EPA 1991). Human exposure to HCCPD occurs primarily in occupational settings (Boogaard et al. 1993; Kominsky et al. 1980; Morse et al. 1979). Individuals in the general population who live in the vicinity of industrial facilities or hazardous waste sites where contamination has been detected may be exposed to potentially higher levels of HCCPD. A unique exposure route that may exist for young children involves hand-mouth activity if they play in or around HCCPD-contaminated soil or sediment in the vicinity of production facilities or hazardous waste sites. However, monitoring data are insufficient to estimate potential exposure levels in children or adults at these sites.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Table 5-1 summarizes information on companies that reported the production, import, or use of HCCPD for the Toxics Release Inventory (TRI) in 2023 (TRI23 2025). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Hexachlorocyclopentadiene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
IN	1	100	999	12
LA	2	1,000	99,999	1,3,5,12,13,14
OH	2	1,000	99,999	6,12
TX	1	1,000	9,999	7

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI23 2025 (Data are from 2023)

HCCPD may be produced commercially by chlorination of cyclopentadiene or dechlorination of octachlorocyclopentene. In the chlorination process, cyclopentadiene is mixed with alkaline hypochlorite and HCCPD is recovered by fractional distillation. The maximum yield of product is about 75%, with impurities including lower chlorinated cyclopentadienes. The dechlorination process involves thermal dechlorination of octachlorocyclopentene at 470–480°C and yields a product of >90% purity. Technical-grade HCCPD usually contains impurities, which may include hexachlorobenzene, octachloropentene, hexachlorobutadiene, tetrachloroethylene, hexachloro-3-cyclopentane-1-one, polychlorinated biphenyls (PCBs), and mirex, depending on the production method used. The commercial product currently available has a minimum purity of 97% (Abdo et al. 1984; EPA 1991; WHO 1991).

National HCCPD production volumes decreased from 433,317 pounds in 2016 to 117,876 pounds in 2019. These nationally aggregated production volumes have decreased significantly from 2011 (9,226,924 pounds). Two U.S. companies produced HCCPD during these years: Velsicol Chemical in Tennessee (2010–2019) and Zeon Chemicals in Kentucky (2016–2017 only) (EPA 2025a). Estimates of past production, based on production volumes of chlorinated cyclodiene pesticides, indicate that production volume for HCCPD was about 50 million pounds/year (22,680 metric tons/year) in the early 1970s and dropped to 8–15 million pounds/year (3,600–6,800 metric tons/year) in the late 1970s due to regulatory restrictions on the use of many of the organochlorine pesticides using HCCPD as a chemical intermediate (EPA 1984, 1991; Lu et al. 1975). HCCPD was a key intermediate in the production of

chlorinated cyclodiene pesticides, including aldrin, dieldrin, endrin, chlordane, heptachlor, Kepone, endosulfan, pentac, isodrin, and mirex (EPA 1984). However, as of February 2025, none of these chlorinated pesticides have active registrations for use in the United States (https://www.npirs.org/ppis/). It was estimated that 8,300 metric tons (18 million pounds) of HCCPD were produced in 1983 (EPA 1984, 1991). No more recent information on production volumes was located.

5.2.2 Import/Export

Little data are available regarding production, import or export volumes of HCCPD. One company listed in the EPA Chemical Data Reporting (CDR) submissions reported the manufacture of 9,226,924 pounds of HCCPD for commercial/industrial use in 2011, the import of 1,257,515 pounds of HCCPD for commercial/industrial use in 2015, and the import of 117,876 pounds of HCCPD for industrial use in 2019 (EPA 2025a). Table 5-2 presents the national aggregate volumes reported for the 2011–2019 reporting years (EPA 2025a).

Table 5-2. Summary of National Aggregate Volumes Reported to U.S. Environmental Protection Agency (EPA) Chemical Data Reporting (CDR)

Year	Amount (pounds)
2019	117,876
2018	141,094
2017	285,312
2016	433,317
2015	1,257,515
2014	2,028,691
2013	2,696,250
2012	1,453,286
2011	9,226,924
2010	24,575,024

Source: EPA 2025a

5.2.3 Use

The historical end use for HCCPD was as a key intermediate in the production of chlorinated cyclodiene pesticides that are now banned in the United States and most other nations, such as aldrin, bromodan, dieldrin, endrin, chlordane, heptachlor, Kepone, endosulfan, pentac, isodrin, and mirex. As of February

2025, none of the chlorinated pesticides listed here have active registrations for use in the United States (https://www.npirs.org/ppis/).

HCCPD is also used as an intermediate in the manufacture of flame retardants such as Dechlorane Plus (bis(hexachlorocyclopentadieno)cyclooctane) and chlorendic anhydride and, to a lesser extent, in the manufacture of nonflammable resins, polyester resins, pharmaceuticals, unbreakable plastics, acids, esters, ketones, fluorocarbons, and dyes (Verschueren 2001). HCCPD was previously used as a biocide (Cole 1954; EPA 1978, 1984, 1991; Mack 2004; WHO 1991).

5.2.4 Disposal

HCCPD and waste containing HCCPD are classified as hazardous waste by EPA. Generators of waste containing this contaminant must conform to EPA regulations for treatment, storage, and disposal. HCCPD is a potential candidate for fluidized bed incineration at a temperature range of 450–980°C and residence times of seconds for liquids and gases and longer for solids. It is also a potential candidate for rotary kiln incineration at a temperature range of 820–1,600°C, with residence times of seconds for liquids and gases and hours for solids. HCCPD is also a candidate for liquid injection incineration at a temperature range of 650–1,600°C and a residence time of 0.1–2 seconds (EPA 1981). Rotary kiln or fluidized bed incineration methods are acceptable disposal methods for these wastes. HCCPD can be incinerated after mixing with a combustible fuel; however, this mixture should be completely combusted to prevent the formation of phosgene, and an acid scrubber is necessary to remove the halogen acids produced (IRPTC 1985; NLM 2025; WHO 1991).

HCCPD can also be buried in specially designated chemical landfills. However, HCCPD should not be disposed of in the same area of a landfill as organic solvents to prevent potential migration (leaching) of HCCPD from the disposal site into groundwater (Chou et al. 1981; ISGS 1983; WHO 1991). Deep well underground injection may also be used as a disposal method (WHO 1991).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2022). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA

Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022).

5.3.1 Air

Estimated releases of 11 pounds (~0.005 metric tons) of HCCPD to the atmosphere from six domestic manufacturing and processing facilities in 2023, accounted for about 2.33% of the estimated total environmental releases from facilities required to report to the TRI (TRI23 2025). These releases are summarized in Table 5-3.

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Hexachlorocyclopentadiene[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
IN	1	0[l]	0	0	0	0	0	0	0
LA	2	0.03	0	0	0	0	0.03	0	0.03
OH	2	1	0	0	0	405	1	405	406
TX	1	10	5	0	0	50	15	50	65
Total	6	11	5	0	0	455	16	455	471

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.
[l]Due to reporting guidelines, a zero may represent that the facility or facilities in each state's row reported "0" or "NA," or left the cell blank in their Form R submission.

NA = not applicable; RF = reporting facilities; UI = underground injection

Source: TRI23 2025 (Data are from 2023)

The major sources of HCCPD releases to the air are from its production, processing, and use as a chemical intermediate (EPA 1980a, 1984, 1991). Releases may also occur from wastewater treatment facilities, hazardous waste sites, and application and disposal of products such as chlorinated cyclodiene pesticides that may contain small amounts of HCCPD (Clark et al. 1982; Elia et al. 1983; EPA 1984; Kominsky et al. 1980). The National Emissions Inventory is a national compilation of air emission estimates for hazardous air pollutants including HCCPD (EPA 2025d). The results for the latest releases of data are presented in Tables 5-4 and 5-5. The total estimated release of HCCPD to air in 2020 was 8,707 pounds. The total estimated release of HCCPD to air in 2021 was 8,707 pounds. These results indicate that the majority of HCCPD released into the atmosphere results from industrial processing at pulp and paper plants where HCCPD is produced or used. Overall, release of HCCPD into air has decreased over time. Historical data from May 1977 indicate that HCCPD was detected at 56 ppbv in air samples collected from a hazardous waste site in Montague, Michigan (EPA 1980a) and an emission rate of 0.26 g/hour HCCPD was reported at an abandoned hazardous waste site in Michigan (EPA 1984). At this rate, emissions from this site would amount to about 5 pounds/year. In the United States, releases of HCCPD during 1978 were estimated to be approximately 60,000 pounds: 94% originated from manufacturing and 6% was due to its use (EPA 1983a). HCCPD has also been previously identified as a combustion product in emissions from a waste incinerator (Junk and Ford 1980).

Table 5-4. Summary of Releases to the Environment from the Emissions Inventory System (EIS) Gateway Emission Sectors in 2020

Sector	Amount (pounds)
Industrial processes; pulp and paper	5,711
Industrial processes; petroleum refineries	1,675
Industrial processes; not elsewhere classified	1,173
Solvent; industrial surface coating and solvent use	91
Fuel combustion; industrial boilers, internal combustion engines; other	34
Waste disposal	19
Fuel combustion; electric generation; oil	4
Industrial processes; chemical manufacturing	0
Industrial processes; cement manufacturing	0
Bulk gasoline terminals	0
Total	8,707

Source: EPA 2025d

Table 5-5. Summary of Releases to the Environment from the Emissions Inventory System (EIS) Gateway Emission Sectors in 2021

Sector	Amount (pounds)
Industrial processes; paper mills; pulp and paper	4,313
Metal coating, engraving (except jewelry and silverware), and allied services to manufacturers	89
All other rubber product manufacturing	28
Cane sugar manufacturing; sugar mill	25
Industrial processes; petroleum refineries; petroleum refinery	16
Waste disposal; solid waste landfill; landfill	11
Plastics material and resin manufacturing	10
Fossil fuel electric power generation; electricity generation via combustion	7
Tire manufacturing (except retreading); tire manufacturing (not retread)	3
Adhesive manufacturing	2
All other basic organic chemical manufacturing; chemical plant	1
All other basic organic chemical manufacturing; chlor-alkali plant	0
Waste disposal; hazardous waste treatment and disposal	0
Waste disposal; sewage treatment facilities; wastewater treatment facility	0
Other basic inorganic chemical industrial processes; manufacturing	0
Industrial processes; cement manufacturing; Portland cement manufacturing	0
Total	4,505

Source: EPA 2025d

5.3.2 Water

Estimated releases of 5 pounds (~0.002 metric tons) of HCCPD to surface water from six domestic manufacturing and processing facilities in 2023, accounted for about 0.01% of the estimated total environmental releases from facilities required to report to the TRI (TRI23 2025). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI23 2025). These releases are summarized in Table 5-3.

Releases of HCCPD to water may occur during production, processing, and disposal of the chemical. Other than the one facility listed in Table 5-3, no recent measurements in water were located. In the past, concentrations of HCCPD in wastewater from a production plant ranged from 0.156 to 18 mg/L (156–18,000 ppb) (EPA 1980a). HCCPD measurements were taken from the effluent stream of the Memphis North Sewage Treatment Plant from February to July 1982. Monthly average HCCPD concentrations in the effluent stream of this sewage treatment plant located near a production facility (Velsicol Chemical Corporation plant) ranged from 0.15 to 0.61 ppb (µg/L), with a maximum concentration of 1.80 ppb (EPA

1984). Nubbe et al. (1995) reported that a concentration of HCCPD around 100 mg/L (100,000 ppb) was in the range of concentrations that were typical of an aqueous HCCPD waste stream from a commercial production facility.

HCCPD was detectable in 0.9% of 1,228 effluent samples reported in the STOrage and RETrieval (STORET) database maintained by EPA from 1980 to 1982 (Staples et al. 1985). The median concentration for all samples was <10 µg/L (ppb). In a study of chlorinated organic chemicals associated with industries along the Passaic River in New Jersey, Shear et al. (1996) reported that HCCPD was associated with the following industries: metal finishing, plastics, inorganic chemicals, electroplating, and steam electric power production. However, no quantitative information on the concentrations of HCCPD in the Passaic River or in industrial effluents was presented for this compound.

In May 1977, HCCPD was detected at 17 mg/L (17,000 ppb) in the aqueous discharge collected from a hazardous waste site in Montague, Michigan (EPA 1980a).

5.3.3 Soil

There were no releases of HCCPD in 2023 to soil from six domestic manufacturing and processing facilities required to report to the TRI (TRI23 2025); see Table 5-3.

HCCPD can be released to soil and sediment directly from manufacturing and processing facilities. HCCPD has been identified in the soil and river sediments downstream from a Virginia manufacturing plant, even after pesticide production at the plant was discontinued (EPA 1980a). Historically, HCCPD may have been released during application of several of the chlorinated cyclodiene pesticides. For example, technical-grade chlordane has been reported to contain up to 1% HCCPD (Dorough and Ranieri 1984; Lu et al. 1975). Since the use of most of these chlorinated cyclodiene pesticides containing HCCPD as an impurity has been banned or restricted in the United States by the EPA, direct deposition on soil currently should be minimal, with the possible exception of disposal at waste sites, accidental spills, or disposal by illegal methods (EPA 1984). Deposition of volatilized HCCPD from air to soil is also not expected to be significant.

5.4 ENVIRONMENTAL FATE

In general, HCCPD is not persistent in air, water, or soil. Volatilization, photolysis, hydrolysis, and biodegradation are key processes influencing the environmental fate and transformation of HCCPD (EPA 1984).

5.4.1 Transport and Partitioning

Air. Because HCCPD has a vapor pressure of 0.06 mm Hg at 25°C (see Table 4-2), when released to the atmosphere, it will exist almost entirely in the vapor phase (Eisenreich et al. 1981). Detection of HCCPD in ambient air downwind (distance not reported) of a hazardous waste site indicates that atmospheric transport of HCCPD may occur (EPA 1984). However, transported distance will be limited by the high reactivity of the chemical in the atmosphere. Limited data were located on deposition of HCCPD from air to water or soil; however, deposition is probably limited by the chemical's high reactivity. In one study, the calculated soil-air exchange fluxes of 0.003–0.20 ng/m^2·day indicate a net deposition from air to soil (Luan et al. 2022). The relatively low water solubility of HCCPD suggests that there is little potential for washout in precipitation.

Water. HCCPD released to water or moist soils may volatilize into the air or adsorb onto soil and sediment particles. Volatilization is most likely to occur from moving water bodies, with estimated removal of about 15% of the HCCPD in a turbid river, compared with <5% removal from a lake or pond (EPA 1979). The volatilization rate from aquatic systems depends on specific conditions, including adsorption to sediments, pH of the medium, and air flow rate (Kilzer et al. 1979). In a laboratory study, 5.87% of ^{14}C-HCCPD per mL of evaporated water volatilized during the first hour (Kilzer et al. 1979). Data from the same study indicated that volatilization is much lower from soils. The volatilization rate of HCCPD was expressed as the percentage of applied radioactivity per mL of evaporated water; for sand, loam, and humus soils, rates were 0.83, 0.33, and 0.14%, respectively, for the first hour and 0.23, 0.11, and 0.05%, respectively, for the second hour. Volatilization was highest from the sand and lowest from the humus. Volatilization was greater in soils with low organic content (Kilzer et al. 1979). In another study, the rate of volatilization of HCCPD from Maury silt loam soils was measured. Following the application of 100 mg of ^{14}C-HCCPD to soil, the cumulative evaporation of HCCPD and its nonpolar metabolites (penta- and tetrachlorocyclopentadiene) on days 1, 2, 3, 5, 7, and 14 were 9.3, 10.2, 10.6, 10.8, 11.0 and 11.2%, respectively. The results indicate that HCCPD evaporation to air occurred mainly

during the first day following application and was probably associated with the soil surface only (EPA 1984).

Sediment and Soil. HCCPD released to soil and sediments is readily adsorbed and likely to have limited mobility with low potential for migration to groundwater under most environmental scenarios (Chou et al. 1981; ISGS 1983; Wolfe et al. 1982). Results of adsorption studies with nine different soil types indicate that adsorption capacity for HCCPD increases with increases in the total organic carbon (TOC) content of the soil (Chou et al. 1981; ISGS 1983). HCCPD was significantly more mobile in low TOC soils. Under the study conditions, HCCPD was fairly immobile in all soils when leached with tap water, landfill leachate, and caustic brine solution, but was highly mobile when the leaching agent was an organic solvent, such as acetone, methanol, or dioxane. Only 0.0005% of the HCCPD spiked into loamy sand was leached with tap water. Thus, the study authors cautioned that to decrease the risk of migration of HCCPD from landfills into groundwater, wastes containing this chemical should not be disposed of in the same landfill location as organic solvents. The mechanisms of attenuation in soil materials were not reported. In another study, an average of about 68% of an applied dose of HCCPD was adsorbed to a flooded soil (EPA 1984).

In aquatic environments, partitioning of HCCPD to sediments is likely. The soil adsorption properties of compounds such as HCCPD can be predicted from their soil organic carbon-water partition coefficient (K_{oc}). Kenaga (1980) examined the adsorption properties of 100 chemicals and concluded that compounds with K_{oc} values >1,000 are tightly bound to soil components and are immobile in soils. Accordingly, the K_{oc} value is useful as an indicator of potential soil leachability of the chemical. Because K_{oc} values for HCCPD ranged from 4,786 to 12,023 (EPA 1982; Wolfe et al. 1982), the compound will tend to be tightly bound to soil and sediment particles. In a computer simulation of the fate of HCCPD in four different aquatic systems, the major portion of the chemical (86–99%) was predicted to be distributed to the sediments (Wolfe et al. 1982). The transport and partitioning data presented were consistent with the measured log K_{ow} of 5.04 (28°C) and the experimental Henry's law constant of 2.7×10^{-2} atm-m^3/mol (EPA 1982; Wolfe et al. 1982).

After 5 days in an activated municipal sludge test system, no CO_2 evolution was observed; a sludge-water accumulation factor of 2,350 was reported, suggesting that HCCPD is likely to accumulate in sludge (Freitag et al. 1979).

Other Media. The reported log K_{ow} of 5.04 (Wolfe et al. 1982) indicates that bioconcentration of HCCPD could be substantial. However, data indicate that HCCPD does not bioconcentrate, bioaccumulate, or biomagnify in the food chain to a substantial degree (Lu et al. 1975; Podowski and Khan 1984; Podowski et al. 1991; Spehar et al. 1979; Wolfe et al. 1982), primarily because it is rapidly degraded in air, water, and soil and because it is metabolized in aquatic organisms. Podowski and Khan (1984) studied elimination, metabolism, and tissue distribution of HCCPD injected intraperitoneally into goldfish (*Carassius auratus*) and concluded that goldfish eliminate HCCPD both rapidly and linearly. Fish were injected with 39.6 µg of ^{14}C-HCCPD and analyzed 3 days later. Of the 97% of the labeled dose recovered, 19% was eliminated by the fish, 47% was extractable in an organic solvent (little of the labeled material could be identified as HCCPD, which indicated that biotransformation had occurred); 11% was water soluble metabolites; and 20% was unextractable. None of the metabolites were identified. A biphasic elimination of HCCPD was observed: rapid at first, followed by a slower phase. Based on a study of goldfish injected with ^{14}C -HCCPD, the elimination of HCCPD occurs in multiple stages, with a reported half-life in the organism of 7 days and predicted clearance of 90 and 95% of the chemical after 162 and 211 days, respectively (Podowski et al. 1991).

In a model ecosystem, a moderate potential for bioaccumulation of HCCPD was reported (Lu et al. 1975). The model ecosystem consisted of 50 sorghum (*Sorghum vulgare*) plants (3–4 inches tall) in the terrestrial portion; 10 snails (*Physa sp.*), 30 water fleas (*Daphnia magna*), filamentous green algae (*Oedogonium cardiacum*), and a plankton culture were added to the aquatic portion. The sorghum plants were treated topically with 5 mg of ^{14}C-HCCPD in acetone to simulate a terrestrial application of 1 pound/acre (1.1 kg/hectare). Ten early-fifth-instar caterpillar larvae (*Estigmene acrea*) were placed on the plants. The insects consumed most of the treated plant surface within 3–4 days. The feces, leaf grass, and the larvae themselves contaminated the moist sand, permitting distribution of the labeled metabolites by water throughout the ecosystem. After 26 days, 300 mosquito larvae (*Culex pipiens quinquefasciatus*) were added to the ecosystem, and on day 30, 3 mosquitofish (*Gambusia affinis*) were added. The experiment was terminated after 33 days, and the various parameters were analyzed. The ecological magnification values reported were 340 for algae, 929 for snails, 1,634 for mosquitoes, and 448 for fish. However, biomagnification of HCCPD was 4.8 from algae to snails and 0.48 from mosquito larvae to fish, which was not substantial.

A measured bioconcentration factor (BCF) of <11 was reported in fathead minnows following a 30-day exposure period (Spehar et al. 1979). After adjustment of the BCF for lipid content, the weighted average BCF for the edible portion of freshwater and estuarine aquatic organisms was calculated as 4.34 (EPA

1980a). Another study using fathead minnows reported a BCF of 29 following a 32-day exposure period (Veith et al. 1979).

The potential for bioaccumulation and biomagnification of HCCPD was evaluated in various samples collected near an agrochemical factory in China (Luan et al. 2022). Bioaccumulation factors measured in wheat and rice grown were 43.6 and 27.0, respectively. The potential for biomagnification of HCCPD through a food chain was evaluated using samples of soil, leaves of black-eyed peas (*Vigna unguiculata*), larvae of *Pieras rapae*, and chickens. Magnifications of 1.19 times from the soil to the leaves, 3.15 times from the leaves to the larvae, and 21.5 times from the larvae to the chickens were observed.

5.4.2 Transformation and Degradation

HCCPD is not persistent in air, water, or soil. Photolysis, hydrolysis, and biodegradation are key processes influencing the environmental transformation and degradation of HCCPD (EPA 1984).

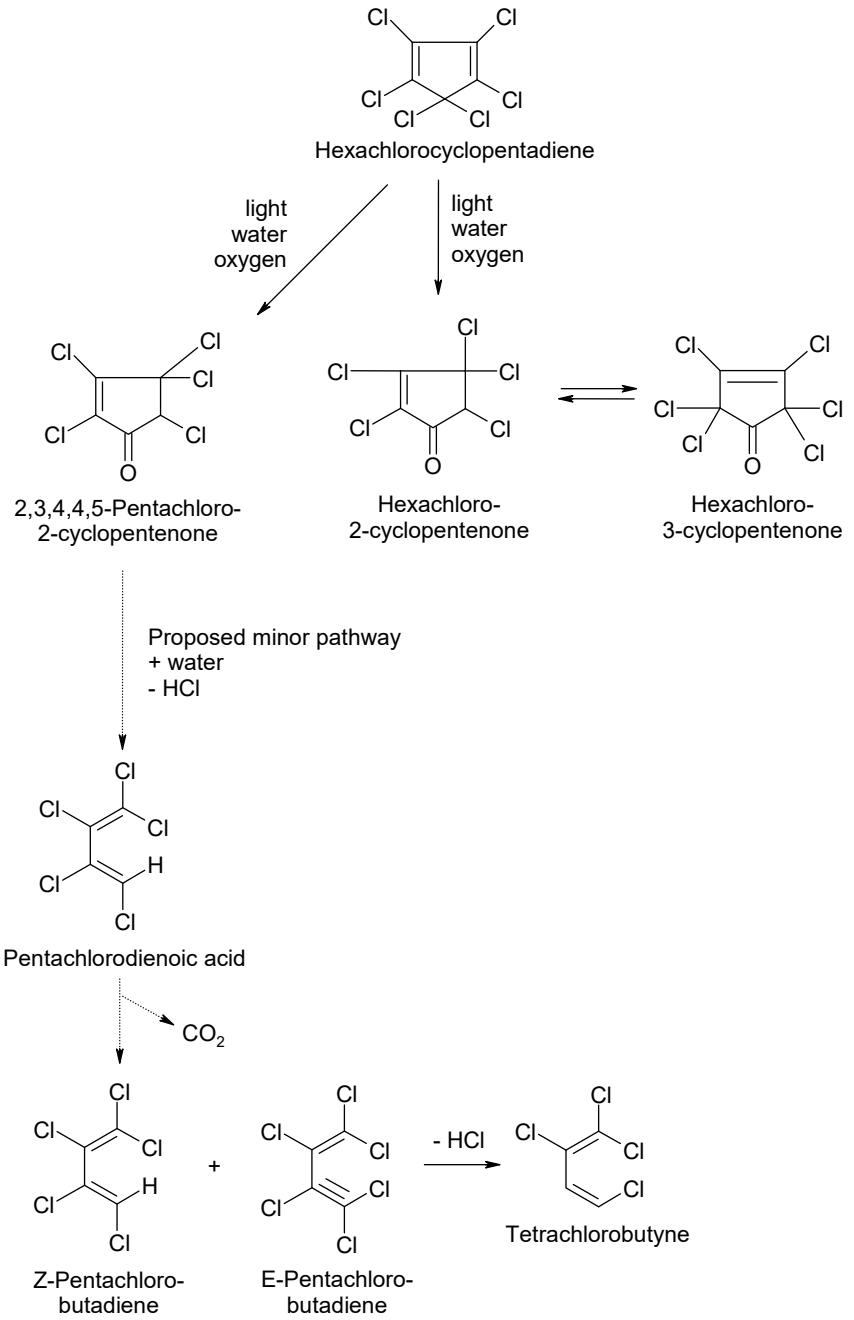
Air. Although no measured values for HCCPD reactions in air were located, it is expected to react rapidly with hydroxyl radicals, nitrate radicals, and ozone, and to be degraded rapidly by direct photolysis. Estimates of reaction rates with hydroxyl and nitrate radicals and ozone are available. Based on estimated reaction rates of the chemical with hydroxyl radicals and ozone of $59x10^{-12}$ and $8x10^{-18}$ cm^3 $molecule^{-1}$ $second^{-1}$, respectively, the tropospheric residence time was estimated to be 5 hours (EPA 1980b). Estimates of the reaction rates with hydroxyl and nitrate radicals are $9.0x10^{-11}$ and $2.14x10^{-12}$ cm^3 $molecule^{-1}$ $second^{-1}$, respectively, based on structure-activity relationships (Grosjean and Williams 1992). Based on the estimated reaction rate and an atmospheric concentration of 10^6 OH molecule/cm^3, the half-life of HCCPD in air is estimated to be <1 day (Grosjean and Williams 1992).

Since HCCPD is known to photolyze rapidly (half-life ~10 minutes) in water (Atallah et al. 1981; Butz et al. 1982; Wolfe et al. 1982), atmospheric photolysis is also expected (EPA 1984). In addition, HCCPD absorbs light in the solar spectral region (EPA 1984). However, no estimate of the reaction rate for atmospheric photolysis was located.

Using fluorescent bulbs similar to, but less intense than, natural sunlight, a rate constant of 0.42 $hour^{-1}$ was measured for the direct photolysis of HCCPD in an aqueous system at pH 7.4. This corresponds to a half-life of approximately 1.67 hours and a quantum yield of 0.49 (Nubbe et al. 1995).

Water. Degradative processes for removal of HCCPD from water include photolysis, hydrolysis, and biodegradation. In shallow or flowing waters, photolysis is the predominant fate process; in deeper waters, hydrolysis and biodegradation may be more important environmental fate processes (EPA 1984). The major pathways for transformation of HCCPD in water are shown in Figure 5-2.

Figure 5-2. Transformation of Hexachlorocyclopentadiene



Source: ISGS 1983

HCCPD undergoes rapid photolysis in water when exposed to sunlight or a mercury-vapor light source (Butz et al. 1982; Chou et al. 1987; Wolfe et al. 1982). Experimental half-life values range from <2 minutes (Wolfe et al. 1982) to 4 minutes in tap water, natural water, and deionized water exposed to natural sunlight (Chou et al. 1987) and <1.03 minutes when irradiated with a mercury-vapor light source (Butz et al. 1982). Podowski and Khan (1996) reported that HCCPD was photolyzed rapidly as a solution in acetone (half-life, <1 day) to apolar, polar, and hydrophilic products. The 15-day photolysis mixture contained no HCCPD. The reported photodegradation products included three primary products (2,3,4,4,5-pentachloro-2-cyclopentenone, hexachloro-2-cyclopentenone, and hexachloro-3-cyclopentenone) and three secondary products (pentachloro-cis-2,4-pentadienoic acid, Z- and E-pentachlorobutadiene, and tetrachlorobutyne (Chou et al. 1987). Dimerization of 2,3,4,4,5-pentachloro-2-cyclopentenone to form higher molecular weight compounds such as hexachloro-indenone may be a minor degradation pathway. This indicates that degradation of HCCPD in water does not always produce lower molecular weight, less toxic products (Butz et al. 1982; Chou et al. 1987). Pentachlorocyclopentenone has been reported to be the primary photolysis product by Butz et al. (1982), and the dimerization has been proposed as an artifact. However, Podowski and Khan (1996) rejected the idea that the dimer is an artifact as they could not produce the dimer compound by injecting pentachlorocyclopentenone into the gas chromatograph (GC) at 190°C. The study authors also reported that the dimer, with a proposed molecular formula of $C_9C_{18}O$, was not mirex or chlordecone as judged by its GC behavior, indicating that HCCPD may not form at least the latter stable chemicals.

Hydrolysis of HCCPD in water occurs much more slowly than photolysis. In a study of the transformation pathways of HCCPD in aquatic systems, the reported average hydrolysis rate constant over a pH range of 3–10 was $1.5x10^{-6}$ $second^{-1}$ at 30°C (Wolfe et al. 1982), which corresponds to a half-life of 5.35 days (EPA 1984). Podowski and Khan (1996) reported that the time it took for HCCPD to reach 50, 10, and 5% of its initial concentration in water (7 ppb) was 4, 27, and 40 days, respectively. A hydrolysis half-life for HCCPD of 7.3 hours was measured in nano pure water at pH 7 and 25°C (Li et al. 2022).

Wolfe et al. (1982) found hydrolysis of HCCPD to be independent of pH over a range of pH 3–10. The rate of hydrolysis at neutral pH and 30°C corresponded to a half-life (first-order kinetics) of 5.45 days. The rate of hydrolysis was temperature dependent, with the half-lives estimated to be 3.3, 1.7, and 0.6 days at 30, 40, and 50°C, respectively. The addition of 0.5 molar NaCl did not affect the hydrolysis rate, suggesting that the rate constant was also applicable to marine environments. Addition of natural

sediments sufficient to adsorb up to 92% of the HCCPD caused the rate constant to vary by less than a factor of 2. Wolfe et al. (1982) therefore concluded that sorption to sediments would not significantly affect the rate of hydrolysis.

Some changes in hydrolysis rate did occur with changes in pH (EPA 1984). The stability of ^{14}C-HCCPD in water at pH 3, 6, 9, and 12 at 25 and 45°C was studied under dark conditions. HCCPD was relatively unstable at alkaline pH. At 25°C, the half-lives were 11.4, 11.4, 6, and 0.1 days at pH 3, 6, 9, and 12, respectively. At 45°C, the half-lives were 9.2, 10.6 and 4.4 days at pH 3, 6, and 9, respectively. This indicates that at neutral pH, the hydrolysis half-life is 3–11 days, compared with a much more rapid photolytic half-life of <10 minutes.

HCCPD also reacts with ozone in ozonated waters (Yao and Haag 1991). The measured rate constant for the consumption of the compound was 90 moles^{-1} second^{-1}, indicating that HCCPD will react significantly (>10% conversion) with ozone at typical treatment conditions of 1 ppm ozone for 10 minutes (Yao and Haag 1991).

Biodegradation of HCCPD occurs in water under laboratory conditions. In a static laboratory culture, 100% of HCCPD was lost within 7 days from both 5 mg/L (ppm) and 10 mg/L (ppm) solutions (Tabak et al. 1981). Volatilization was not reported to occur under the test conditions. However, in an evaluation of the potential for biodegradation as a spill-cleanup technique, HCCPD was reported not to be directly accessible to microorganisms in aquatic media (EPA 1983b). The reported degradation of HCCPD ranged from 16 to 40% after 7 days and from 35 to 60% after 14 days. Addition of methanol as a solubilizer increased the rate of biodegradation in three of seven test cultures, with degradation up to 76%. Atallah et al. (1981) conducted an aqueous aerobic biodegradation study to determine whether, and at what rate, HCCPD can be degraded to CO_2. The inoculum was a mixed acclimated culture containing secondary municipal waste effluent and several bacterial strains of *Pseudomonas putida*. HCCPD labeled with ^{14}C was the sole source of carbon in the study with the exception of trace levels of vitamins. Total removal of ^{14}C, primarily as volatile organics, was >80% in the first day in both uninoculated and inoculated media, although removal was slightly higher in inoculated media. $^{14}CO_2$ was released from both media, indicating that CO_2 was a product of hydrolysis as well as biodegradation. These studies show that HCCPD can be degraded in aquatic media under laboratory conditions. However, another study of the fate of HCCPD found biodegradation to be a relatively unimportant process in aquatic systems, based on the observation that there was no detectable difference in hydrolysis rates between sterile and nonsterile studies and measured numbers of microorganisms (Wolfe et al. 1982).

Sediment and Soil. Degradation of HCCPD occurs via both abiotic and biotic degradation processes in both sterile and nonsterile soil systems. Limited information shows that degradation rates are faster under nonsterile aerobic and anaerobic conditions, indicating that biodegradation has a role in the degradation process (EPA 1984; Tabak et al. 1981). Potential exists for significant losses via photolysis of HCCPD on soil surfaces, while hydrolysis may also occur in moist soils. The relative importance of each process is difficult to assess and is dependent on site specific physical, chemical, and biological conditions (EPA 1984).

The metabolism of HCCPD by soil microbial populations is an important process in its environmental degradation. Soil degradation is rapid under nonsterile aerobic and anaerobic conditions. In one study, several types of treatments and soil pHs were used to determine if the biodegradation of HCCPD in Maury loam soil was biologically and/or chemically mediated (EPA 1984). Soil was incubated in glass flasks covered with perforated aluminum foil and maintained in the laboratory, presumably exposed to ambient lighting. When ^{14}C-HCCPD was applied to nonsterile soil at 1 ppm, only 6% was recovered as nonpolar material (either HCCPD or nonpolar degradation products) 7 days after treatment; 72% was polar and unextractable material. By comparison, in autoclaved soil (control), 36% of the applied dose was recovered as nonpolar material and only 33% was recovered as polar and unextractable material. The degradation of HCCPD under anaerobic (flooded) conditions occurred at a slightly faster rate than under aerobic conditions (EPA 1984). However, no single, flooded control was used to determine the effects of hydrolysis, which could have accounted for the observed difference in this treatment.

A study was undertaken to examine the feasibility of using selected pure cultures of organisms (strains not identified) to biodegrade spills of hazardous chemical including HCCPD. Seven test strains were found to remove 9–59 and 34–76% of the HCCPD from the aqueous culture medium within 6–7 days and 14 days, respectively (EPA 1983b).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to HCCPD depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of HCCPD in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on HCCPD levels monitored or estimated in the

environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-6 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-7. Current data on environmental concentrations of HCCPD in the United States are limited, and sampling from previous decades likely overestimate present-day environmental levels.

Table 5-6. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Drinking water	0.004 µg/L	EPA 1995
Surface water and groundwater	0.8 µg/L	USGS 2016
Soil	10 µg/L	EPA 2018a
Sediment	10 µg/L	EPA 2018a

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-7. Summary of Environmental Levels of HCCPD

Media	Low	High	For more information
Outdoor air (ppbv)	0.032	56	Section 5.5.1
Indoor air (ppbv)	0.0053	0.0089	Section 5.5.1
Surface water (µg/L)	0.001	100	Section 5.5.2
Groundwater (µg/L)	0.005	15	Section 5.5.2
Drinking water (µg/L)	<0.05	<0.36	Section 5.5.2

5.5.1 Air

HCCPD is a hazardous air pollutant (parameter code 16826) included in the national Air Quality System (AQS) database, which contains ambient air pollution data collected by EPA, state, local, and tribal air pollution control agencies from monitors throughout the country. For the monitoring years 2017–2024 at monitoring stations across the United States, there were no detections for HCCPD (EPA 2025c).

Because HCCPD is readily degraded in the atmosphere, it is not expected to be detected frequently in ambient outdoor air, and no recent monitoring studies conducted in the United States were located.

Data reported from a study conducted in 2021 measured concentrations of HCCPD in seasonal air samples collected around an agrochemical factory in China. HCCPD levels ranged from 0.01 to 12.7 ng/m^3, with an average of 2.60 ng/m^3; levels in autumn, winter, spring, and summer were 1.44–12.7 ng/m^3 (mean 5.68 ng/m^3), 1.26–9.19 ng/m^3 (mean 4.44 ng/m^3), 0.27–3.44 ng/m^3 (mean 0.92 ng/m^3), and 0.01–0.18 ng/m^3 (mean 0.09 ng/m^3), respectively (Luan et al. 2022).

Historical data measured within the United States from 1978 reported HCCPD was detected in indoor air at levels of 0.06–0.10 pg/m^3 (0.0053–0.0089 ppb) in three of five Tennessee homes where a contaminated groundwater supply was used as a source of potable water. The groundwater supply was contaminated with leachate from a pesticide waste dump operated by the Velsicol Corporation near Memphis, Tennessee (Clark et al. 1982). HCCPD was also detected in air samples collected in June 1978 at the Memphis North Treatment Plant, the POTW that handled wastewater from the pesticide manufacturer (Clark et al. 1982; Elia et al. 1983). Concentrations of HCCPD ranged from 0.03 to 39 µg/m^3 (Elia et al. 1983). HCCPD also was detected in ambient outdoor air near a hazardous waste site at concentrations of 0.032–0.053 ppb (0.36–0.59 µg/m^3) (EPA 1984).

In May 1977, HCCPD was detected at 56 ppb in air samples collected from a hazardous waste site in Montague, Michigan (EPA 1980a). An emission rate of 0.26 g/hour HCCPD was reported at an abandoned hazardous waste site in Michigan (EPA 1984).

5.5.2 Water

HCCPD is rarely found in drinking water, surface water, or groundwater. HCCPD is regulated under the EPA Safe Drinking Water Act with a Maximum Contaminant Level (MCL) of 0.05 mg/L (50 µg/L) (EPA 2015, 2024a). Under the Safe Drinking Water Act (SDWA), the EPA's Drinking Water Program conducts a review of national primary drinking water regulations every 6 years. Data for review are compiled from the National Compliance Monitoring Information Collection Request Datasets. HCCPD is included in this review as a Category 1 contaminant that may enter drinking water systems via discharge from chemical factories (EPA 2024a). Details of the results from 1998 to 2019 are presented in Table 5-8. From 1998 to 2005, 135,290 samples were collected across 32,801 public water systems (PWS) located in 44 U.S. states. There were zero systems with estimated mean concentrations >25 µg/L (EPA 2009, 2010). HCCPD was detected in <1% (0.949%) surface water samples and <0.1% (0.098%) groundwater samples (EPA 2009). From 2006 to 2011, 140,004 samples were collected from 38,743 PWS located in 50 U.S. states. There were no systems with estimated mean concentrations

>40 µg/L (EPA 2016). Concentrations in the PWS ranged from 0.006 to 100 µg/L, with a median value of 0.12 µg/L and an average of 0.68 µg/L. The highest concentration (100 µg/L) was reported for a system in New York; the second highest concentration (14 µg/L) was reported for a system in New Mexico (EPA 2016, 2024c). From 2012 to 2019, 196,236 samples were collected from 38,471 PWS located in 58 U.S. states and jurisdictions (EPA 2024b). Concentrations in the PWS ranged from 0.006 to 4.9 µg/L, with a median value of 0.096 µg/L and an average of 0.12 µg/L (EPA 2024d).

Table 5-8. Summary of Water Monitoring Data for Hexachlorocyclopentadiene Across the United States

Location(s)	Type	Date(s)	Range	Mean concentration	Notes	Reference
United States (44 states)	Surface water, national compliance monitoring information	1998–2005	0.001–10 µg/L	0.1 µg/L	Detection frequency <1% (268/27,371 samples); 2,766 PWS sampled	EPA 2010
United States (47 states)	Surface water, national compliance monitoring information	2006–2011	0.01–100 µg/L	0.82 µg/L	Detection frequency <1% (175/24,794 samples); 2,957 PWS sampled	EPA 2024c
United States (51 states)	Surface water, national compliance monitoring information	2012–2019	0.01–0.9 µg/L	0.12 µg/L	Detection frequency 1.1% (387/33,031 samples); 3,020 PWS sampled	EPA 2024d
United States	Surface water monitoring	2024	–	–	253 samples; 0% quantified; 211 below quantification limit	WQP 2025
United States	Surface water monitoring	2023	0 ppb	0 ppb	401 samples; 0.25% quantified; 149 below quantification limit; 3 below reporting limit	WQP 2025
United States	Surface water monitoring	2022	–	–	625 samples; 0% quantified; 183 below quantification limit; 7 below reporting limit	WQP 2025
United States	Surface water monitoring	2021	–	–	781 samples; 0% quantified; 160 below quantification limit; 35 below reporting limit	WQP 2025
United States	Surface water monitoring	2020	–	–	553 samples; 0% quantified; 146 below quantification limit; 28 below reporting limit	WQP 2025

Table 5-8. Summary of Water Monitoring Data for Hexachlorocyclopentadiene Across the United States

Location(s)	Type	Date(s)	Range	Mean concentration	Notes	Reference
United States	Surface water monitoring	2019	–	–	604 samples; 0% quantified; 179 below quantification limit; 1 below reporting limit	WQP 2025
United States (44 states)	Groundwater, national compliance monitoring information	1998–2005	0.005–15 µg/L	0.10 µg/L	Detection frequency 0.1% (108/107,922 samples); 30,035 PWS sampled	EPA 2010
United States (47 states)	Groundwater, national compliance monitoring information	2006–2011	0.006–14 µg/L	0.46 µg/L	Detection frequency <0.1% (112/115,210 samples); 35,786 PWS sampled	EPA 2024c
United States (51 states)	Groundwater, national compliance monitoring information	2012–2019	0.006–4.9 µg/L	0.11 µg/L	Detection frequency 0.1% (270/163,205 samples); 35,451 PWS sampled	EPA 2024d
United States	Groundwater monitoring	2024	–	–	47 samples; 0% quantified; 1 below quantification limit	WQP 2025
United States	Groundwater monitoring	2023	–	–	322 samples; 0% quantified; 1 below quantification limit;1 below reporting limit	WQP 2025
United States	Groundwater monitoring	2022	–	–	324 samples; 0% quantified; 8 below quantification limit; 3 below reporting limit	WQP 2025
United States	Groundwater monitoring	2021	–	–	390 samples; 0% quantified	WQP 2025
United States	Groundwater monitoring	2020	–	–	197 samples; 0% quantified	WQP 2025
United States	Groundwater monitoring	2019	–	–	342 samples; 0% quantified; 4 below reporting limit	WQP 2025
United States (Indiana)	Facility public water supply; raw water, Michigan City Waterworks	2019–2024	–	–	Present below quantification limit (0.08–0.36 µg/L)	WQP 2025

Table 5-8. Summary of Water Monitoring Data for Hexachlorocyclopentadiene Across the United States

Location(s)	Type	Date(s)	Range	Mean concentration	Notes	Reference
United States (Minnesota, Arizona, Georgia, Indiana, Washington, California)	Storm sewer outfall; canal transport; canal drainage; land runoff	2019–2024	–	–	Not detected in 161 samples (method/reporting limits were 0.05–10 µg/L)	WQP 2025
United States (Pennsylvania)	Groundwater monitoring	2020	–	–	Below reporting limits (method reporting limit was 5.6 µg/L)	PennDOT 2021

PWS = public water systems

The Water Quality Portal (WQP) is an aggregated database of environmental monitoring data collected by EPA, U.S. Department of Agriculture (USDA), National Water Quality Monitoring Council, state, local, and tribal water pollution control agencies, and other volunteer groups. There is a total of 29 organizations across the United States for surface water and 12 organizations across the United States for groundwater, including data from the U.S. Geological Survey (USGS). Table 5-8 provides the details for HCCPD in surface water and groundwater obtained from the database. The most recent monitoring data compiled in the WQP indicate that HCCPD was not detected in ambient surface water monitored between 2020 and 2024 or groundwater monitored between 2019 and 2023 (WQP 2025).

In the past, HCCPD was tentatively identified in 1 of 16 samples of Philadelphia drinking water analyzed during 1976 (Suffet et al. 1980). HCCPD was also detected at a median concentration of 0.05 µg/L (ppb) (range, trace–2.2 µg/L) in private wells used for drinking water by residents in the Toone-Teague area of Hardeman County, Tennessee (Clark et al. 1982). The source of the well water contamination was leachate from a pesticide waste dump site. HCCPD was detected in treated drinking water samples in Ottawa, Canada at concentrations of 57–110 ng/L (0.057–0.11 ppb) but was not detected (<50 ng/L [<050 ppb]) in raw water (Benoit and Williams 1981). Chlorination of the drinking water may be the source of the HCCPD, since the chemical reportedly formed during chlorination of a humic acid solution (Meier et al. 1985). To investigate the formation of HCCPD during disinfection processes, samples of lignin, tannic acid, and Suwannee River Natural Organic Matter (SRNOM) were chlorinated using sodium hypochlorite (NaClO) solutions at 21°C and pH 6.5–7.0 for up to 24 hours. The results showed that HCCPD formation initially increased but then decreased over time, possibly due to further

transformation processes such as hydrolysis. In lignin samples, HCCPD peaked at 8.10 ng/L after 12 hours, then decreased to ~7 ng/L after 24 hours; in tannic acid samples, HCCPD peaked at 24.25 ng/L after 4 hours, decreasing to 11.52 ng/L after 24 hours. In the SRNOM samples, HCCPD peaked at 47.66 ng/L after 6 hours and HCCPD reached concentrations of 9.54 ng/L in disinfected tap water (Xie et al. 2024). From data collected during the summer months of 2020, Li et al. (2022) identified HCCPD as a disinfection byproduct in three drinking water treatment plants in South Carolina. The process used by these plants included pre-oxidation, coagulation, precipitation, filtration, and disinfection with chlorine or chloramine for the treatment of surface waters. The estimated concentrations of HCCPD in the finished water were 7.8 ng/L for the plant using chloramine, and 51.0 and 65.6 ng/L for the two plants using chlorine.

Data from the 1980s reported in the STORET database indicate that the chemical was detectable in only 0.1% of 854 surface water samples (Staples et al. 1985). The median concentration for all samples was <10 µg/L (<10 ppb).

In a study of chlorinated organic chemicals associated with industries along the Passaic River in New Jersey, Shear et al. (1996) reported that HCCPD was associated with metal finishing, plastics, inorganic chemicals, electroplating, and steam electric power production facilities. However, no quantitative information or concentrations of HCCPD in the Passaic River were presented for this compound.

HCCPD was detected in leachate from a hazardous waste site (Hauser and Bromberg 1982).

5.5.3 Sediment and Soil

Limited monitoring data were located documenting HCCPD concentrations in soil or sediments. Data from the early 1980s reported HCCPD was not detectable in any of 344 sediment analyses reported in the STORET database (Staples et al. 1985). The median detection limit was ≤500 µg/kg (ppb). Results from sampling efforts conducted by organizations such as the USGS and EPA Great Lakes National Program indicate that HCCPD was not detected in 590 sediment samples collected across the United States between 2019 and 2024 or in 10 soil samples collected across the United States in 2023 (WQP 2025). Detection limits were 0.9–250 and 190–630 µg/kg in sediment and soil, respectively.

HCCPD was not detected in soil samples collected during the years 2018–2019 from McMurdo Station located in Ross Island, Antarctica, an area where accidental spills and chemical contamination (e.g., oil-

based paints, lubricants, grease, cleaners, and fuels) occurred in the late 1950s and 1970s. The EPA SW-846 standard method used had detection and reporting limits of 0.35 and 5.1 µg/g, respectively (U.S. Army 2020). HCCPD was included in a soil monitoring effort in Harrisburg, Pennsylvania during 2020 (PennDOT 2021). Soil samples were collected from 22 waste sites containing or likely containing regulated waste or petroleum substances from an existing release, a past release, or a material threat of a release into the surrounding area. HCCPD was not detected above method reporting limits at any of the sites (reporting limits: 182–3,590 µg/kg dry soil).

Outside of the United States, HCCPD was measured in seasonal soil samples collected around an agrochemical factory in China. The highest concentrations were observed downwind of the factory and storage tanks; concentrations ranged from 0.14 to 51.5 ng/g, with an average of 4.11 ng/g (Luan et al. 2022). Levels measured in autumn, winter, spring, and summer were 0.14–51.5 ng/g dry weight (dw) (mean 3.11 ng/g dw), 0.64–4.98 ng/g dw (mean 2.22 ng/g dw), 0.62–3.88 ng/g dw (mean 0.99 ng/g dw), and 1.68–40.6 ng/g dw (mean 10.1 ng/g dw), respectively.

No additional monitoring data were located on the occurrence of HCCPD in sediments or soils.

5.5.4 Other Media

In the 1970s, HCCPD was qualitatively detected in fish samples collected from waters near one industrial source (a pesticide manufacturing plant in Michigan (EPA 1977). However, the chemical was not detected in any of the 116 fish samples reported in the STORET database (Staples et al. 1985), nor was it detected in fish samples from waters near other industrial sources (EPA 1984) or from 14 Lake Michigan tributaries (Camanzo et al. 1987). HCCPD was qualitatively identified in fish collected from the Great Lakes and major watersheds to the Great Lakes during 1979 in 28 whole fish composite samples (7% positive detections; however, no detection limits were reported) (Kuehl et al. 1983). No recent information was located on detection of HCCPD in any commercially available fish or shellfish species, and no information was located on detection of HCCPD in raw or prepared foods.

In a study of the semiconductor industry, Bauer et al. (1995) reported detecting HCCPD at a concentration of 1.26 mg/kg (ppm) in waste oil samples collected from vacuum pump oils contaminated from aluminum plasma etching processes.

HCCPD was measured in tree bark samples collected over a year-long sampling period around an agrochemical factory in China at concentrations of 2.55–68.4 ng/g dw (mean 33.3 ng/g dw) (Luan et al. 2022). The trees with the highest concentration were in the area where the highest levels of HCCPD in air were measured. Measured concentrations were 0.44–55.7 ng/g dw (average 21.3 ng/g dw) and 6.69–91.4 ng/g dw (average 22.1 ng/g dw), in rice and wheat samples, respectively, 12.1–1,596 ng/g lipid weight (lw) in terrestrial organisms, and up to 32,995 ng/g lw (average 9,013 ng/g lw) in chickens.

Concentrations of HCCPD measured in bird eggs, collected from the Selenga river estuary, an area near industrial activity, were <10 µg/kg dw in 10/16 of the sampled species, and ranged from 18.45 to 493.79 µg/kg dw in 6/16 of the sampled species (Lebedev et al. 1998). HCCPD was detected but not quantified in long-finned pilot whale blubber samples collected during 2018 in Tasiilaq and Kulusuk, Greenland (Zhu et al. 2024).

5.6 GENERAL POPULATION EXPOSURE

Exposure of the general population to HCCPD is expected to be extremely low (EPA 1991). This chemical has not been frequently detected in any environmental medium. However, this may be due to analytical limitations. Due to the high reactivity of HCCPD, it is unlikely to remain in air or in other environmental media for extended periods. Contaminated water and ambient air are the most likely sources of exposure for the general population. Using data from the 2017 National Emissions Inventory (NEI), Li and Li (2021) estimated the ratio of the average daily dose of HCCPD via inhalation and ingestion routes to the median effective dose (ED_{50}) for three age groups. The average daily dose to ED_{50} ratios were estimated as $1.38x10^{-4}$, $4.79x10^{-5}$, and $4.39x10^{-5}$ for 3-, 14-, and 25-year-olds, respectively in the U.S. population. This ratio was used to estimate the probability of the occurrence of adverse health effects (unitless), which was negligible (less than 1 in a million) for each age group. However, out of 95 chemicals studied, HCCPD was ranked 7th in estimated risk even though its emission rate was ranked 76th out of the 95 chemicals due to its high estimated inhalation toxicity.

There are no recent data available regarding occupational exposures to HCCPD. Historical data likely reflect exposures from when this compound was used in the manufacture of now-banned pesticides. Occupational exposure to HCCPD was mainly by inhalation, but dermal exposure was also possible. The National Institute for Occupational Safety and Health (NIOSH) estimated that 1,427 workers were potentially exposed to HCCPD in 1980, and the Velsicol Chemical Company of Memphis, Tennessee, estimated that about 157 employees were potentially exposed to HCCPD at their facility (EPA 1991).

Exposure to HCCPD has been determined for operators employed in a chemical plant producing chlorinated hydrocarbons, including HCCPD, for an average of 8.2 years (range, 0.5–23 years) (Boogaard et al. 1993). Exposures, calculated as mean airborne concentrations over an 8-hour time-weighted average (TWA), occasionally exceeded 0.11 mg/m^3 and were higher during maintenance stops than during routine operation of the plant.

Yalçin et al. (2024) sampled cord blood levels for persistent organic pollutants from mothers in Sanlurfa, Turkey. HCCPD was detected above the detection limit in 25.8% of samples with the 75th, 90th, and maximum levels reported as 2.7, 12.5, and 50.51 ng/g, respectively (n=120). HCCPD is a lipophilic compound, so there should be no significant barrier to its crossing the placenta. No information was located on measurements of HCCPD in breast milk that might result in postnatal exposure of a nursing infant. Because HCCPD is a lipophilic molecule, its passage into breast milk is also possible and could result in exposure of breastfed infants.

There is no information on HCCPD concentrations in infant and toddler foods, baby formula, or prepared foods for infants and children.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

There are few populations expected to have very high exposures to HCCPD other than workers involved in the production or use of this substance. While many of the pesticides that HCCPD was previously used to manufacture are persistent in the environment, HCCPD itself is not. It is possible that select groups within the general population may receive potentially higher inhalation exposures if they reside or work near manufacturing and processing facilities or near hazardous waste sites where HCCPD has been detected in some environmental media. HCCPD has been identified in at least 34 NPL sites across the United States with soil concentrations quantified at 7 NPL sites with a median value of 2,800,000 ppb (ATSDR 2022). In homes with groundwater supplies contaminated with HCCPD, indoor air concentrations of 0.06–0.10 $\mu g/m^3$ were reported (EPA 1984).

CHAPTER 6. 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 NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of HCCPD.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk 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.

6.1 EXISTING INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to HCCPD that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of HCCPD. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

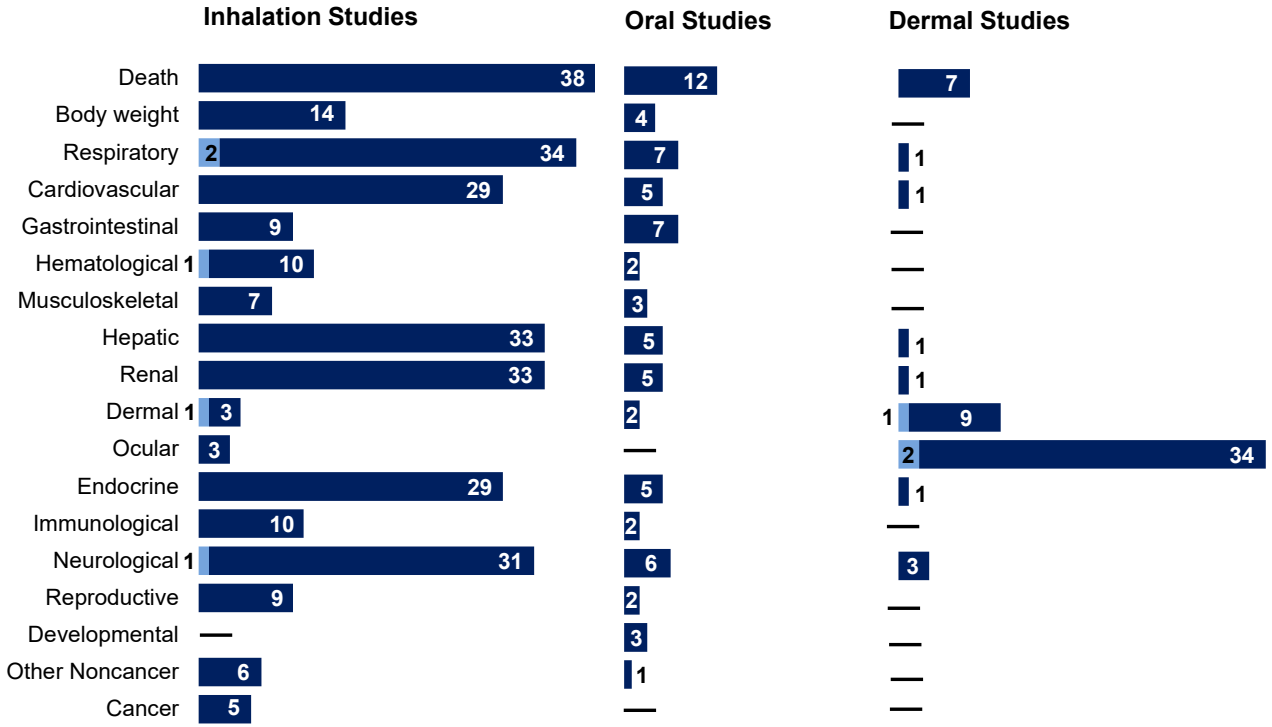
6.2 IDENTIFICATION OF DATA NEEDS

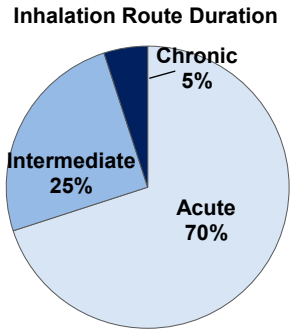
Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

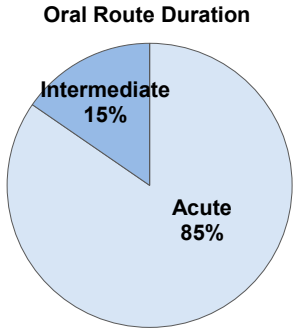
Figure 6-1. Summary of Existing Health Effects Studies on HCCPD by Route and Endpoint*

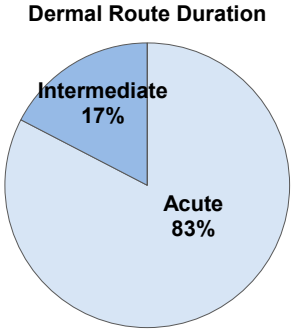
Potential death, respiratory, ocular, neurological, renal, and hepatic effects were the most studied endpoints

The majority of the studies examined inhalation and dermal exposure in **animals** (versus **humans**)









*Includes studies discussed in Chapter 2. Most studies examined multiple endpoints; the number of studies include those finding no effect.

Acute-Duration MRLs. The available acute-duration inhalation and oral databases were inadequate for deriving provisional MRLs. For both routes, the most sensitive effects include increased mortality. Additional studies designed to establish dose-response relationships for sensitive targets of toxicity in animals at exposure levels below those associated with lethality could provide data needed to develop these MRLs. The currently identified sensitive targets, based on longer-duration studies, include respiratory and hematological for the inhalation route and gastrointestinal and renal for the oral route.

Intermediate-Duration MRLs. The inhalation database was adequate to derive a provisional intermediate-duration MRL based on respiratory effects (nasal suppurative inflammation). Dose-response data, including identification of a NOAEL (0.146 ppm), were available for the critical effect. Additional studies designed to identify NOAELs and/or establish better dose-response relationships in animals for nasal effects may be useful to increase confidence in the MRL. The oral database was adequate to derive a provisional intermediate-duration MRL for HCCPD based on gastrointestinal effects (increased forestomach epithelial hyperplasia and focal inflammation); dose-response data including identification of a NOAEL and LOAEL value were available for the critical effect.

Chronic-Duration MRLs. The chronic database was adequate to derive a provisional chronic-duration MRL based on respiratory effects. The provisional MRL is based on a 95% lower confidence limit on the benchmark concentration associated with 10% extra risk ($BMCL_{10}$ of 0.052 ppm). No chronic-duration oral studies of HCCPD were located, precluding derivation of a provisional chronic-duration oral MRL. A comprehensive chronic-duration oral toxicity study could provide data needed to develop an MRL.

Health Effects.

Hematology. Altered red blood cell hematology parameters were identified in rats and mice following acute- and intermediate-duration inhalation exposures (Alexander et al. 1980a; Clark 1981; NTP 1994; Rand et al. 1982a). However, species and sex differences were observed, and the special hematology study by NTP (1994) did not reproduce the effects observed in the main study. The concentration at which effects occurred also varied between studies; additional dose-response studies could help clarify the potential dose-response relationship. Also, based on the lack of treatment-related effects on bone marrow histopathology in these studies, it is plausible that the effects on red blood cell hematology parameters are secondary to altered gas exchange following HCCPD-induced toxicity to the respiratory tract. As the only available intermediate-duration oral exposure study (Abdo et al. 1984; Velsicol 1981a, 1981b) did not evaluate

hematology parameters, an additional oral exposure study that included hematology evaluations would clarify whether HCCPD directly affects red blood cells.

Endocrine. There have been no studies of endocrine function following HCCPD exposure by any route. This compound does not appear to have effects on endocrine organs (adrenals, thyroid, parathyroid, or pituitary glands) after inhalation or oral exposure levels relevant for the general public (Alexander et al. 1980a, 1980b; Abdo et al. 1984; Clark 1981; NTP 1994; Rand et al. 1982a; Velsicol 1981a, 1981b), but there are many aspects of endocrine function that have not been evaluated. A well-conducted study of the endocrine-related effects of HCCPD, including evaluation of circulating hormone levels and hormone-sensitive endpoints, after inhalation exposure would be useful. The available data do not suggest that the potential of HCCPD to cause endocrine effects would be route- or species-specific.

Immunotoxicity. There have been no studies of immunological function following HCCPD exposure by any route. This compound does not appear to have effects on the spleen or thymus after inhalation or oral exposure (Alexander et al. 1980a, 1980b; Abdo et al. 1984; Clark 1981; NTP 1994; Rand et al. 1982a; Velsicol 1981a, 1981b), but there are many aspects of immunotoxicity that have not been evaluated. A well-conducted study of the immunotoxicity of HCCPD, including potential modification of antigen response, after inhalation exposure would be useful. The available data do not suggest that the potential of HCCPD to cause immune effects would be route- or species-specific.

Neurotoxicity. Inhalation exposure to HCCPD for 3–15 days was associated with complaints of headaches in workers in a WWTP following an inadvertent industrial release (Morse et al. 1979). High-concentration, acute-duration 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; findings may have been due to autolysis (Treon et al. 1955). Accordingly, detailed investigation of the brain lesions that are observed with HCCPD exposure is justified. Additional neurotoxicity studies evaluating functional endpoints after inhalation exposure that might be relevant to the occupational setting could provide useful information. 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.

Reproductive. No studies were located regarding the effects of HCCPD on human reproduction. Acute-, intermediate, and chronic-duration inhalation exposure in rats, mice, and monkeys (Alexander et al. 1980a, 1980b; Clark 1981; NTP 1994; Rand et al. 1982a) and intermediate-duration oral exposure in rats and mice (Abdo et al. 1984; Velsicol 1981a, 1981b) 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 a 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 on the effect of the compound on reproductive function, occupational exposure studies and 1- or 2-generation studies with functional reproductive and fertility assessments in animals by the inhalation, oral, and dermal routes would be useful in judging whether reproductive toxicity is an endpoint of concern for humans following exposure to HCCPD.

Developmental. The developmental effects of HCCPD have been studied after oral exposure in mice (Chernoff and Kavlock 1982, 1983; Gray and Kavlock 1984; Gray et al. 1986; Murray et al. 1980) and rabbits (Murray et al. 1980). Adverse developmental effects were limited to an increased incidence of 13 ribs in rabbits at a maternally toxic dose (75 mg/kg/day) (Murray et al. 1980); no adverse developmental effects were observed in mice. 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 a potential for developmental toxicity by HCCPD, including its ability to pass through the placenta and/or distribute to the milk of lactating maternal animals. There is limited evidence of placental transfer of HCCPD in humans based on its detection in cord blood (Yalçin et al. 2024). Because environmental exposure to HCCPD may occur in humans at or near hazardous waste sites, additional animal studies by the inhalation route would enhance understanding of the potential effects of the compound on human development.

Epidemiological and Human Dosimetry Studies. No epidemiological studies of HCCPD exposure in humans were identified. This material is a reactant in the manufacture several pesticides (aldrin, dieldrin, chlordane, and heptachlor). The toxicity of these pesticides makes it difficult to evaluate occupational exposure to the HCCPD at facilities that manufacture or use these pesticides. There would

be difficulties 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 possibly identifying biomarkers of exposure or effect.

Biomarkers of Exposure and Effect. 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. 1980). No data were located regarding the fate of the chlorine atoms in HCCPD. If isotopic labeling experiments were to identify a unique chlorine-containing metabolite, it might be possible to extract this metabolite from urine and perform analysis for total organic halogen as a biomarker of exposure.

Inadequate information is available at the present time regarding biomarkers of effect for acute- and 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) especially when compared to a reference population. With a larger database on HCCPD-associated changes in serum liver enzymes such as LDH, AST, ALT, ALP, and 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 following chronic-duration inhalation exposure (NTP 1994) appears to be a biomarker of exposure, rather than effect, because other respiratory lesions did not co-occur with the pigmentation, and it does not appear to be a precursor to more significant lesions (i.e., does not indicate an initial phase in the progression of a disease state).

Absorption, Distribution, Metabolism, and Excretion. Little is known concerning the mechanism of HCCPD absorption or the mechanism(s) of its metabolism. Data on distribution to tissues in rats demonstrate that absorption occurs through the inhalation and oral exposure routes (El Dareer et al. 1983; Lawrence and Dorough 1981,1982), although the degree of oral absorption is less than that via the inhalation route. Additionally, results of dermal toxicity studies include systemic toxicity following exposure via the skin (Gardner 1986b; OxyChem 1972, 1992; Treon et al. 1955), indicating that HCCPD is absorbed following dermal exposures. In distribution studies using ^{14}C-labeled HCCPD, the liver, kidneys, lungs, fat, and ovaries contain the highest amounts of ^{14}C-radiolabel (Dorough and Ranieri 1984; El Dareer et al. 1983; Yu and Atallah 1981). HCCPD and/or unidentified HCCPD metabolites are

excreted in urine 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 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 endogenous substances would increase understanding of its metabolism and distribution and potentially allow for the development of 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 HCCPD oral toxicity than mice (Abdo et al. 1984; Velsicol 1981a, 1981b) and mice are more susceptible to HCCPD inhalation toxicity than rats (NTP 1994; Treon et al. 1955). Male animals appear to be more sensitive than female animals (Abdo et al. 1984; Rand et al. 1982a; Velsicol 1981a, 1981b).

Before additional studies of comparative toxicokinetics are conducted, it is important to establish the mechanism of HCCPD toxicity for the most sensitive responses. An understanding of these mechanisms would make it possible to evaluate the contribution that species differences in anatomy and physiology make to the observed differences in HCCPD toxicity. For example, differences in the bronchiole diameters may be the critical factor in determining respiratory toxicity. Regardless, there is a need for a well-conducted pharmacokinetic study of HCCPD.

Children's Susceptibility. Data needs relating to developmental effects are discussed above under Developmental. There are no data describing the effects of HCCPD exposure on children; developmental toxicity findings in experimental animals are limited to an increased incidence of 13 ribs in rabbits orally exposed prenatally to a maternally toxic dose (Murray et al. 1980). As noted in Chapter 5, there are still hazardous waste scenarios that could result in exposure of children. 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 1982, 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 sufficiently high HCCPD exposures may affect the liver, kidney, and 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 health risk to children.

Physical and Chemical Properties. The physical and chemical properties of HCCPD are sufficiently well characterized for most properties to allow estimation of its environmental fate (Amoore and Hautala 1983; EPA 1982, 1991; Rumble 2018; Ruth 1986; WHO 1991; Wolfe et al. 1982). Detailed information on the autoignition temperature, flashpoint, flammability limits, and explosive limits are not available; however, based on its chemical structure and thermokinetics, these properties are of minor importance (EU 2007).

Production, Import/Export, Use, Release, and Disposal. The most recent data reported that HCCPD was manufactured by one facility in 2012 (EPA 2025a). Production volume and import/export information are available for this facility. Additional information on import and export volumes of the chemical and on uses of this compound would be helpful, as would additional information on any current registered uses of any pesticides in which HCCPD might be present as an impurity. Current comprehensive information on disposal volumes and methods is also needed. This information would be useful in assessing current exposure risk of workers and the general population to HCCPD.

Environmental Fate. The environmental fate of HCCPD has been well described (Chou et al. 1981; EPA 1984; ISGS 1983; Wolfe et al. 1982). The chemical is highly reactive and degrades readily in environmental media. However, further research on the metabolic, degradation, and reactive products would help in assessing the impact of HCCPD on the environment and humans. Exposure of the general public outside of hazardous waste scenarios is unlikely. Nevertheless, because it appears to migrate at a higher rate in soil in the presence of other organic chemicals (Chou et al. 1981; ISGS 1983), additional studies might be useful to assess the potential for leaching of this chemical from soil into groundwater at hazardous waste sites.

Bioavailability from Environmental Media. The occurrence of toxic effects in animals following inhalation, oral, and dermal exposures to HCCPD demonstrates that it is bioavailable from the media used in these studies (air, corn oil, peanut oil, and Ultrasene) (Abdo et al. 1984; Treon et al. 1955). Bioavailability from the gastrointestinal tract appears to be limited, presumably due to binding of HCCPD to intestinal contents (El Dareer et al. 1983). No data were available concerning bioavailability of HCCPD from soil or sediments. Research on the nature of the HCCPD interactions with soils, sediments, and food materials would help in evaluating the risk posed by contamination at hazardous waste sites.

Food Chain Bioaccumulation. Bioaccumulation and biomagnification of HCCPD are not expected to be substantial in the food chain, since the chemical is rapidly metabolized in aquatic organisms (Lu et al. 1975; Podowski and Khan 1984; Podowski et al. 1991; Spehar et al. 1979; Wolfe et al. 1982). HCCPD has only rarely been detected in edible aquatic species (Camanzo et al. 1987; EPA 1984). On this basis, it does not appear that exposure of humans by this route is of concern, and further research in this area does not seem to be a high priority.

Exposure Levels in Environmental Media. HCCPD is infrequently detected in environmental media (EPA 1984, 1991; Staples et al. 1985). This may be due to difficulties in analysis and/or its rapid degradation in air, water, and soil. Insufficient data are available to estimate exposure levels in drinking water, food, or air (EPA 199Oc), but exposure of the general population to HCCPD from these sources is not expected to be significant. However, exposure in the workplace and in the vicinity of hazardous waste sites may occur at levels that could be of concern. Additional monitoring data for various inhalation exposure situations would be useful for determining occupational exposure risk as well as risk of exposures of individuals in the general population living near manufacturing and processing facilities or near hazardous waste sites where HCCPD has been detected.

Reliable monitoring data for the levels of HCCPD in contaminated media at hazardous waste sites are needed so that the information obtained on levels of HCCPD in the environment can be used in combination with the known body burdens of HCCPD to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Detection of HCCPD in urine of WWTP workers indicates occupational exposures to this chemical is possible; however, these data arise from decades ago (Elia et al. 1983). Since HCCPD is rapidly metabolized *in vivo*, it was not possible to directly associate urine levels with environmental concentrations. Additional information on exposure levels in humans would be

helpful. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. A unique exposure route that potentially exists for children involves intentional ingestion and hand-mouth activity associated with young children. Exposure may arise if these behaviors occur in children who play in or around contaminated soil or sediment (e.g., hazardous waste sites). As soil is at least a short-term reservoir of HCCPD in the environment, additional studies of the transfer of HCCPD via both oral and dermal routes of exposure in children are warranted as are studies of the bioavailability of the chemical from soil and sediment. Quantitative information is also needed to determine the concentrations of HCCPD in air associated with hazardous waste sites.

Current information on whether children are different in their weight-adjusted intake of HCCPD via inhalation, oral, or dermal exposures was not located. Studies conducted to determine if there are any HCCPD residues in breast milk, especially in women residing in areas in proximity to production facilities and hazardous waste sites are needed. This information would be useful in determining which exposure pathway is most important for children. Since exposure to HCCPD is likely to be negligible in members of the general population, exposure and body burden studies for children would be helpful especially in those children living in proximity to production facilities or hazardous waste sites.

6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2025) database, which tracks projects funded by NIH.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding HCCPD in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for HCCPD.

Table 7-1. Regulations and Guidelines Applicable to Hexachlorocyclopentadiene

Agency	Description	Information	Reference
	Air		
EPA	RfC	$2x10^{-4}$ mg/m^3 ($2x10^{-5}$ ppm)	IRIS 2003[a]
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018b
	DWEL	0.2 mg/L	
	National primary drinking water regulations		EPA 2024a
	MCL	0.05 mg/L	
	MCLG	0.05 mg/L	
	RfD	$6x10^{-3}$ mg/kg/day	IRIS 2003[a]
WHO	Drinking water quality guidelines	Not listed	WHO 2022
FDA	Substances added to food (formerly EAFUS)	Not listed	FDA 2025
	Allowable level in bottled water	0.05 mg/L	FDA 2024
	Cancer		
HHS	Carcinogenicity classification	Not evaluated	NTP 2021
EPA	Carcinogenicity classification	Not likely to be a human carcinogen by the inhalation route	IRIS 2003[a]
IARC	Carcinogenicity classification	Not evaluated	IARC 2025
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	Not established	OSHA 2024a, 2024b, 2024c
NIOSH	REL (up to 10-hour TWA)	0.01 ppm (0.1 mg/m^3)	NIOSH 2019

Table 7-1. Regulations and Guidelines Applicable to Hexachlorocyclopentadiene

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air	Not listed	EPA 2018c
DOE	PACs-air		DOE 2025a
	PAC-1[b]	0.33 mg/m^3 (0.030 ppm)	
	PAC-2[b]	1.9 mg/m^3 (0.17 ppm)	
	PAC-3[b]	11 mg/m^3 (0.99 ppm)	

[a]IRIS values were derived in 2001; the most recent revision to the IRIS chemical assessment summary was in 2003.
[b]Definitions of PAC terminology are available from DOE (2025b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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 for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substances than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Hexachlorocyclopentadiene (HCCPD)
CAS Numbers: 77-47-4
Date: October 2026
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of a provisional acute-duration inhalation MRL for HCCPD. No adequate human exposure studies for this duration were identified, and the lowest identified acute-duration LOAEL in animal inhalation studies is associated with increased morbidity and mortality.

Rationale for Not Deriving an MRL: No concentration-response data are available for humans. Available animal data following acute-duration inhalation exposure are limited and are primarily restricted to acute lethality studies. The lowest identified acute-duration inhalation adverse effect level is a serious LOAEL of 0.5 ppm, identified in rats exposed 6 hours/day, 5 days/week for 1–2 weeks (Alexander et al. 1980a; Rand et al. 1982a). At this concentration, exposed rats exhibited increased morbidity/mortality, decreased body weights and food and water intake, altered hematology parameters, labored respiration, and histopathological changes in the respiratory tract (bronchiole inflammation, hyperplasia, and epithelial erosion). Data in other species are restricted to mortality studies, reporting 80–100% mortality in 5-day studies following daily 7-hour exposures to 1 ppm (Treon et al. 1955). Due to the observation of significant morbidity/mortality at the lowest identified LOAEL, a provisional acute-duration inhalation MRL cannot be derived for HCCPD.

Agency Contacts (Chemical Managers): Gaston Casillas

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Hexachlorocyclopentadiene (HCCPD)
CAS Numbers: 77-47-4
Date: October 2026
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate
Provisional MRL: $1x10^{-4}$ ppm (0.001 mg/m^3)
Critical Effect: Nasal suppurative inflammation
Reference: NTP 1994
Point of Departure: $NOAEL_{HEC}$ of 0.00344 ppm
Uncertainty Factor: 30
LSE Graph Key: 30
Species: Rat

MRL Summary: A provisional intermediate-duration inhalation MRL of $1x10^{-4}$ ppm was derived for HCCPD based on increased nasal suppurative inflammation in male rats exposed to ≥0.385 ppm for 13 weeks (6 hours/day, 5 days/week); a NOAEL of 0.146 ppm was identified (NTP 1994). The provisional MRL is based on the NOAEL of 0.146 ppm, which was adjusted to continuous duration exposure and converted to a human equivalent concentration ($NOAEL_{HEC}$) of 0.00344 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability). The same study identified a $LOAEL_{HEC}$ of 0.00908 ppm (NTP 1994).

Selection of the Critical Effect: No concentration-response data are available for humans. In laboratory animals, dose-response data are available for a comprehensive set of endpoints from multiple studies in rats and mice following intermediate-duration exposure to HCCPD (Alexander et al. 1980b; Clark 1981; Huntingdon Research Centre 1980; NTP 1994; Rand et al. 1982a, 1982b). A 14-week study in cynomolgus monkeys is also available (Alexander et al. 1980b; Rand et al. 1982a). Increased mortality was observed after exposure to concentrations as low as 0.389 ppm, identified in male mice in the 13-week study by NTP (1994). The only adverse effects observed at concentrations below those associated with mortality included respiratory and hematological effects. Therefore, only these effects were further considered as candidate critical effects for the provisional intermediate-duration inhalation MRL for HCCPD. Available respiratory and hematological data from intermediate-duration inhalation studies at concentrations below the lowest reported lethal concentration of 0.389 ppm are summarized in Table A-1.

Table A-1. Select NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure[a] to Hexachlorocyclopentadiene

		Effect level (ppm)			
Species (sex)	Duration	NOAEL	LOAEL	Effect	Reference
Respiratory effects					
Cynomolgus monkey (both)	14 weeks	0.2	ND	None	Alexander et al. 1980b; Rand et al. 1982a, 1982b

Table A-1. Select NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure[a] to Hexachlorocyclopentadiene

Species (sex)	Duration	Effect level (ppm) NOAEL	LOAEL	Effect	Reference
Sprague-Dawley rat (both)	14 weeks	0.2	ND	None	Alexander et al. 1980b; Huntingdon Research Centre 1980; Rand et al. 1982a, 1982b
B6C3F1 mouse (male)	33 weeks	ND	0.2	Nasal suppurative inflammation	NTP 1994
Fischer-344 rat (male)	13 weeks	0.146	0.385	Nasal squamous metaplasia and suppurative inflammation; suppurative and necrotizing inflammation of the bronchus/ bronchiole; increased absolute and relative lung weights	NTP 1994
Hematological effects					
B6C3F1 mouse (female)	13 weeks	ND	0.039	Increased MCHC	NTP 1994 (hematology study)
Sprague-Dawley rat (both)	14 weeks	0.05	ND	None	Alexander et al. 1980b; Rand et al. 1982a
Wistar rat (male)	30 weeks	0.06	0.14	Increased red blood cell counts, hemoglobin, hematocrit, and neutrophil counts; decreased lymphocyte percentage	Clark 1981
Cynomolgus monkey (both)	14 weeks	0.2	ND	None	Alexander et al. 1980b; Rand et al. 1982a
Fischer-344 rat (male)	13 weeks	0.039	0.385	Increased MCV	NTP 1994 (hematology study)
Fischer-344 rat (female)	13 weeks	0.039	0.385	Increased MCV, packed cell volume, hemoglobin, and erythrocytes	NTP 1994 (hematology study)
Fischer-344 rat (male)	13 weeks	0.146	0.385	Increased packed cell volume, hemoglobin, erythrocytes, and MCHC	NTP 1994 (main study)
Fischer-344 rat (female)	13 weeks	0.146	0.385	Decreased erythrocytes and increased MCV	NTP 1994 (main study)

[a]All studies were intermittent exposure (5 hours/day, 6 days/week) via whole-body exposure.

Green shading indicates the study selected for derivation of the provisional intermediate-duration inhalation MRL.

F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); MCHC = mean corpuscular hemoglobin concentration; MCV = mean cell volume; ND = not determined; NOAEL = no-observed-adverse-effect level; (WB) = whole-body inhalation exposure

In order to best compare the relative sensitivity of the candidate endpoints, HEC values were calculated for the most sensitive LOAELs for respiratory effects (0.2 ppm for nasal suppurative inflammation) and hematological effects (0.039 ppm for increased MCHC).

The LOAEL values were first adjusted for intermittent exposure ($LOAEL_{ADJ}$) as follows:

$$LOAEL_{ADJ} = LOAEL \times \frac{6\ hours/day}{24\ hours} \times \frac{5\ days/week}{7\ days}$$

$$Hematological\ LOAEL_{ADJ} = 0.039\ ppm \times \frac{6\ hours/day}{24\ hours} \times \frac{5\ days/week}{7\ days} = 0.0070\ ppm$$

$$Nasal\ LOAEL_{ADJ} = 0.2\ ppm \times \frac{6\ hours/day}{24\ hours} \times \frac{5\ days/week}{7\ days} = 0.04\ ppm$$

For the hematological effects, the $LOAEL_{ADJ}$ was converted into a $LOAEL_{HEC}$ using guidance from EPA (1994) on dosimetric adjustments for systemic effects using the ratio of animal:human blood gas partition coefficients. Blood gas partition coefficient values were not located for humans or animals; therefore, a default value of 1 is used to derive the $LOAEL_{HEC}$.

$$Hematological\ LOAEL_{HEC} = 0.0070\ ppm \times 1 = 0.0070\ ppm$$

For the nasal effects, the $LOAEL_{ADJ}$ value was converted to a $LOAEL_{HEC}$ value using guidance from EPA (1994) on dosimetric adjustments for respiratory effects using the regional gas dose ratio (RGDR) for extrathoracic effects ($RGDR_{ET}$). This $RGDR_{ET}$ is calculated using the following equation as defined by EPA (1994):

$$RGDR_{ET} = \frac{V_{E_a}}{SA_a} \div \frac{V_{E_h}}{SA_h}$$

where:
V_{E_a} = ventilation rate in male B6C3F1 mice (subchronic) = 0.037 L/minute
SA_a = surface area of the extrathoracic region in mice = 3 cm^2
V_{E_h} = ventilation rate for humans = 13.8 L/minute
SA_h = surface area of the extrathoracic region in humans = 200 cm^2

$$RGDR_{ET} = \frac{0.037\ L/min}{3\ cm^2} \div \frac{13.8\ L/min}{200\ cm^2} = 0.179$$

$$Nasal\ LOAEL_{HEC} = LOAEL_{ADJ} \times RGDR_{ET} = 0.04\ ppm \times 0.179 = 0.007\ ppm$$

Based on $LOAEL_{HEC}$ values, respiratory and hematological effects are equally sensitive targets of toxicity following HCCPD exposure. However, the consistency of the databases differs between these two endpoints. For respiratory effects, consistent evidence of concentration-related toxicity and portal-of-entry effects were observed in the respiratory tract following intermediate-duration exposure to HCCPD in rats and mice (Clark 1981; NTP 1994). While several studies reported alterations in red blood cell parameters, observed effects were generally of low magnitude (<10% difference from controls) and were inconsistent between studies and sexes within a given species (Clark 1981; NTP 1994; Rand et al. 1982a;

Alexander et al. 1980b). Notably, special 13-week hematology studies conducted by NTP (1994) were not able to reproduce results consistent with those observed in the main 13-week toxicity study and hematological effects were not seen in the 2-year bioassays. Consistent with these findings, systematic review (Appendix C) indicates that respiratory effects are presumed health effects while hematological effects (altered red blood cell parameters) are suspected health effects in humans following inhalation exposure to HCCPD. Based on the greater consistency in the respiratory effects database and a stronger hazard conclusion from the systematic review, respiratory effects are selected as the critical effects for the provisional intermediate-duration inhalation MRL.

Selection of the Principal Study: NTP (1994) was selected as the principal study because it identified the lowest LOAEL for the critical effect (respiratory lesions). Only the 13-week study in rats and the 33-week study in male mice were considered during MRL derivation (and summarized below). The 13-week study in mice was not considered due to 50% mortality in male mice at the LOAEL of 0.389 ppm for respiratory lesions (and 100% mortality at concentrations above the LOAEL) and 60% accidental death in control female mice. The 26- and 42-week studies in male mice were not considered because the respiratory LOAELs of 0.5 ppm exceed the lowest serious LOAEL for mortality of 0.389 ppm identified in male mice in the main 13-week study.

Summary of the Principal Study:

NTP. 1994. Toxicology and carcinogenesis studies of hexachlorocyclopentadiene (CAS No. 77-47-4) in F344 rats and B6C3F1 mice (inhalation studies). National Toxicology Program. PB94214186. NTP TR 437. NIH 94-33168. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB94214186.xhtml. September 23, 2025.

13-Week Study in Rats. Groups of F344 rats (10/sex/group) were exposed to HCCPD vapors at nominal concentrations of 0, 0.04, 0.15, 0.4, 1, or 2 ppm for 6 hours/day, 5 days/week for 13 weeks. Analytical concentrations were 0, 0.039, 0.146, 0.385, 0.941, and 2.065 ppm HCCPD, respectively. Following exposure, survival and clinical signs were monitored, and body weights were determined. Food and water intake were not measured. Blood was collected for hematological and clinical chemistry examinations at the end of the exposure period. Gross necropsy was performed, and organs were weighed (liver, right kidney, lung, brain, adrenal gland, heart, right testis, and thymus). Histological examinations were performed for the following tissues: liver, lung, kidney, urinary bladder, brain, heart, lymph nodes (mandibular, mesenteric, tracheobronchial), bone and bone marrow, gastrointestinal tract (esophagus, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum), nose, pancreas, spleen, thymus, reproductive organs (epididymis, ovary, prostate, testis, uterus), larynx, trachea, and adrenal, mammary, parathyroid, pituitary, salivary, and thyroid glands.

No male or female rats survived after exposure to 0.941–2.065 ppm for 4 weeks. Decreased mean final body weights and mean body weight changes were observed in male rats exposed to 0.385 and 0.039–0.0385 ppm, respectively. Clinical signs of toxicity, reported qualitatively only, included listlessness and respiratory distress at ≥0.385 ppm and ≥0.941 ppm, respectively. Treatment-related effects on hematology parameters included increased packed cell volume, hemoglobin, erythrocytes, and MCHC in male rats at 0.385 ppm and decreased erythrocytes and increased MCV in female rats at 0.385 ppm. No changes to clinical chemistry parameters were observed with treatment. Histopathological changes identified in the nasal region of the respiratory tract included increased incidences of squamous metaplasia in male rats at 0.385 and 0.941 ppm, suppurative inflammation in male rats at 0.385 ppm, and necrotizing inflammation in male and female rats at ≥0.941 ppm. Increased incidences of necrotizing inflammation were also identified in the larynx and trachea of male and female rats exposed to ≥0.941 ppm. In the lungs of male rats, increased incidences of bronchus/bronchiole suppurative inflammation were identified at 0.385 ppm, bronchus/bronchiole necrotizing inflammation was observed

at ≥0.385 ppm, alveolar suppurative inflammation was identified at 0.941 ppm, and alveolar hemorrhage was evident at ≥0.941 ppm. In the lungs of female rats, an increased incidence of alveolar suppurative inflammation was identified at 0.941 ppm and increased incidences of bronchus/bronchiole necrotizing inflammation and alveolar hemorrhage were observed at ≥0.941 ppm. In general, these lesions demonstrated concentration-dependent increases in severity scores and/or evidence of progression to a more serious lesion type.

33-Week Study in Mice: Groups of male mice were exposed to 0 or 0.2 ppm for 33 weeks (6 hours/day, 5 days/week) and immediately sacrificed (10/group) or maintained without further exposure for up to 105 weeks (50/group) to evaluate potential reversibility of nonneoplastic lesions. Analytical concentration was not reported.

No exposure-related changes in survival, clinical signs, or body weight were observed. Histopathological findings immediately after exposure to 0.2 ppm for 33 weeks were limited to focal suppurative inflammation of the nose. Findings did not persist at the 2-year evaluation. Male mice exposed to 0.2 ppm for 33 weeks also exhibited increased incidences of mucosal epithelium pigmentation in the nose, trachea, and lungs. Described as a "pale, yellow-brown, granular pigment," this pigmentation was observed at the end of the exposure periods and at the 2-year sacrifice and evaluation. NTP (1994) performed tissue staining of affected sections for various substances and identified positive results for reducing substances in many, but not all, affected cells. NTP (1994) postulated that lipid peroxidation reactions between HCCPD and endogenous substances may have generated the pigment. It should be noted that other respiratory lesions did not co-occur with the pigmentation, and it does not appear to be a precursor to more significant lesions (i.e., does not indicate an initial phase in the progression of a disease state). Therefore, pigmentation likely serves as a marker of exposure and is not considered an adverse effect for this assessment.

Selection of the Point of Departure for the MRL: The $NOAEL_{HEC}$ of 0.00344 ppm based on nasal suppurative inflammation in male rats was selected as the point of departure (POD) as it provided the lowest POD for the critical effect.

In order to identify the most sensitive POD, benchmark dose (BMD) modeling was attempted for the most sensitive adverse respiratory lesions reported by NTP (1994). Modeled data were restricted to bronchus/bronchiole necrotizing inflammation (Table A-2). Nasal suppurative inflammation data were not modeled due to 0% incidence at the two highest doses (potential censoring of data due to early deaths and/or progression to more serious lesion); the incidences in the three lower dose groups were 0/10 at 0 ppm, 1/10 at 0.146 ppm, and 7/10 at 0.385 ppm, and only the incidence at 0.385 ppm was statistically significantly different from the concurrent control incidence. Restricting data to the lowest three doses only was considered an inadequate dataset (limited dose groups, small animal numbers), which leads to uncertainty in the estimates. Data from male mice exposed for 33 weeks were not amenable to modeling due to use of a single exposure level (0.2 ppm). For endpoints with data unsuitable for BMD modeling (nasal suppurative inflammation in rats and mice), ATSDR used the NOAEL/LOAEL approach for POD selection.

BMD modeling was performed with BMD Desktop (25.1) and a benchmark response (BMR) of 10% extra risk. Adequate model fit was judged by the following four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% lower confidence limit on the BMD (BMCL) that is not 10 times lower than the lowest non-zero dose, and a scaled residual within ±2 units at the data point (except the control) closest to the predefined benchmark response (BMR). Among all of the models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike information criterion (AIC) was chosen.

Table A-2. Respiratory Lesions in F344 Rats Selected for BMD Modeling Following Inhalation to Hexachlorocyclopentadiene for 13 Weeks (5 Days/Week, 6 Hours/Day)

		Concentration (ppm)/incidence				
Endpoint name	Sex	0	0.146	0.385	0.941	2.065
Bronchus/bronchiole necrotizing inflammation	Male	0/10	0/10	5/10[a]	10/10[a]	10/10[a]

[a]p≤0.05 compared with concurrent controls, based on logistic regression test performed by the study authors.

Source: NTP 1994

BMD modeling provided adequate model fits for bronchus/bronchiole necrotizing inflammation in male rats; modeling results are shown in Table A-3. All models provided adequate statistical fit; however, the Multistage 1-degree/Quantal linear models did not provide adequate visual fits to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Logistic). BMC and BMCL values were 0.338 and 0.170 ppm, respectively.

Table A-3. Results from Benchmark Dose (BMD) Analysis of Bronchus/Bronchiole Necrotizing Inflammation in Male F344 Rats Following Inhalation to Hexachlorocyclopentadiene for 13 Weeks (5 Days/Week, 6 Hours/Day) (NTP 1994)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-value[b]	AIC	Scaled residual at control	Scaled residual near BMC
Dichotomous Hill	0.314	0.167	1	17.865	-0	<0.001
Gamma[c]	0.279	0.147	1	15.867	-0	0.002
Log-Logistic[d]	0.314	0.167	1	17.865	-0	<0.001
Multistage Degree 1[e]			0.245	25.361	-0	-0
Multistage Degree 2[e]	0.153	0.083	0.878	18.164	-0	-1.002
Multistage Degree 3[e]	0.211	0.097	0.984	16.592	-0	-0.598
Multistage Degree 4[e]	0.242	0.106	0.998	16.145	-0	-0.374
Weibull[c]	0.214	0.121	0.941	18.582	-0	-0.578
Logistic[f]	**0.338**	**0.170**	**1**	**15.863**	**-0**	**<0.001**
Log-Probit	0.332	0.159	1	17.863	-0	0

Table A-3. Results from Benchmark Dose (BMD) Analysis of Bronchus/Bronchiole Necrotizing Inflammation in Male F344 Rats Following Inhalation to Hexachlorocyclopentadiene for 13 Weeks (5 Days/Week, 6 Hours/Day) (NTP 1994)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-value[b]	AIC	Scaled residual at control	Scaled residual near BMC
Probit	0.246	0.149	0.979	18.216	-0.056	-0.401
Quantal Linear			0.245	25.361	-0	-0

[a]BMC and BMCL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided adequate statistical fit; however, the Multistage 1-degree/Quantal linear models did not provide adequate visual fits to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Logistic).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk)

In order to accurately compare candidate PODs across different species and target tissues, effect levels (NOAEL, LOAEL, BMC, $BMCL_{10}$) were converted into HECs. As discussed above, animal exposure was 6 hours/day, 5 days/week. Therefore, prior to HEC calculations, all values were adjusted for intermittent exposure (POD_{ADJ}) using the following calculation:

$$POD_{ADJ} = POD \times \frac{6\ hours/day}{24\ hours} \times \frac{5\ days/week}{7\ days}$$

For nasal suppurative inflammation in rats and mice, candidate POD_{ADJ} values were converted to candidate POD_{HEC} values using guidance from EPA (1994) on dosimetric adjustments for respiratory effects using the $RGDR_{ET}$, calculated based on the following equation as defined by EPA (1994):

$$RGDR_{ET} = \frac{V_{E_a}}{SA_a} \div \frac{V_{E_h}}{SA_h}$$

where:
V_{E_a} = ventilation rate for animals in a subchronic study
male F344 rats = 0.137 L/minute
male B6C3F1 mice = 0.037 L/minute
SA_a = surface area of the extrathoracic region in animals
rats = 15 cm^2
mice = 3 cm^2
V_{E_h} = ventilation rate for humans = 13.8 L/minute
SA_h = surface area of the extrathoracic region in humans = 200 cm^2

For bronchus necrotizing inflammation in male rats, the candidate POD_{ADJ} value was converted to a candidate POD_{HEC} value using guidance from EPA (1994) on dosimetric adjustments for respiratory

effects using the RGDR for tracheobronchial effects ($RGDR_{TB}$). The $RGDR_{TB}$ is calculated using the following equation as defined by EPA (1994):

$$RGDR_{TB} = \frac{(Dose_{TB})_a}{(Dose_{TB})_h} = \frac{(\frac{V_E}{SA_{TB}})_a}{(\frac{V_E}{SA_{TB}})_h} \frac{(e^{\frac{-SA_{ET}}{V_E}})_a}{(e^{\frac{-SA_{ET}}{V_E}})_h}$$

where:

$[V_E]_a$ = minute volume for animals
male F344 rats = 0.137 L/minute
$SA_{TB\,a}$ = TB surface area for rats = 22.5 cm^2 (EPA 1994)
$e^{-(SAET/Ve)_a}$ = fraction of chemical concentration penetrating the ET region and available for uptake in the TB region in animals
male F344 rats = 0.896
$[V_E]_h$ = minute volume for humans = 13.8 L/minute (EPA 1994)
$SA_{TB\,h}$ = TB surface area for humans = 3,200 cm^2 (EPA 1994)
$e^{-(SAET/Ve)_h}$ = fraction of chemical concentration penetrating the ET region and available for uptake in the TB region in humans = 0.986

The resulting $RGDR_{ET}$, $RGDR_{TB}$, and candidate POD_{HEC} values are presented in Table A-4.

Table A-4. Candidate POD_{HEC} Values for Treatment-Related Respiratory Lesions in Experimental Animals Administered Intermediate-Duration Inhalation Exposures to Hexachlorocyclopentadiene (NTP 1994)

Species (sex), duration	Endpoint (POD type)	BMC_{10} or LOAEL (ppm)	$BMCL_{10}$ or NOAEL (ppm)	BMC_{ADJ} or $LOAEL_{ADJ}$ (ppm)	$BMCL_{ADJ}$ or $NOAEL_{ADJ}$ (ppm)	RGDR	BMC_{HEC} or $LOAEL_{HEC}$ (ppm)	$BMCL_{HEC}$ or $NOAEL_{HEC}$ (ppm)
Extrathoracic lesions								
F344 rat (male), 13 weeks	Nasal suppurative inflammation (NOAEL/LOAEL)	0.385	0.146	0.0688	0.0261	0.132	**0.00908**	**0.00344**
B6C3F1 mouse (male), 33 weeks	Nasal suppurative inflammation (NOAEL/LOAEL)	0.2	ND	0.04	ND	0.179	**0.007**	**ND**

Table A-4. Candidate POD_{HEC} Values for Treatment-Related Respiratory Lesions in Experimental Animals Administered Intermediate-Duration Inhalation Exposures to Hexachlorocyclopentadiene (NTP 1994)

Species (sex), duration	Endpoint (POD type)	BMC_{10} or LOAEL (ppm)	$BMCL_{10}$ or NOAEL (ppm)	BMC_{ADJ} or $LOAEL_{ADJ}$ (ppm)	$BMCL_{ADJ}$ or $NOAEL_{ADJ}$ (ppm)	RGDR	BMC_{HEC} or $LOAEL_{HEC}$ (ppm)	$BMCL_{HEC}$ or $NOAEL_{HEC}$ (ppm)
Tracheobronchial lesions								
F344 rat (male), 13 weeks	Bronchus/ bronchiole necrotizing inflammation (BMC/BMCL)	0.338	0.170	0.0604	0.0304	1.29	**0.0779**	**0.0392**

ADJ = adjusted; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no observed-adverse-effect level; POD = point of departure; RGDR = regional gas dose ratio

Selected endpoint (lowest POD_{HEC}).

To select the POD for the provisional intermediate-duration inhalation MRL, the candidate BMC_{HEC} values and $LOAEL_{HEC}$ values from the principal study by NTP (1994) were compared (Table A-4). Of these, the $LOAEL_{HEC}$ values for the nasal lesions were approximately an order of magnitude lower than the BMC_{HEC} for the tracheobronchial lesions. Since the $LOAEL_{HEC}$ values for nasal suppurative inflammation in rats and mice were nearly identical in magnitude (0.00908 and 0.007 ppm, respectively), and the mouse study only evaluated a single exposure level, the $NOAEL_{HEC}$ of 0.00344 ppm for male rats exposed to HCCPD for 13 weeks was selected as the POD for the provisional intermediate-duration inhalation MRL.

Adjustment for Intermittent Exposure and Human Equivalent Concentration: As shown above, the NOAEL of 0.146 ppm was adjusted for continuous exposure and converted into a $NOAEL_{ADJ}$ of 0.0261 ppm and a $NOAEL_{HEC}$ of 0.00344 ppm.

$$NOAEL_{ADJ} = \text{NOAEL} \times \frac{\text{hours/day}}{24\ hours} \times \frac{days/week}{7\ days}$$

$$= 0.146\ ppm \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.00261\ ppm$$

$$NOAEL_{HEC} = NOAEL_{ADJ} \times RGDR_{ET}$$

$$= 0.00261\ ppm \times 0.132 = 0.00344\ ppm$$

Uncertainty Factor: The following uncertainty factors were applied to the $NOAEL_{HEC}$ to derive the provisional MRL.

- Uncertainty factor of 3 for extrapolation from animals to humans with dosimetric adjustments
- Uncertainty factor of 10 for human variability.

Subsequently, the provisional MRL for intermediate-duration exposure to HCCPD via inhalation is:

$$Provisional\ MRL = \frac{NOAEL_{HEC}}{(UF)} = \frac{0.00344\ ppm}{30} = 1.15x10^{-4}\ ppm \approx 1x10^{-4} ppm$$

Other Additional Studies of Pertinent Information that Lend Support to this MRL: Systematic review concluded that respiratory effects are a presumed health effect following exposure to HCCPD based on inadequate evidence from human case series/reports and a high level of evidence from animal studies (Appendix C).

In humans exposed following an inadvertent release of HCCPD, clinical signs of respiratory tract irritation, including sinus congestion, dyspnea, and chest discomfort, were reported (Kominsky et al. 1980). Concentration reporting was insufficient in this study to allow for identification of effect levels with confidence. In animals, the respiratory tract is a consistent target of toxicity in rodents following acute-, intermediate-, and chronic-duration inhalation exposure (Clark 1981; Jackson and Hardy 1986, 1987; NTP 1994; OxyChem 1972; Treon et al. 1955). Findings show a dose- and duration-dependent increase in the incidence and severity of lesions throughout the upper and lower respiratory tract. Although differences in respiratory tract anatomy and physiology exist between humans and rodents, which are obligate nose-breathers (Stucki et al. 2024), inhalation exposures to HCCPD are expected to cause adverse effects in the human respiratory tract due to its reactive and irritant properties.

Agency Contacts (Chemical Managers): Gaston Casillas

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Hexachlorocyclopentadiene (HCCPD)
CAS Numbers: 77-47-4
Date: October 2026
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic
Provisional MRL: $6x10^{-5}$ ppm ($7x10^{-4}$ mg/m^3)
Critical Effect: Nasal suppurative inflammation
Reference: NTP 1994
Point of Departure: $BMCL_{10}$ of 0.052 ppm ($BMCL_{HEC}$ of 0.0019 ppm)
Uncertainty Factor: 30
LSE Graph Key: 31
Species: Mouse

MRL Summary: A provisional chronic-duration inhalation MRL of $6x10^{-5}$ ppm was derived for HCCPD based on increased nasal suppurative inflammation in female mice exposed to 0.2 ppm for 2 years (6 hours/day, 5 days/week); a NOAEL of 0.05 ppm was identified (NTP 1994). The provisional MRL is based on a 95% lower confidence limit on the benchmark concentration associated with 10% extra risk ($BMCL_{10}$) of 0.052 ppm. The $BMCL_{10}$ was adjusted for continuous duration exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.0019 ppm and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: No concentration-response data are available for humans. In laboratory animals, a comprehensive chronic-duration inhalation study is available in rats and mice exposed to concentrations up to 0.2 ppm for 2 years (NTP 1994). No adverse effects were detected in male or female rats with treatment. In mice, adverse respiratory effects at 0.2 ppm included suppurative inflammation of the nose in both sexes and suppurative inflammation and alveolar epithelial hyperplasia in the lungs of males only. Female mice also showed suppurative inflammation of the ovaries at ≥0.05 ppm and decreased survival, attributable to this lesion, at 0.2 ppm. NTP (1994) speculated that this lesion may have been a result of stress-induced deficits in immunity, similar to utero-ovarian infections observed in other chronic-duration NTP studies conducted around the same time period. Due to this, the potential relationship between exposure and ovarian lesions, and associated mortalities, is unclear, and ovarian effects were not further considered as candidate critical effects. Based on available data, respiratory effects were selected as the candidate critical effect for derivation of the provisional chronic-duration inhalation MRL.

Selection of the Principal Study: The 2-year study in mice conducted by NTP (1994) was selected as the principal study because it identified the lowest LOAEL for the critical effect (respiratory lesions).

Summary of the Principal Study:

NTP. 1994. Toxicology and carcinogenesis studies of hexachlorocyclopentadiene (CAS No. 77-47-4) in F344 rats and B6C3F1 mice (inhalation studies). National Toxicology Program. PB94214186. NTP TR 437. NIH 94-33168. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB94214186.xhtml. September 23, 2025.

Groups of B6C3F1 mice (50/sex/group) were exposed to HCCPD vapors at nominal concentrations of 0, 0.01, 0.05, or 0.2 ppm for 6 hours/day, 5 days/week for 2 year (103–104 weeks). Average analytical concentrations were 0, 0.01, 0.05, and 0.2 ppm HCCPD, respectively. Following exposure, clinical signs

were monitored and body weights were determined. Gross necropsy was performed and organs were weighed (brain, right kidney, liver, and lung). Histological examinations of major organs were performed for the following tissues in the controls, animals dying before study termination, and the highest exposure group: adrenal gland, bone and marrow, brain, epididymis, esophagus, gall bladder, heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph nodes (bronchial, mandibular, mediastinal, and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, prostate, salivary gland, seminal vesicle, small intestine (duodenum, jejunum, ileum), spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. The lungs, nose, and trachea were also evaluated in the 0.01 and 0.05 ppm exposure groups.

At the highest exposure test, 28/49 mortality was observed in female mice. Female survival rates at 0.01 or 0.05 ppm did not differ significantly from unexposed controls. No exposure-related changes in survival were observed in male mice. Mean body weights were comparable among exposed and control groups. Histopathological findings in the respiratory tract at 0.2 ppm included suppurative inflammation of the nose in both sexes and suppurative inflammation of the lungs and alveolar epithelium hyperplasia in males. A "pale, yellow-brown, granular" pigmentation of the nasal, tracheal, and lung mucosal epithelium was observed at ≥0.05 ppm. NTP (1994) postulated that lipid peroxidation reactions between HCCPD and endogenous substances may have generated the pigment. It should be noted that other respiratory lesions did not co-occur with the pigmentation, and it does not appear to be a clear precursor to more significant lesions (i.e., does not indicate an initial phase in the progression of a disease state). Therefore, pigmentation likely serves as a marker of exposure and is not considered an adverse effect for this assessment. Suppurative inflammation of the ovaries was observed at ≥0.05 ppm. The relationship of this finding to HCCPD exposure is questionable, as the study authors indicated that the lesions were similar to those observed in other chronic NTP studies attributable to stress-induced deficits in immunity to a utero-ovarian bacterial infection (*Klebsiella* species*)*. The study authors attributed early mortality in females at 0.2 ppm to observed ovarian inflammation/infection. There was no significant increase in tumors in the exposed animals, compared to the controls.

Selection of the Point of Departure: The $BMCL_{HEC}$ of 0.0018 ppm based on nasal suppurative inflammation in female mice was selected as it provided the lowest POD for the critical effect.

BMD modeling was performed on data shown in Table A-5 using BMD Desktop (25.1) and a BMR of 10% extra risk; adequate model fit was judged as described above for chronic-duration data. Data for suppurative inflammation of the lungs in male mice were not amenable to BMD modeling due to lack of a dose-response information at the lower concentrations (incidence was 0% in controls and two lowest concentration groups).

Table A-5. Respiratory Lesions in B6C3F1 Mice Selected for BMD Modeling Following Inhalation to Hexachlorocyclopentadiene for 2 Years (5 Days/Week, 6 Hours/Day)

		Concentration (ppm)			
Species, sex	Lesion name	0	0.01	0.05	0.2
Mouse, male	Alveolar epithelial hyperplasia	0/49	1/50	3/50	5/50[a]
Mouse, male	Nasal suppurative inflammation	0/50	0/50	1/50	36/50[a]
Mouse, female	Nasal suppurative inflammation	4/49	0/50	3/50	40/48[a]

[a]p≤0.05 compared with concurrent controls, based on logistic regression test performed by the study authors.

Source: NTP 1994

BMD modeling provided adequate model fits for all data sets. Details of the modeling results for the model predictions for alveolar epithelial hyperplasia in male mice are shown in Table A-6. All models provided an adequate statistical fit to the data. Among the fit models, BMCLs were sufficiently close (differed by <3-fold). While the model with the lowest AIC is the Hill model, this model is over-parameterized for the dataset (n=4 dose groups); therefore, the model with the next lowest AIC was selected (Log-Probit). BMC and BMCL values were 0.185 and 0.064 ppm, respectively. Details of the modeling results for the model predictions for nasal suppurative inflammation in male and female mice are shown in Tables A-7 and A-8, respectively. For males, all models provided an adequate statistical fit to the data except for the Multistage 1-degree and Quantal linear models. Among the fit models, BMCLs were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected (Multistage 3-degree). BMC and BMCL values were 0.087 and 0.061 ppm, respectively. For females, only the Multistage 3-degree model provided adequate fit to the data, calculating BMC and BMCL values of 0.078 and 0.052ppm, respectively.

Table A-6. Results from Benchmark Dose (BMD) Analysis for Alveolar Epithelium Hyperplasia in Male B6C3F1 Mice Following Inhalation to Hexachlorocyclopentadiene for 2 Years (5 Days/Week, 6 Hours/Day) (NTP 1994)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-value[b]	AIC	Scaled residual at control	Scaled residual near BMC
Dichotomous Hill	0.203	0.015	1	69.01	-0.001	0.008
Gamma[c]	0.171	0.091	0.472	70.718	-0.581	-0.48
Log-Logistic[d]	0.166	0.085	0.491	70.607	-0.538	-0.506
Multistage Degree 1[e]	0.171	0.091	0.472	70.718	-0.581	-0.48
Multistage Degree 2[e]	0.171	0.091	0.472	70.718	-0.581	-0.48
Multistage Degree 3[e]	0.171	0.091	0.472	70.718	-0.581	-0.48
Weibull[c]	0.171	0.091	0.472	70.718	-0.581	-0.48
Logistic	0.213	0.153	0.295	72.149	-1.005	-0.163
Log-Probit[f]	**0.185**	**0.064**	**0.973**	**69.062**	**-0.001**	**-0.081**
Probit	0.211	0.146	0.309	72.025	-0.981	-0.194
Quantal Linear	0.171	0.091	0.472	70.718	-0.581	-0.48

[a]BMC and BMCL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided an adequate statistical fit to the data. Among the fit models, BMCLs were sufficiently close (differed by <3-fold). While the model with the lowest AIC is the Hill model, this model is over-parameterized for the dataset (n=4 dose groups); therefore, the model with the next lowest AIC was selected (Log-Probit).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk)

Table A-7. Results from Benchmark Dose (BMD) Analysis for Nasal Suppurative Inflammation in Male B6C3F1 Mice Following Inhalation to Hexachlorocyclopentadiene for 2 Years (5 Days/Week, 6 Hours/Day) (NTP 1994)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-value[b]	AIC	Scaled residual at control	Scaled residual near BMC
Dichotomous Hill	0.058	0.051	0.999	75.099	-0.001	<0.001
Gamma[c]	0.08	0.059	1	73.101	-0.001	0.003
Log-Logistic[d]	0.081	0.058	0.998	73.107	-0.001	0.008
Multistage Degree 1[e]			0.001	94.314	-0.001	-1.459
Multistage Degree 2[e]	0.06	0.051	0.509	74.276	-0.001	-1.388
Multistage Degree 3[e,f]	**0.087**	**0.061**	**1**	**71.115**	**-0.001**	**0.015**
Weibull[c]	0.087	0.061	0.996	73.115	-0.001	0.017
Logistic	0.111	0.087	0.791	73.812	-0.336	0.441
Log-Probit	0.075	0.057	1	73.099	-0.001	<0.001
Probit	0.098	0.077	0.895	73.46	-0.227	0.276
Quantal Linear			0.001	94.314	-0.001	-1.459

[a]BMC and BMCL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided an adequate statistical fit to the data except for the Multistage 1-degree and Quantal linear models. Among the fit models, BMCLs were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected (Multistage 3-degree).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk)

Table A-8. Results from Benchmark Dose (BMD) Analysis for Nasal Suppurative Inflammation in Female B6C3F1 Mice Following Inhalation to Hexachlorocyclopentadiene for 2 Years (5 Days/Week, 6 Hours/Day) (NTP 1994)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-value[b]	AIC	Scaled residual at control	Scaled residual near BMC
Dichotomous Hill			NA	107.457	1.466	<0.001
Gamma[c]			0.039	105.458	1.465	0.002
Log-Logistic[d]			0.039	105.461	1.461	0.007
Multistage Degree 1[e]			<0.001	129.289	1.979	-2.114
Multistage Degree 2[e]			0.02	106.608	1.941	-1.38
Multistage Degree 3[e,f]	**0.078**	**0.052**	**0.109**	**103.505**	**1.543**	**-0.138**
Weibull[c]			0.04	105.469	1.453	0.021
Logistic			0.017	105.509	2.416	-0.728
Log-Probit			0.039	105.457	1.466	<0.001
Probit			0.007	106.68	2.655	-1.022
Quantal Linear			<0.001	129.289	1.979	-2.114

[a]BMC and BMCL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. Only the Multistage 3-degree model provided adequate fit to the data.

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); NA = saturated model, goodness-of-fit test could not be calculated

In order to accurately compare candidate PODs across different target tissues, effect levels (NOAEL, LOAEL, BMC, $BMCL_{10}$) were converted into HECs. Since animal exposure was 6 hours/day, 5 days/week, all values were adjusted for intermittent exposure (POD_{ADJ}) prior to HEC calculations using the following calculation:

$$BMCL_{ADJ} = BMCL_{10} \times \frac{6\ hours/day}{24\ hours} \times \frac{5\ days/week}{7\ days}$$

$BMCL_{ADJ}$ values were converted into $BMCL_{HEC}$ values via adjustment of the $BMCL_{ADJ}$ by an RGDR as follows:

$$BMCL_{HEC} = BMCL_{ADJ} \times RGDR$$

For nasal suppurative inflammation, $BMCL_{ADJ}$ values were converted to $BMCL_{HEC}$ values using guidance from EPA (1994) on dosimetric adjustments for respiratory effects using the $RGDR_{ET}$. This $RGDR_{ET}$ is calculated using the following equation as defined by EPA (1994):

$$RGDR_{ET} = \frac{V_{E\,a}}{SA_a} \div \frac{V_{E\,h}}{SA_h}$$

where:

$V_{E\,a}$ = ventilation rate for animals in a chronic study:
male B6C3F1 mice = 0.044 L/minute
female B6C3F1 mice = 0.041 L/minute

SA_a = surface area of the extrathoracic region in animals (EPA 1994)
mice = 3 cm^2 (EPA 1994)

$V_{E\,h}$ = ventilation rate for humans = 13.8 L/minute = 13,800 mL/minute (EPA 1994)

SA_h = surface area of the extrathoracic region in humans = 200 cm^2 (EPA 1994)

For each pulmonary (alveolar) endpoint, $BMCL_{ADJ}$ values were converted to $BMCL_{HEC}$ values using guidance from EPA (1994) on dosimetric adjustments for respiratory effects using the pulmonary RGDR ($RGDR_{PU}$). The $RGDR_{PU}$ is calculated using the following equation as defined by EPA (1994):

$$RGDR_{TB} = \frac{(Dose_{PU})_a}{(Dose_{PU})_h} = \frac{(\frac{Q_{alv}}{SA_{PU}})_a}{(\frac{Q_{alv}}{SA_{PU}})_h} \frac{(e^{\frac{-SA_{TB}}{V_E}})_a}{(e^{\frac{-SA_{TB}}{V_E}})_h} \frac{(e^{\frac{-SA_{ET}}{V_E}})_a}{(e^{\frac{-SA_{ET}}{V_E}})_h}$$

where:

$[V_E]_a$ = minute volume for animals
male B6C3F1 mice = 0.044 L/minute = 44 mL/minute

$[Q_{alv}]_a$ = alveolar ventilation rate for animals = 67% of V_E
male B6C3F1 mice = 0.137 L/minute = 29 mL/minute

$SA_{PU\,a}$ = PU surface area for mice = 500 cm^2 (EPA 1994)

$SA_{TB\,a}$ = TB surface area for mice = 3.5 cm^2 (EPA 1994)

$SA_{ET\,a}$ = ET surface area for mice = 3 cm^2 (EPA 1994)

$e^{-(SAET/Ve)_a}$ = fraction of chemical concentration penetrating the ET region and available for uptake in the TB region in animals
male B6C3F1 mice = 0.934

$e^{-(SATB/Ve)_a}$ = fraction of chemical concentration penetrating the TB region and available for uptake in the PU region in animals
male B6C3F1 mice = 0.923

$[V_E]_h$ = minute volume for humans = 13.8 L/minute = 13,800 mL/minute (EPA 1994)

$[Q_{alv}]_h$ = alveolar ventilation rate for humans = 67% of V_E = 9,246 mL/minute

$SA_{PU\,h}$ = PU surface area for humans = 540,000 cm^2 (EPA 1994)

$SA_{TB\,h}$ = TB surface area for humans = 3,200 cm^2 (EPA 1994)

$SA_{ET\,h}$ = ET surface area for humans = 200 cm^2 (EPA 1994)

$e^{-(SAET/Ve)_h}$ = fraction of chemical concentration penetrating the ET region and available for uptake in the TB region in humans = 0.986

$e^{-(SATB/Ve)_h}$ = fraction of chemical concentration penetrating the TB region and available for uptake in the PU region in humans = 0.793

The resulting $RGDR_{ET}$, $RGDR_{PU}$, and candidate POD_{HEC} values are presented in Table A-9.

Table A-9. Candidate POD_{HEC} Values for Treatment-Related Respiratory Lesions in Mice Administered Chronic-Duration Inhalation Exposures to Hexachlorocyclopentadiene (NTP 1994)

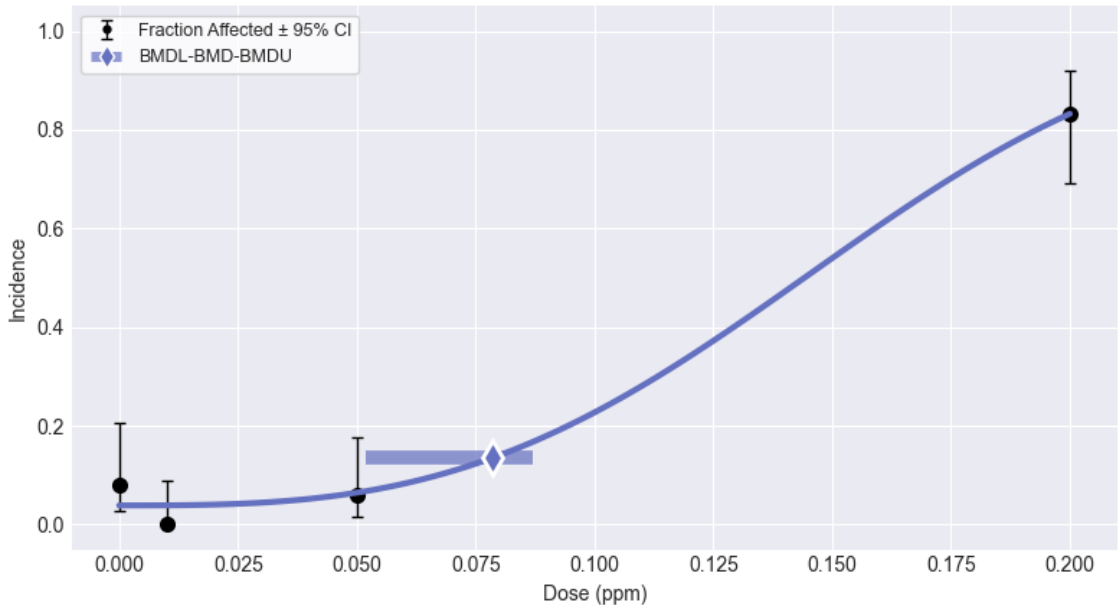
Species (sex), duration	Endpoint (POD type)	BMC_{10} or LOAEL (ppm)	$BMCL_{10}$ or NOAEL (ppm)	BMC_{ADJ} or $LOAEL_{ADJ}$ (ppm)	$BMCL_{ADJ}$ or $NOAEL_{ADJ}$ (ppm)	RGDR	BMC_{HEC} or $LOAEL_{HEC}$ (ppm)	$BMCL_{HEC}$ or $NOAEL_{HEC}$ (ppm)
Extrathoracic lesions								
B6C3F1 mouse (male), 2 years	Nasal suppurative inflammation (BMC/BMCL)	0.087	0.061	0.016	0.011	0.21	0.0034	0.0023
B6C3F1 mouse (female), 2 years	Nasal suppurative inflammation (BMC/BMCL)	0.078	0.052	0.014	0.0093	0.20	0.0028	0.0019
Pulmonary lesions								
B6C3F1 mouse (male), 2 years	Alveolar epithelial hyperplasia (BMC/BMCL)	0.185	0.064	0.0330	0.011	3.8	0.125	0.042
B6C3F1 mouse (male), 2 years	Suppurative inflammation of the lungs (NOAEL/ LOAEL)	0.2	0.05	0.04	0.009	3.8	0.2	0.03

ADJ = adjusted; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; RGDR = regional gas dose ratio

Selected endpoint (lowest POD_{HEC}).

To select the POD for the provisional chronic-duration inhalation MRL, the POD_{HEC} values for respiratory lesions in experimental animals were compared (Table A-9). Of these, the lowest was the BMC_{HEC} of 0.0028 ppm associated with an increased incidence for nasal suppurative inflammation in female B6C3F1 mice exposed to HCCPD for 2 years (NTP 1994). Based on this, the corresponding $BMCL_{HEC}$ of 0.0019 was selected as the POD for the provisional chronic-duration inhalation MRL. The fit of the selected BMD model is presented in Figure A-1.

Figure A-1. Fit of the Multistage 3 Model to Data for Nasal Suppurative Inflammation in Female B6C3F1 Female Mice Following Inhalation to Hexachlorocyclopentadiene for 2 Years (5 Days/Week, 6 Hours/Day) (NTP 1994)



Adjustment for Intermittent Exposure and Human Equivalent Concentration: As shown above, the $BMCL_{10}$ of 0.052 ppm was adjusted for continuous exposure and converted into a $BMCL_{ADJ}$ of 0.0093 ppm and a $BMCL_{HEC}$ of 0.0019 ppm.

$$BMCL_{ADJ} = \text{BMCL}_{10} \times \frac{\text{hours/day}}{24\ hours} \times \frac{days/week}{7\ days}$$

$$= 0.052\ ppm \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.0093\ ppm$$

$$BMCL_{HEC} = BMCL_{ADJ} \times RGDR_{ET} = 0.0093\ ppm \times 0.20 = 0.0019\ ppm$$

Uncertainty Factor: The following uncertainty factors were applied to the $BMCL_{HEC}$ to derive the provisional MRL.

- Uncertainty factor of 3 for extrapolation from animals to humans with dosimetric adjustments
- Uncertainty factor of 10 for human variability.

Subsequently, the provisional MRL for intermediate-duration exposure to HCCPD via inhalation is:

$$Provisional\ MRL = \frac{BMCL_{HEC}}{(UF)} = \frac{0.0019\ ppm}{30} = 6.3x10^{-5}\ ppm \approx 6x10^{-5}\ ppm$$

Other Additional Studies of Pertinent Information that Lend Support to this MRL: Systematic review concluded that respiratory effects are a presumed health effect following exposure to HCCPD based on

inadequate evidence from human case series/reports and a high level of evidence from animal studies (Appendix C).

In humans exposed following an inadvertent release of HCCPD, clinical signs of respiratory tract irritation, including sinus congestion, dyspnea, and chest discomfort, were reported (Kominsky et al. 1980). Concentration reporting was insufficient in this study to allow for identification of effect levels with confidence. In animals, the respiratory tract is a consistent target of toxicity in rodents following acute-, intermediate-, and chronic-duration inhalation exposure (Clark 1981; OxyChem 1972; Jackson and Hardy 1986, 1987; NTP 1994; Treon et al. 1955). Findings show a dose- and duration-dependent increase in the incidence and severity of lesions throughout the upper and lower respiratory tract. Although differences in respiratory tract anatomy and physiology exist between humans and rodents, which are obligate nose-breathers (Stucki et al. 2024), inhalation exposures to HCCPD are expected to cause adverse effects in the human respiratory tract due to its reactive and irritant properties.

Agency Contacts (Chemical Managers): Gaston Casillas

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Hexachlorocyclopentadiene (HCCPD)
CAS Numbers: 77-47-4
Date: October 2026
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of a provisional acute-duration oral MRL for HCCPD. No adequate human exposure studies for this duration were identified, and the lowest identified acute-duration LOAEL in animal oral studies is associated with increased mortality.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Available animal data following acute-duration oral exposure are limited and are primarily restricted to acute lethality and developmental toxicity studies. No adverse effects were noted at doses below those associated with mortality in available acute-duration studies evaluating HCCPD. The lowest identified acute-duration oral adverse effect level is a serious LOAEL of 75 mg/kg/day based on increased maternal mortality and developmental effects (increased incidence of 13 ribs) in a gestational exposure study in rabbits (Murray et al. 1980). Increased mortality was also observed at the lowest identified adverse effect levels for mice (250 mg/kg/day; Murray et al. 1980) and rats (505 mg/kg/day; Treon et al. 1955). Due to the observation of significant mortality at the lowest identified LOAELs for all evaluated species, a provisional acute-duration oral MRL cannot be derived for HCCPD.

Agency Contacts (Chemical Managers): Gaston Casillas

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Hexachlorocyclopentadiene (HCCPD)
CAS Numbers: 77-47-4
Date: October 2026
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
Provisional MRL: 0.06 mg/kg/day
Critical Effect: Combined incidence of forestomach epithelial hyperplasia and focal inflammation
Reference: Abdo et al. 1984; Velsicol 1981b
Point of Departure: $BMDL_{10}$ of 7.7 mg/kg/day ($BMDL_{ADJ}$ of 5.5 mg/kg/day)
Uncertainty Factor: 100
LSE Graph Key: 12
Species: Rat

MRL Summary: A provisional intermediate-duration oral MRL of 0.06 mg/kg/day was derived for HCCPD based on increased forestomach epithelial hyperplasia and focal inflammation in female rats following exposure to HCCPD for 13 weeks (5 days/week) (Abdo et al. 1984; Velsicol 1981b); the NOAEL and LOAEL values were 19 and 38 mg/kg/day, respectively. The provisional MRL is based on a 95% lower confidence limit on the BMD associated with 10% extra risk ($BMDL_{10}$) of 7.7 mg/kg/day, which was adjusted for continuous exposure ($BMDL_{ADJ}$ of 5.5 mg/kg/day), and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: No dose-response data are available for humans. One intermediate-duration oral study evaluating a comprehensive set of endpoints in rats and mice is available (Abdo et al. 1984; Velsicol 1981a, 1981b). The most sensitive effects observed in these studies are summarized in Table A-10. The lowest LOAEL identified in rats in this study was 38 mg/kg/day based on increased incidences of forestomach lesions in both sexes (epithelial hyperplasia and focal inflammation), renal lesions in both sexes (toxic nephrosis), and a 13% decrease in terminal body weight in males. In mice, the lowest LOAEL identified was 75 mg/kg/day based on forestomach lesions in both sexes and renal lesions in females. Therefore, rats appear to be more sensitive than mice in the available intermediate-duration oral study (Abdo et al. 1984; Velsicol 1981a, 1981b). While humans lack a forestomach, oral exposures in humans are expected to result in effects at the regions of the gastrointestinal tract where HCCPD comes into contact with tissues. Available data indicate that HCCPD is a reactive chemical that can produce irritation and other adverse effects at portals of entry (see Section 2.21). Thus, as the most sensitive endpoint in available studies, the forestomach lesions are considered suitable endpoints to derive the provisional intermediate-duration oral MRL in order to be protective of human health.

Table A-10. Select NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to Hexachlorocyclopentadiene via Gavage

Species (strain)	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Gastrointestinal effects					
Rat (F344)	13 weeks, 5 days/week	19	38	Increased forestomach epithelial hyperplasia and focal inflammation	Abdo et al. 1984; Velsicol 1981b

Table A-10. Select NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to Hexachlorocyclopentadiene via Gavage

Species (strain)	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Mouse (B6C3F1)	13 weeks, 5 days/week	38	75	Increased forestomach epithelial hyperplasia and focal inflammation	Abdo et al. 1984; Velsicol 1981a
Renal effects					
Rat (F344)	13 weeks, 5 days/week	19	38	Increased toxic nephrosis	Abdo et al. 1984; Velsicol 1981b
Mouse (B6C3F1) (female)	13 weeks, 5 days/week	38	75	Increased toxic nephrosis	Abdo et al. 1984; Velsicol 1981a
Mouse (B6C3F1) (male)	13 weeks, 5 days/week	150	300	Increased acute tubular necrosis	
Body weight effects					
Rat (F344) (male)	13 weeks, 5 days/week	19	38	13% decreased terminal body weight	Abdo et al. 1984; Velsicol 1981b
Rat (F344) (female)	13 weeks, 5 days/week	38	75	15% decreased terminal body weight	
Mouse (B6C3F1)	13 weeks, 5 days/week	75	150	11% decreased terminal body weight in males, 13% decreased terminal body weight in females	Abdo et al. 1984; Velsicol 1981a

Green shading indicates that the study selected for derivation of the provisional intermediate-duration oral MRL.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

In order to compare the relative sensitivity of candidate critical effects in rats, BMD modeling was conducted on datasets that were amenable to modeling. Datasets selected for modeling are shown in Table A-11, including the incidence of combined forestomach lesions (forestomach epithelial hyperplasia and focal inflammation) in male and female rats and body weight in male rats. Regarding the kidney lesions, data in rats were not amenable to modeling because incidence went from 0% at the NOAEL dose to 100% at the LOAEL dose.

Table A-11. Endpoints Selected for BMD Modeling in F344 Rats Exposed to Hexachlorocyclopentadiene via Gavage for 13 Weeks (5 days/week)

		Dose (mg/kg/day)					
Sex	Endpoint	0	10	19	38	75	150
Male	Combined forestomach lesions	0/10	0/10	0/10	5/10 [a]	9/10 [a]	8/9[a]
Female	Combined forestomach lesions	0/10	0/10	2/10	5/10[a]	9/10[a]	9/10[a]
Male	Terminal body weight (g)[b]	386.4±13.8 (7)	370.4±19.2 (-4%) (9)	358.0±26.1[c] (-7%) (9)	334.6±12.9[c] (-13%) (9)	268.7±13.8[c] (-30%) (7)	250.3±22.2[c] (-35%) (3)

[a]p≤0.05 compared with concurrent controls, based on a two-tailed Fisher's exact test performed for this review (GraphPad).
[b]Mean±standard deviation (% change from control) (N). Standard deviation was calculated from reported standard error using the following equation: standard deviation = standard error × √N.
[c]p≤0.05 compared with concurrent controls, based on a two-tailed Student's t-test performed for this review (GraphPad). Note: Body weight changes are considered biologically significant when findings are both statistically significant and decreased ≥10%, compared to control.

Sources: Abdo et al. 1984 (all data); Velsicol 1981b (forestomach lesions)

BMD modeling was performed with BMD Desktop (25.1), a BMR of 10% extra risk for forestomach lesions, and a BMR of 10% relative deviation for body weight effects. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a BMDL that is not 10 times lower than the lowest non-zero dose, and a scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL was selected as the POD when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen.

Results of BMD modeling for combined forestomach lesions are presented in Tables A-12 and A-13 for male and female rats, respectively. For combined forestomach lesions in male rats, while several models had sufficient statistical fit, inspection of the recommended and alternate models showed poor visual fit, particularly in the low-exposure region of the curves. Based on visual fit, only the Dichotomous Hill model provided adequate fit to the data. For combined forestomach lesions in female rats, all models provided adequate fit except the Logistic and Probit models. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Log-Logistic). Selected BMD and BMDL values for forestomach lesions were 15–32 and 7.8–19 mg/kg/day, with lower values observed in females. Results of BMD modeling for terminal body weights in male rats are shown in Table A-14. The only model that provided adequate fit was the Exponential 5 model, with a BMD of 31 mg/kg/day and a BMDL of 23 mg/kg/day.

Table A-12. Results from Benchmark Dose (BMD) Analysis of Combined Forestomach Lesions in Male F344 Rats Following Oral Exposure to Hexachlorocyclopentadiene via Gavage for 13 Weeks (5 Days/Week) (Abdo et al. 1984; Velsicol 1981b)

Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-value[b]	AIC	Scaled residual at control	Scaled residual near BMD
Dichotomous Hill[c]	**31.791**	**18.737**	**1**	**32.653**	**-0**	**0.002**
Gamma[d]			0.095	37.606	-0	-1.067
Log-Logistic[e]			0.315	34.806	-0	-0.897
Multistage Degree 1[f]			0.194	40.333	-0	-1.277
Multistage Degree 2[f]			0.036	40.561	-0	-1.244
Multistage Degree 3[f]			0.036	40.561	-0	-1.244
Multistage Degree 4[f]			0.036	40.561	-0	-1.244
Multistage Degree 5[f]			0.036	40.561	-0	-1.244
Weibull[d]			0.114	39.153	-0	-1.28
Logistic			<0.001	43.582	-0.68	-1.172
Log-Probit			0.298	35.213	-0	-0.915
Probit			<0.001	45.498	-0.737	-1.231
Quantal Linear			0.194	40.333	-0	-1.277

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Selected model. Of the models showing adequate statistical fit (Dichotomous Hill, Log-Logistic, Multistage (1-degree), Weibull, Log-Probit, Quantal Linear), only the Dichotomous Hill model provided adequate visual fit. Therefore, the Dichotomous Hill model was selected.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk)

Table A-13. Results from Benchmark Dose (BMD) Analysis of Combined Forestomach Lesions in Female F344 Rats Following Oral Exposure to Hexachlorocyclopentadiene via Gavage for 13 Weeks (5 Days/Week) (Abdo et al. 1984; Velsicol 1981b)

Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-value[b]	AIC	Scaled residual at control	Scaled residual near BMD
Dichotomous Hill	16.778	9.102	0.836	43.93	-0	0.544
Gamma[c]	12.406	4.956	0.425	44.805	-0	-0.878
Log-Logistic[d,e]	**14.738**	**7.721**	**0.764**	**42.921**	**-0**	**0.281**
Multistage Degree 1[f]	6.103	4.277	0.575	44.611	-0	-1.373
Multistage Degree 2[f]	7.476	4.354	0.402	46.338	-0	-1.236
Multistage Degree 3[f]	7.476	4.354	0.402	46.338	-0	-1.236
Multistage Degree 4[f]	7.476	4.354	0.402	46.338	-0	-1.236
Multistage Degree 5[f]	7.476	4.354	0.402	46.338	-0	-1.236
Weibull[c]	10.228	4.659	0.424	45.438	-0	-1.038
Logistic			0.002	50.588	-0.914	0.193
Log-Probit	14.61	7.949	0.725	43.081	-0	0.212
Probit			0.01	52.198	-0.981	0.114
Quantal Linear	6.103	4.277	0.575	44.611	-0	-1.373

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. All models provided adequate fit except the Logistic and Probit models. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Log-Logistic).
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk)

Table A-14. Results from Benchmark Dose (BMD) Analysis (Constant Variance) of Terminal Body Weights in Male F344 Rats Following Oral Exposure to Hexachlorocyclopentadiene via Gavage for 13 Weeks (5 Days/Week) (Abdo et al. 1984)

Model	BMD_{RD10}[a] (ppm)	$BMDL_{RD10}$[a] (ppm)	p-value[b]	AIC	Scaled residual at control	Scaled residual near BMD
Exponential 3[c]			0.002	398.194	0.469	0.267
Exponential 5[c,d]	**31.114**	**22.643**	**0.182**	**388.567**	**0.956**	**0.936**
Hill[c]			0.067	390.569	1.122	1.111
Polynomial 2[c]			<0.001	407.559	1.594	-0.291
Power[c]			<0.001	424.52	2.098	-0.848
Linear			<0.001	405.778	1.104	-0.243

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Restricted model.
[d]Selected model. The Exponential 5 is the only model that provided adequate fit to the data.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMDL_{RD10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., RD10 = dose associated with 10% relative deviation)

To select the critical effect, the candidate POD values for gastrointestinal, renal, and body weight effects in rats were compared to determine the most sensitive effect (Table A-15). Comparing available BMD values (and LOAEL values for data that were not amenable to BMD modeling) indicates that gastrointestinal effects in female rats are the most sensitive effects following oral exposure to HCCPD based on the BMD of 15 mg/kg/day. Therefore, gastrointestinal effects are selected as the critical effects for the provisional intermediate-duration oral MRL.

Table A-15. Summary of Candidate Critical Effects and POD Values in F344 Rats Exposed to Hexachlorocyclopentadiene via Gavage 13 Weeks (5 Days/Week) (Abdo et al. 1984; Velsicol 1981b)

Sex	Effect	LOAEL (mg/kg/day)	NOAEL (mg/kg/day)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Male	Combined forestomach lesions[a]	38	19	32	19
	Toxic nephrosis	38	19	ND	ND
	Decreased terminal body weight	38	19	31	23
Female	Combined forestomach lesions[a]	38	19	15	7.7
	Toxic nephrosis	38	19	ND	ND

[a]Reflects the combined incidences of forestomach epithelial hyperplasia and focal inflammation.

Selected POD for derivation of provisional intermediate-duration oral MRL.

BMD = maximum likelihood estimate of the dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure

Selection of the Principal Study: The 13-week oral study in rats (Abdo et al. 1984; Velsicol 1981b) is selected as the principal study because it provides the lowest POD for the selected critical effect (gastrointestinal).

Summary of the Principal Study:

Abdo KM, Montgomery CA, Kluwe WM, et al. 1984. Toxicity of hexachlorocyclopentadiene: subchronic (13-week) administration by gavage to F344 rats and B6C3F1 mice. J Appl Toxicol 4(2):75-81. https://doi.org/10.1002/jat.2550040204.

Velsicol. 1981b. Subchronic toxicity report on hexachlorocyclopentadiene (C53607) in Fischer-344 rats. Velsicol Chemical Corporation. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4, 29-62. OTS0507497. 408349130. 42022FI2. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0507497.xhtml. September 23, 2025.

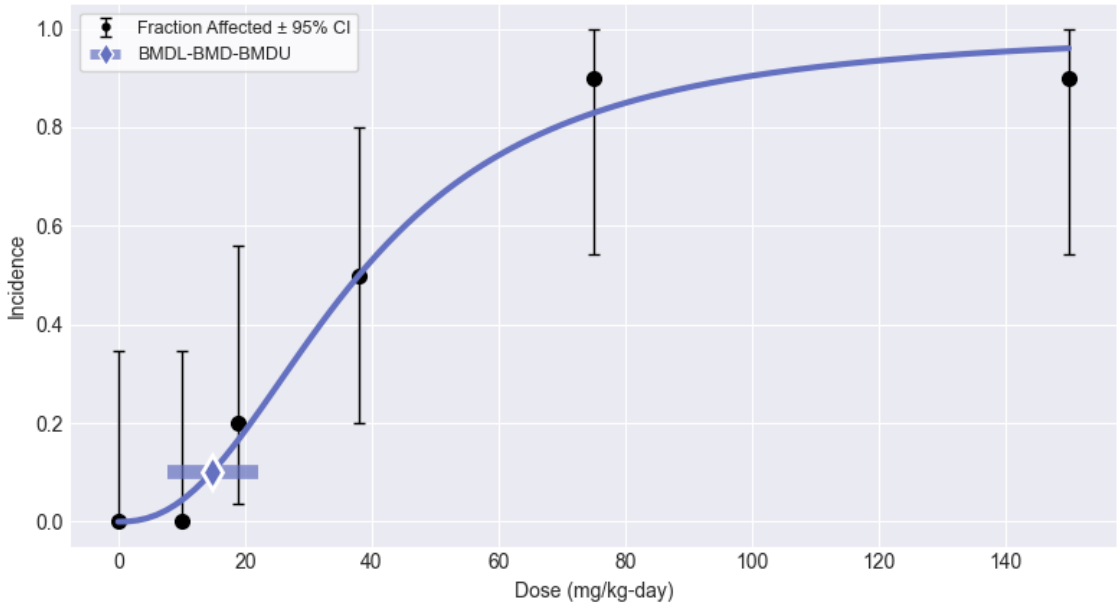
Male and female F344 rats (10/sex/group) were administered HCCPD at doses of 0, 10, 19, 38, 75, or 150 mg/kg/day via gavage in corn oil 5 days/week for 13 weeks. Body weights were determined prior to study initiation and weekly during the treatment period. Clinical signs and mortality were monitored daily. Animals were sacrificed within a week of the final treatment. At death or scheduled sacrifice, gross necropsy was performed, and organ weights (liver, right kidney, thymus, heart, brain, and lungs) were determined. Histopathological examination was performed on the following organs or tissues collected at scheduled sacrifice from the control, 75, and 150 mg/kg/day dose groups as well as tissues collected at unscheduled deaths from any dose group: liver, lungs and bronchi, larynx, trachea, heart, brain, spinal cord, thymus, thyroid, parathyroid, esophagus, duodenum, jejunum, ileum, colon, mesenteric nodes, pancreas, spleen, adrenal, urinary bladder, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), seminal vesicle, prostate, testes, ovaries, uterus, nasal cavity, and pituitary. In addition, histopathological examinations were performed on the stomachs and kidneys of all dose groups at scheduled sacrifice.

Treatment-related deaths included one male at 75 mg/kg/day and six males at 150 mg/kg/day; additional details were not provided. Numerous additional deaths occurred during the study and were attributed to gavage error by the study authors. Gavage deaths in males included three rats each at 0 and 75 mg/kg/day and one rat each at 10, 19, 38, and 150 mg/kg/day. In females, gavage deaths included one rat each at 0 and 38 mg/kg/day; two rats each at 10 and 38 mg/kg/day; and three and five rats at 75 and 150 mg/kg/day, respectively. Gavage errors occurred throughout the experiment (weeks 1–12). Clinical signs qualitatively reported included ruffled fur and slight inactivity at ≥75 mg/kg/day. Significantly decreased body weight gains were observed in males at ≥38 mg/kg/day and females at ≥75 mg/kg/day, resulting in terminal body weight decreases ≥10%. Males showed serious body weight decreases of 30–35%, compared to control, at ≥75 mg/kg/day. Absolute and relative (to brain weight) organ weights were not significantly altered in male rats exposed to HCCPD, compared to control. In female rats, relative (to brain weight) liver and kidney weights were increased at ≥38 and ≥75 mg/kg/day, respectively; no significant changes in absolute organ weights were observed. Treatment-related histopathological changes were limited to the forestomach and kidney. Combined forestomach lesions (epithelial hyperplasia and focal inflammation) showed statistically significant, dose-related increases in incidence in males and females at ≥38 mg/kg/day, based on statistics performed for this review (2-tailed Fisher's Exact Test, GraphPad). The study authors noted that lesion incidence increased in severity with increasing dose; however, quantitative lesion severity scores were not reported. Toxic nephrosis was observed in 100% of males and females at 38 mg/kg/day; lesion incidence was 80–90% in males and 100% in females at ≥75 mg/kg/day. This lesion was largely limited to the terminal section of the proximal tubule of the inner cortex. Toxic nephrosis was not observed in rats at ≤19 mg/kg/day.

Selection of the Point of Departure for the MRL: The $BMDL_{10}$ of 7.7 mg/kg/day for combined forestomach lesions in female rats was selected as the POD for derivation of the provisional intermediate-duration oral MRL.

As shown in Table A-15, BMD modeling of combined forestomach lesions in male and female rats resulted in BMD_{10} values of 32 and 15 mg/kg/day, respectively. Since the female rat BMD value was lower, the corresponding $BMDL_{10}$ of 7.7 mg/kg/day was selected as the POD. The fit of the selected BMD model is presented in Figure A-2.

Figure A-2. Fit of the Log-Logistic Model to Data for Combined Forestomach Lesions in Female F344 Rats Following Oral Exposure to HCCPD via Gavage for 13 Weeks (5 Days/Week) (Abdo et al. 1984; Velsicol 1981b)



Calculations

Adjustment for Intermittent Exposure: Female rats in the principal study were administered HCCPD via gavage 5 days/week (Abdo et al. 1984; Velsicol 1981b). Therefore, the $BMDL_{10}$ of 7.7 mg/kg/day was adjusted for a daily exposure scenario:

$$BMDL_{ADJ} = BMDL_{10} \times \frac{days\ exposed}{7\ days} = 7.7\ mg/kg/day \times \frac{5\ days}{7\ days} = 5.5\ mg/kg/day$$

Human Equivalent Concentration: Not applicable

Uncertainty Factors: The following uncertainty factors were applied to the $BMDL_{ADJ}$ to derive the provisional MRL.

- Uncertainty factor of 10 for extrapolation from animals to humans
- Uncertainty factor of 10 for human variability.

Subsequently, the provisional oral MRL for intermediate-duration exposure to HCCPD is:

$$Provisional\ MRL = \frac{BMDL_{ADJ}}{(UF)} = \frac{5.5\ mg/kg/day}{100} = 0.055\ mg/kg\ /day\ \approx\ 0.06\ mg/kg/day\ (rounded)$$

Other Additional Studies of Pertinent Information that Lend Support to this MRL: Systematic review concluded that gastrointestinal effects are a presumed health effect following exposure to HCCPD based on inadequate evidence from humans and a high level of evidence from animal studies (Appendix C).

No additional intermediate-duration oral studies in animals are available; however, limited qualitative data from acute-duration oral studies support that HCCPD is irritative to the gastrointestinal tract. Acute necrosis lesions were qualitatively described in rats at ≥280 mg/kg (Treon et al. 1955) and diarrhea was observed in rats and mice at ≥464 and 1,260 mg/kg, respectively (Dean 1977; Gardner 1986a).

Agency Contacts (Chemical Managers): Gaston Casillas

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Hexachlorocyclopentadiene (HCCPD)
CAS Numbers: 77-47-4
Date: October 2026
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a provisional chronic-duration oral MRL for HCCPD due to the lack of studies evaluating oral toxicity following chronic-duration exposure.

Rationale for Not Deriving an MRL: No exposure-dose-response data are available for humans. No chronic-duration oral data were located for experimental animals. Available data are insufficient to determine if the provisional intermediate-duration oral MRL would be protective of chronic-duration oral exposure scenarios.

Agency Contacts (Chemical Managers): Gaston Casillas

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR HCCPD

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to HCCPD.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for HCCPD. ATSDR primarily focused on peer-reviewed articles without language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of HCCPD have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of HCCPD are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen[a]

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects

Table B-1. Inclusion Criteria for the Literature Search and Screen[a]

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

[a]Physical-chemical properties are not generally obtained from literature searches, but rather from curated governmental databases such as PubChem.

B.1.1 Literature Search

The current literature search was intended to update the 1999 Toxicological Profile for HCCPD; thus, the literature search was restricted to studies published between January 1996 and November 2024. The following main databases were searched in November 2024:

- PubMed
- Embase
- SciFinder
- Scopus

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for HCCPD. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to HCCPD were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
11/2024	(77-47-4[rn] OR "hexachlorocyclopentadiene"[nm] OR "1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene"[tw] OR "1,2,3,4,5,5-Hexachlorocyclopenta-1,3-diene"[tw] OR "1,2,3,4,5,5-Hexachlorocyclopentadiene"[tw] OR "Graphlox"[tw] OR "HCCPD"[tw] OR "Hexachlorcyclopentadien"[tw] OR "Hexachlorcyklopentadien"[tw] OR "Hexachloro-1,3-cyclopentadiene"[tw] OR "Hexachlorocyclo-pentadiene"[tw] OR "Hexachlorocyclopentadiene"[tw] OR "Hexachloromyclopentadiene"[tw] OR "Hexachloropentadiene"[tw] OR "hexaclorociclopentadieno"[tw] OR "HRS 1655"[tw] OR "Perchloro-1,3-cyclopentadiene"[tw] OR "Perchlorocyclopentadiene"[tw] OR "1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro-"[tw] OR "1,3-Cyclopentadiene, hexachloro-"[tw] OR "1,3-Cyclopentadiene,1,2,3,4,5,5-hexachloro-"[tw] OR "CYCLOPENTADIENE, HEXACHLORO-"[tw]) AND (1996:3000[edat] OR 1996:3000[crdt] OR 1996:3000[mhda] OR 1996:3000[dp])
Embase	
12/2024	Limit to Publication Year = "1996 -Current" and Records from = Embase Hexachlorocyclopentadiene/ or 179601-23-1.rn. or (1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene or 1,2,3,4,5,5-Hexachlorocyclopenta-1,3-diene or 1,2,3,4,5,5-Hexachlorocyclopentadiene or Graphlox or HCCPD or Hexachlorcyclopentadien or Hexachlorcyklopentadien or Hexachloro-1,3-cyclopentadiene or Hexachlorocyclo-pentadiene or Hexachlorocyclopentadiene or Hexachloromyclopentadiene or Hexachloropentadiene or hexaclorociclopentadieno or HRS 1655 or Perchloro-1,3-cyclopentadiene or Perchlorocyclopentadiene or 1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro- or 1,3-Cyclopentadiene, hexachloro- or 1,3-Cyclopentadiene,1,2,3,4,5,5-hexachloro- or CYCLOPENTADIENE, HEXACHLORO-).ti,ab,kf.
SciFinder	
12/2024	Advanced Search: Substance: CAS Registry Number: 77-47-4 Publication Year: 1996 to No Maximum Filtered By: Document Type: Journal, Review, Conference, Letter, Report Substance Role: Biological Study, Adverse Effect, Pharmacokinetics

Table B-2. Database Query Strings

Database search date	Query string
	CA Section: Toxicology, Air Pollution and Industrial Hygiene, Water, Waste Treatment and Disposal Database: CAplus
Scopus	
12/2024	(((TITLE-ABS-KEY ({1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene} OR {1,2,3,4,5,5-Hexachlorocyclopenta-1,3-diene} OR {1,2,3,4,5,5-Hexachlorocyclopentadiene} OR {Graphlox} OR {HCCPD} OR {Hexachlorcyclopentadien} OR {Hexachlorcyklopentadien} OR {Hexachloro-1,3-cyclopentadiene} OR {Hexachlorocyclo-pentadiene} OR {Hexachlorocyclopentadiene} OR {Hexachloromyclopentadiene} OR {Hexachloropentadiene} OR {hexaclorociclopentadieno} OR {HRS 1655} OR {Perchloro-1,3-cyclopentadiene} OR {Perchlorocyclopentadiene} OR {1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro-} OR {1,3-Cyclopentadiene, hexachloro-} OR {1,3-Cyclopentadiene,1,2,3,4,5,5-hexachloro-} OR {CYCLOPENTADIENE, HEXACHLORO-})) AND (TITLE-ABS-KEY ("death" OR "lethal" OR "fatal" OR "fatality" OR "necrosis" OR lc50* OR "lc 50" OR ld50* OR "ld 50" OR "overweight" OR "obesity" OR "weight loss" OR "weight gain" OR "weight change" OR "weight changes" OR "poisoning" OR "morbidity" OR "inflammation" OR "inflammatory response" OR "irritation" OR "irritant" OR "sensitization" OR "sensitizer" OR "asthma" OR "bronchitis" OR "heart failure" OR "heart attack" OR "myocardial infarction" OR "chest pain" OR "circulatory function" OR "circulatory effect" OR "circulatory effects" OR "circulatory toxicity" OR cardiotox* OR "digestive function" OR "digestive effect" OR "digestive effects" OR "gi disorder" OR "diarrhea" OR "nausea" OR vomit* OR ulcer* OR "constipation" OR "emesis" OR "anorexia" OR "cyanosis" OR "cyanotic" OR "erythrocytopenia" OR "leukopenia" OR "thrombocytopenia" OR "hematocrit" OR "arthritis" OR "altered bone" OR "joint pain" OR "limb pain" OR "cirrhosis" OR "jaundice" OR "liver toxicity" OR "liver lesions" OR "liver weight" OR "liver weights" OR "hepatocellular degeneration" OR "hepatocellular hypertrophy" OR "hepatomegaly" OR hepatotox* OR "renal toxicity" OR "kidney weights" OR "blood urea nitrogen" OR "bun" OR nephropath* OR nephrotox* OR "skin rash" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin effects" OR "acanthosis" OR "dermatitis" OR "psoriasis" OR "eczema" OR "edema" OR "acne" OR "eye function" OR "eye effects" OR "eye effect" OR "eye irritation" OR "blurred vision" OR "blindness" OR "myopia" OR "cataracts" OR ototoxic* OR "hormone changes" OR "hormone excess" OR "hormone deficiency" OR "hormone secretion" OR "hormone toxicity" OR "hormone levels" OR "infertility" OR "sella turcica" OR immunotox* OR "neurotoxic" OR "neurotoxicity" OR "neuropathy" OR neurodegenerat* OR "neurodevelopment" OR "neurotoxicant" OR "neuropathology" OR "motor changes" OR "tremor" OR "tremors" OR "behavior changes" OR "sensory changes" OR "vertigo" OR "drowsiness" OR "headache" OR "ataxia" OR "endocrine disruption" OR "reproduction function" OR "reproduction effect" OR "reproduction toxicity" OR "maternal toxicity" OR placenta* OR terata* OR terato* OR embryo* OR fetus* OR foetus* OR fetal* OR foetal* OR neonat* OR newborn* OR zygote* OR "child" OR "children" OR infant* OR "offspring" OR "elderly" OR weanling* OR "altered food consumption" OR "altered water consumption" OR "metabolic effect" OR "metabolic toxicity" OR "fever" OR "histopathology" OR cytotox* OR "cancer" OR "cancerous" OR neoplas* OR tumor* OR tumour* OR malignan* OR carcinoma* OR "carcinogen" OR carcinogen* OR angiosarcoma* OR blastoma* OR fibrosarcoma* OR glioma* OR leukemia* OR leukaemia* OR lymphoma* OR melanoma* OR meningioma* OR mesothelioma* OR myeloma* OR neuroblastoma* OR osteosarcoma* OR sarcoma* OR "mutation" OR "mutations" OR "genotoxicity" OR "genotoxic" OR "micronuclei" OR "micronucleus"

Table B-2. Database Query Strings

Database search date	Query string
	OR "chromosome aberrations" OR "mutagenicity" OR "mutagenic" OR "gene expression" OR "adverse effect" OR "adverse effects" OR "health effects" OR "noncancer" OR "nhanes" OR "nutrition examination survey"))) OR ((TITLE-ABS-KEY ({1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene} OR {1,2,3,4,5,5-Hexachlorocyclopenta-1,3-diene} OR {1,2,3,4,5,5-Hexachlorocyclopentadiene} OR {Graphlox} OR {HCCPD} OR {Hexachlorcyclopentadien} OR {Hexachlorcyklopentadien} OR {Hexachloro-1,3-cyclopentadiene} OR {Hexachlorocyclo-pentadiene} OR {Hexachlorocyclopentadiene} OR {Hexachloromyclopentadiene} OR {Hexachloropentadiene} OR {hexaclorociclopentadieno} OR {HRS 1655} OR {Perchloro-1,3-cyclopentadiene} OR {Perchlorocyclopentadiene} OR {1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro-} OR {1,3-Cyclopentadiene, hexachloro-} OR {1,3-Cyclopentadiene,1,2,3,4,5,5-hexachloro-} OR {CYCLOPENTADIENE, HEXACHLORO-})) AND (TITLE-ABS-KEY ("body weight" OR "body mass index" OR "respiratory" OR "pulmonary" OR "airway" OR "trachea" OR "tracheobronchial" OR "lung" OR "lungs" OR "nose" OR "nasal" OR "nasopharyngeal" OR "larynx" OR "laryngeal" OR "pharynx" OR "bronchial" OR "bronchi" OR "bronchioles" OR "hemothorax" OR "alveolar" OR "alveoli" OR "cilia" OR "mucocilliary" OR "cardio" OR "heart muscle" OR "heart rate" OR "heartbeat" OR "circulatory system" OR "vascular" OR "cardiovascular" OR "cardiac" OR "coronary" OR "artery" OR "arteries" OR "veins" OR "venules" OR "gastro intestinal" OR "gastrointestinal" OR "digestive system" OR "digestive organs" OR "intestinal" OR intestine* OR "gi tract" OR "abdominal" OR esophag* OR "stomach" OR "pancreas" OR "pancreatic" OR "gut microbes" OR "gut flora" OR "gut microflora" OR "hematological" OR "hematology" OR "hemato" OR "haemato" OR "blood" OR "anemia" OR "anaemia" OR "hemoglobin" OR erythrocyte* OR "bone marrow" OR reticulocyte* OR "methemoglobin" OR "red blood cell" OR "musculoskeletal" OR "skeletal" OR "muscle" OR "muscular" OR "hepatic" OR "liver" OR "hepatocytes" OR "gallbladder" OR "renal" OR kidney* OR "urinary" OR "bladder" OR "urine" OR "dermal" OR "ocular" OR "retinal" OR "auditory system" OR "endocrine" OR "thyroid" OR "thyroxine" OR "adrenal" OR "pituitary" OR "immunological" OR "immunologic" OR "immune" OR "lymphoreticular" OR "lymph node" OR "lymph nodes" OR "spleen" OR "thymus" OR macrophage* OR leukocyt* OR lymphocyt* OR "white blood cell" OR "white blood cells" OR "neurological" OR "neurologic" OR "nervous system" OR "nerve" OR "brain" OR "cerebrovascular" OR "neurochemistry" OR "neurophysiology" OR "motor activity" OR "behavioral" OR "cognitive" OR "cognition" OR "reproductive" OR "reproduction system" OR "developmental" OR "oocyte" OR "ovary" OR "ovarian" OR "uterus" OR "uterine" OR "testes" OR "testicular" OR "sperm" OR estrogen* OR androgen* OR "human milk" OR "breast milk"))) OR ((TITLE-ABS-KEY ({1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene} OR {1,2,3,4,5,5-Hexachlorocyclopenta-1,3-diene} OR {1,2,3,4,5,5-Hexachlorocyclopentadiene} OR {Graphlox} OR {HCCPD} OR {Hexachlorcyclopentadien} OR {Hexachlorcyklopentadien} OR {Hexachloro-1,3-cyclopentadiene} OR {Hexachlorocyclo-pentadiene} OR {Hexachlorocyclopentadiene} OR {Hexachloromyclopentadiene} OR {Hexachloropentadiene} OR {hexaclorociclopentadieno} OR {HRS 1655} OR {Perchloro-1,3-cyclopentadiene} OR {Perchlorocyclopentadiene} OR {1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro-} OR {1,3-Cyclopentadiene, hexachloro-} OR {1,3-Cyclopentadiene,1,2,3,4,5,5-hexachloro-} OR {CYCLOPENTADIENE, HEXACHLORO-})) AND (TITLE-ABS-KEY ((toxic* AND "mechanism of action") OR (toxic* AND "mode of action") OR "mechanism of toxicity" OR "antagonist" OR "inhibitor" OR "inhibition" OR "metabolism" OR "toxicokinetic" OR "toxicokinetics" OR "pharmacokinetic" OR "pharmacokinetics" OR "pbpk" OR "adverse outcome pathway"

Table B-2. Database Query Strings

Database search date	Query string
	OR metabolom* OR proteom* OR genomic* OR transcriptom* OR epigenom* OR epigene* OR "transcription factor"))) OR ((TITLE-ABS-KEY ({1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene} OR {1,2,3,4,5,5-Hexachlorocyclopenta-1,3-diene} OR {1,2,3,4,5,5-Hexachlorocyclopentadiene} OR {Graphlox} OR {HCCPD} OR {Hexachlorcyclopentadien} OR {Hexachlorcyklopentadien} OR {Hexachloro-1,3-cyclopentadiene} OR {Hexachlorocyclo-pentadiene} OR {Hexachlorocyclopentadiene} OR {Hexachloromyclopentadiene} OR {Hexachloropentadiene} OR {hexaclorociclopentadieno} OR {HRS 1655} OR {Perchloro-1,3-cyclopentadiene} OR {Perchlorocyclopentadiene} OR {1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro-} OR {1,3-Cyclopentadiene, hexachloro-} OR {1,3-Cyclopentadiene,1,2,3,4,5,5-hexachloro-} OR {CYCLOPENTADIENE, HEXACHLORO-})) AND (INDEXTERMS ("bioinformatics" OR "medical informatics" OR "genomics" OR "genome" OR "proteomics" OR "proteome" OR "metabolomics" OR "metabolome" OR "genes" OR "gene expression" OR "phenotype" OR "genetics" OR "genotype" OR "transcriptome" OR "epidemiological monitoring" OR "genetic transcription" OR "messenger rna" OR "transfer rna" OR "protein synthesis" OR "reverse transcriptase polymerase chain reaction" OR "nucleotide sequence" OR "transactivator protein" OR "gene expression profiling"))) AND PUBYEAR > 1995 AND PUBYEAR < 2026) AND (LIMIT-TO (SUBJAREA , "ENVI") OR LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "BIOC") OR LIMIT-TO (SUBJAREA , "PHAR") OR LIMIT-TO (SUBJAREA , "AGRI") OR LIMIT-TO (SUBJAREA , "IMMU") OR LIMIT-TO (SUBJAREA , "EART") OR LIMIT-TO (SUBJAREA , "NEUR") OR LIMIT-TO (SUBJAREA , "HEAL") OR LIMIT-TO (SUBJAREA , "VETE") OR LIMIT-TO (SUBJAREA , "PSYC") OR LIMIT-TO (SUBJAREA , "NURS") OR LIMIT-TO (SUBJAREA , "DENT"))

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
11/2024	Compounds searched: 77-47-4
NTP	
11/2024	"77-47-4" "Hexachloro-1,3-cyclopentadiene" "Hexachlorocyclo-pentadiene" "Hexachlorocyclopentadiene" "Graphlox" "HCCPD" "Hexachloropentadiene" "Perchlorocyclopentadiene" "Hexachlorcyclopentadien" "Hexachlorcyklopentadien" "Hexachloromyclopentadiene" "hexaclorociclopentadieno" "HRS 1655" "Perchloro-1,3-cyclopentadiene" "1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro-" "1,3-Cyclopentadiene, hexachloro-" "1,3-Cyclopentadiene,1,2,3,4,5,5-hexachloro-" "CYCLOPENTADIENE, HEXACHLORO-"
NTRL	
11/2024	Limited to 1996 to present, terms appearing in title or keyword "1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene" OR "1,2,3,4,5,5-Hexachlorocyclopenta-1,3-diene" OR "1,2,3,4,5,5-Hexachlorocyclopentadiene" OR "Graphlox" OR "HCCPD" OR "Hexachlorcyclopentadien" OR "Hexachlorcyklopentadien" OR "Hexachloro-1,3-cyclopentadiene" OR "Hexachlorocyclo-pentadiene" OR "Hexachlorocyclopentadiene" OR "Hexachloromyclopentadiene" OR "Hexachloropentadiene" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"hexaclorociclopentadieno" OR "Perchloro-1,3-cyclopentadiene" OR "Perchlorocyclopentadiene"
Regulations.gov	
11/2024	"Hexachloro-1,3-cyclopentadiene" "Hexachlorocyclo-pentadiene" "Hexachlorocyclopentadiene" "HCCPD" "Hexachloropentadiene" "Perchlorocyclopentadiene"
NIH RePORTER	
05/2025	Search Criteria: Fiscal Year: Active Projects; Text Search: "Hexachlorocyclopentadiene" OR "HCCPD" OR "1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene" OR "1,2,3,4,5,5-Hexachlorocyclopenta-1,3-diene" OR "1,2,3,4,5,5-Hexachlorocyclopentadiene" OR "Graphlox" OR "Hexachlorcyclopentadien" OR "Hexachlorcyklopentadien" OR "Hexachloro-1,3-cyclopentadiene" OR "Hexachlorocyclo-pentadiene" OR "Hexachloromyclopentadiene" OR "Hexachloropentadiene" OR "hexaclorociclopentadieno" OR "HRS 1655" OR "Perchloro-1,3-cyclopentadiene" OR "Perchlorocyclopentadiene" OR "1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro-" OR "1,3-Cyclopentadiene, hexachloro-" OR "1,3-Cyclopentadiene,1,2,3,4,5,5-hexachloro-" OR "CYCLOPENTADIENE, HEXACHLORO-" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2024 results were:

- Number of records identified from PubMed, Embase, SciFinder, and Scopus (after duplicate removal): 169
- Number of records identified from other strategies: 111
- Total number of records to undergo literature screening: 280

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on HCCPD:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

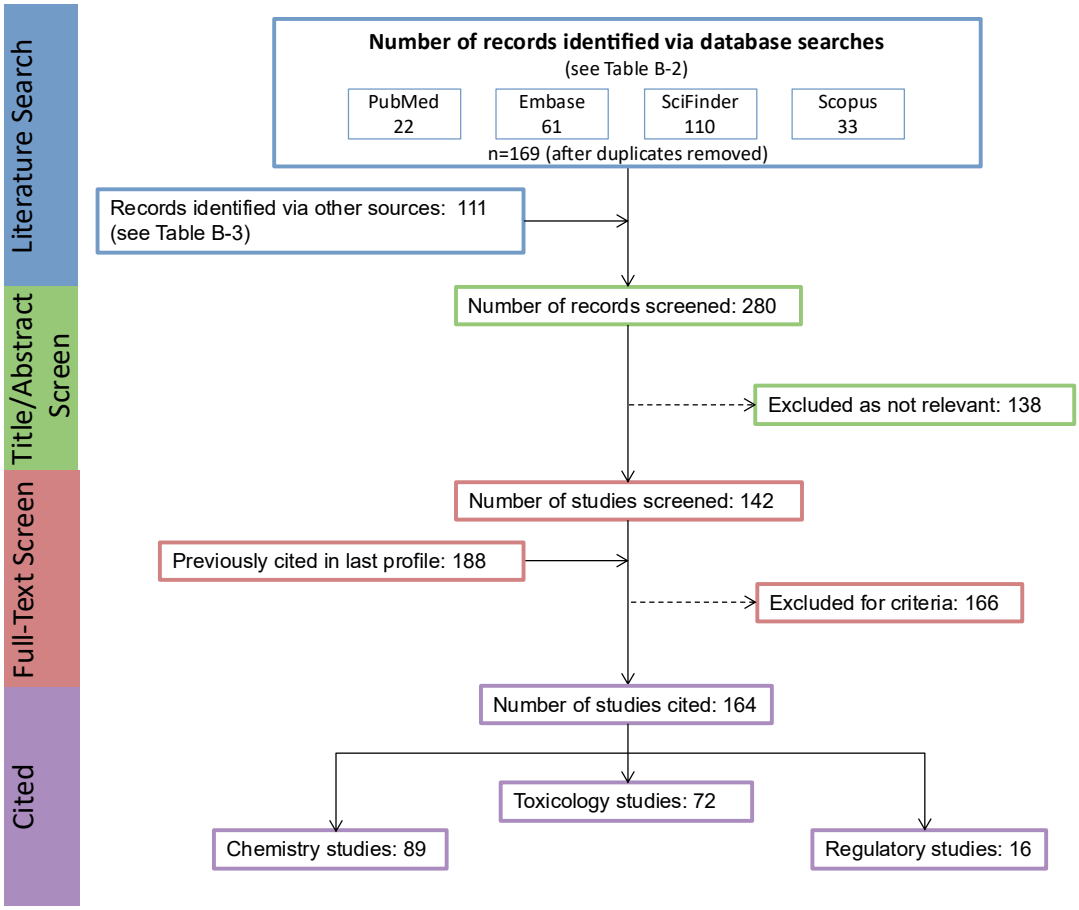
- Number of titles and abstracts screened: 280
- Number of studies considered relevant and moved to the next step: 142

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 142
- Number of studies cited in the previous draft of the toxicological profile: 188
- Total number of studies cited in the profile: 164

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. November 2024 Literature Search Results and Screen for HCCPD



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR HCCPD

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to HCCPD, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to HCCPD:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to HCCPD. The inclusion criteria used to identify relevant studies examining the health effects of HCCPD are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of HCCPD. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the 1999 Toxicological Profile for HCCPD; thus, the literature search was restricted to studies published between January 1996 and November 2024. See Appendix B for the databases searched and the search strategy.

A total of 279 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of HCCPD.

Title and Abstract Screen. In the Title and Abstract Screen step, 279 records were reviewed; 21 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 21 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 21 documents (70 studies), 13 documents (21 studies) were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for HCCPD and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1, 2-2, and 2-3, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for HCCPD identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The available human studies are limited to case series/reports assessing ocular, skin, and respiratory tract irritation following inhalation exposure to HCCPD. Most animal studies evaluated dermal and inhalation exposure, although oral studies were available. The most sensitive effects in laboratory animals and humans following exposure to HCCPD include respiratory effects (inhalation), hematology effects (inhalation), gastrointestinal effects (oral), and renal effects (oral). There were 21 studies (published in 13 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Hexachlorocyclopentadiene Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort																	
Case control																	
Population																	
Case series		2 2			1 1				1 1				1 1				
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series									1 1	2 2							
Number of studies examining endpoint				0	1	2	3	4	5–9	≥10							
Number of studies reporting outcome				0	1	2	3	4	5–9	≥10							

APPENDIX C

Table C-4. Overview of the Health Outcomes for Hexachlorocyclopentadiene Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	4	24	22		1		22	22			21	1	23			3	
	4	24	21		1		21	21			20	0	22			3	
Intermediate-duration	8	8	5	7	7	5	9	9	1	3	6	7	6	7		3	3
	1	6	0	0	5	0	1	0	0	0	0	0	0	0		1	0
Chronic-duration	2	2	2	2	2	2	2	2	2		2	2	2	2			2
	0	1	0	0	0	0	0	0	0		0	0	0	1			0
Oral studies																	
Acute-duration	2	5	3	5		1	3	3			3		4		3	1	
	0	5	3	5		1	3	3			3		4		1	0	
Intermediate-duration	2	2	2	2	2	2	2	2	2		2	2	2	2			
	2	0	0	2	0	0	0	2	0		0	0	0	0			
Chronic-duration																	
Dermal studies																	
Acute-duration		1	1				1	1	9	26	1		3				
		1	1				1	1	9	26	1		3				
Intermediate-duration										8							
										3							
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of HCCPD health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-8 and C-9, respectively.

Table C-8. Summary of Risk of Bias Assessment for Hexachlorocyclopentadiene—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects (inhalation only)							
Case study/series							
Morse et al. 1979	– –	–	+	–	–	+	Second
Kominsky et al. 1980	– –	–	+	+	–	+	Second
Outcome: Hematological effects (inhalation only)							
Case study/series							
Kominsky et al. 1980	– –	–	+	+	–	–	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

Table C-9. Summary of Risk of Bias Assessment for Hexachlorocyclopentadiene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory Effects (inhalation only)									
Inhalation acute exposure									
Alexander et al. 1980a; Rand et al. 1982a (rats; 1–2 weeks)	–	+	+	+	++	+	+	++	First
Treon et al. 1955 (rats, mice, rabbits, guinea pigs; ≤5 days)	–	+	–	+	++	+	+	–	First
OxyChem 1972 (rats; 4 hours)	–	+	+	+	++	–	+	–	First
Jackson and Hardy 1986 (rats; 1 hour)	+	+	+	+	++	–	+	++	First
Jackson and Hardy 1986 (rats; 4 hours)	+	+	+	+	++	–	+	++	First

APPENDIX C

Table C-9. Summary of Risk of Bias Assessment for Hexachlorocyclopentadiene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Inhalation intermediate exposure									
Alexander et al. 1980b; Huntingdon Research Centre 1980; Rand et al. 1982a, 1982b (rats; 14 weeks)	–	+	+	+	++	+	+	++	First
Alexander et al. 1980b; Rand et al. 1982a, 1982b (monkeys; 14 weeks)	–	+	+	+	++	+	+	++	First
Treon et al. 1955 (rats, mice, rabbits, guinea pigs; 6 or 30 weeks)	–	+	–	+	++	+	+	–	First
Clark 1981 (rats; 30 weeks)	++	+	+	+	++	++	+	++	First
NTP 1994 (rats; 13 weeks)	++	+	+	+	++	++	+	+	First
NTP 1994 (mice; 13 weeks)	++	+	+	+	++	++	+	+	First
NTP 1994 (mice; 26 weeks)	++	+	+	+	++	+	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Hexachlorocyclopentadiene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
NTP 1994 (mice; 33 weeks)	++	+	+	+	++	+	+	++	First
NTP 1994 (mice; 42 weeks)	++	+	+	+	++	+	+	++	First
Inhalation chronic exposure									
NTP 1994 (rats; 103–104 weeks)	++	+	+	+	++	++	+	++	First
NTP 1994 (mice; 103–104 weeks)	++	+	+	+	++	++	+	++	First
Outcome: Hematological effects (red blood cell endpoints, inhalation only)									
Inhalation acute exposure									
Alexander et al. 1980a; Rand et al. 1982a (rats; 1–2 weeks)	–	+	+	+	++	+	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Hexachlorocyclopentadiene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Inhalation intermediate exposure									
Alexander et al. 1980b; Rand et al. 1982a (rats; 14 weeks)	–	+	+	+	++	+	+	++	First
Alexander et al. 1980b; Rand et al. 1982a (monkeys; 14 weeks)	–	+	+	+	++	+	+	++	First
Clark 1981 (rats; 30 weeks)	++	+	+	+	++	++	+	++	First
NTP 1994 (rats; 13 weeks)	++	+	+	+	++	++	+	+	First
NTP 1994 (mice; 13 weeks)	++	+	+	+	++	++	+	+	First
NTP 1994 (rats; 13 weeks; special hematology, clinical chemistry, urinalysis study)	++	+	+	+	++	++	+	++	First
NTP 1994 (mice; 13 weeks; special	++	+	+	+	++	++	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Hexachlorocyclopentadiene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
hematology, clinical chemistry, urinalysis study)									
Inhalation chronic exposure									
NTP 1994 (rats; 103–104 weeks)	++	+	+	+	++	++	+	++	First
NTP 1994 (mice; 103–104 weeks)	++	+	+	+	++	++	+	++	First
Outcome: Hematological effects (white blood cell endpoints, inhalation only)									
Inhalation acute exposure									
Alexander et al. 1980a; Rand et al. 1982a (rats; 1-2 weeks)	–	+	+	+	++	+	+	++	First
Inhalation intermediate exposure									
Alexander et al. 1980b; Rand et al. 1982a (rats; 14 weeks)	–	+	+	+	++	+	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Hexachlorocyclopentadiene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Alexander et al.1980b; Rand et al. 1982a; (monkeys; 14 weeks)	–	+	+	+	++	+	+	++	First
Clark 1981 (rats; 30 weeks)	++	+	+	+	++	++	+	++	First
NTP 1994 (rats; 13 weeks)	++	+	+	+	++	++	+	+	First
NTP 1994 (mice; 13 weeks)	++	+	+	+	++	++	+	+	First
NTP 1994 (rats; 13 weeks; special hematology, clinical chemistry, urinalysis study)	++	+	+	+	++	++	+	++	First
NTP 1994 (mice; 13 weeks; special hematology, clinical chemistry, urinalysis study)	++	+	+	+	++	++	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Hexachlorocyclopentadiene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Inhalation chronic exposure									
NTP 1994 (rats; 103–104 weeks)	++	+	+	+	++	++	+	++	First
NTP 1994 (mice; 103–104 weeks)	++	+	+	+	++	++	+	++	First
Outcome: Gastrointestinal effects (oral only)									
Oral acute exposure									
Dean 1977 (mice, single dose)	+	+	+	+	++	+	+	++	First
Gardner 1986a (rats, single dose)	–	+	+	+	++	+	+	++	First
Treon et al. 1955 (rats; single dose)	–	+	–	+	++	+	+	–	First
Treon et al. 1955 (rabbits; single dose)	–	+	–	+	++	+	+	–	First
Oral intermediate exposure									
Abdo et al. 1984; Velsicol 1981b (rats; 13 weeks)	++	+	+	+	++	++	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Hexachlorocyclopentadiene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Abdo et al. 1984; Velsicol 1981a (mice; 13 weeks)	++	+	+	+	++	++	+	++	First
Outcome: Renal effects (oral only)									
Oral acute exposure									
Treon et al. 1955 (rats; single dose)	–	+	–	+	++	+	+	–	First
Treon et al. 1955 (rabbits; single dose)	–	+	–	+	++	+	+	–	First
Oral intermediate exposure									
Abdo et al. 1984; Velsicol 1981b (rats; 13 weeks)	++	+	+	+	++	++	+	++	First
Abdo et al. 1984; Velsicol 1981a (mice; 13 weeks)	++	+	+	+	++	++	+	++	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to HCCPD and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** The true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** The true effect may be reflected in the apparent relationship
- **Low confidence:** The true effect may be different from the apparent relationship
- **Very low confidence:** The true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to HCCPD and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-10. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-11. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining respiratory (inhalation only), hematology (inhalation only), and gastrointestinal (oral only) effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-13 and C-14, respectively.

Table C-13. Presence of Key Features of Study Design for Hexachlorocyclopentadiene—Observational Epidemiology Studies

	Key features				
Reference	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Respiratory effects (inhalation only)					
Case study/series					
Morse et al. 1979	No	Yes	Yes	No	Low

Table C-13. Presence of Key Features of Study Design for Hexachlorocyclopentadiene—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Kominsky et al. 1980	No	Yes	Yes	No	Low
Outcome: Hematological effects (inhalation only)					
Case study/series					
Kominsky et al. 1980	No	Yes	Yes	No	Low

Table C-14. Presence of Key Features of Study Design for Hexachlorocyclopentadiene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects (inhalation only)					
Inhalation acute exposure					
Alexander et al. 1980a; Rand et al. 1982a (rats; 1–2 weeks)	Yes	Yes	Yes	Yes	High
Treon et al. 1955 (rats, mice, rabbits, guinea pigs; ≤5 days)	No	No	Yes	No	Very Low
OxyChem 1972 (rats; 4 hours)	No	Yes	Yes	No	Low
Jackson and Hardy 1986 (rats; 1 hour)	No	Yes	Yes	Yes	Moderate
Jackson and Hardy 1986 (rats; 4 hours)	No	Yes	Yes	Yes	Moderate
Inhalation intermediate exposure					
Alexander et al. 1980b; Huntingdon Research Centre 1980; Rand et al. 1982a, 1982b (rats; 14 weeks)	Yes	Yes	Yes	Yes	High
Alexander et al. 1980b; Rand et al. 1982a, 1982b (monkeys; 14 weeks)	Yes	Yes	Yes	Yes	High
Treon et al. 1955 (rats, mice, rabbits, guinea pigs; 6 or 30 weeks)	No	No	Yes	No	Very Low

Table C-14. Presence of Key Features of Study Design for Hexachlorocyclopentadiene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Clark 1981 (rats; 30 weeks)	Yes	Yes	Yes	Yes	High
NTP 1994 (rats; 13 weeks)	Yes	Yes	Yes	Yes	High
NTP 1994 (mice; 13 weeks)	Yes	Yes	Yes	Yes	High
NTP 1994 (mice; 26 weeks)	Yes	Yes	Yes	Yes	High
NTP 1994 (mice; 33 weeks)	Yes	Yes	Yes	Yes	High
NTP 1994 (mice; 42 weeks)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
NTP 1994 (rats; 103–104 weeks)	Yes	Yes	Yes	Yes	High
NTP 1994 (mice; 103–104 weeks)	Yes	Yes	Yes	Yes	High
Outcome: Gastrointestinal effects (oral only)					
Oral acute exposure					
Dean 1977 (mice, single dose)	No	Yes	Yes	Yes	Moderate
Gardner 1986a (rats, single dose)	No	Yes	Yes	Yes	Moderate
Treon et al. 1955 (rats; single dose)	No	Yes	Yes	No	Low
Treon et al. 1955 (rabbits; single dose)	No	No	Yes	No	Very Low
Oral intermediate exposure					
Abdo et al. 1984; Velsicol 1981b (rats; 13 weeks)	Yes	Yes	Yes	Yes	High
Abdo et al. 1984; Velsicol 1981a (mice; 13 weeks)	Yes	Yes	Yes	Yes	High
Outcome: Hematological effects (inhalation only)					
Inhalation acute exposure					
Alexander et al. 1980a; Rand et al. 1982a (rats; 1–2 weeks)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Alexander et al. 1980b; Rand et al. 1982a (rats; 14 weeks)	Yes	Yes	Yes	Yes	High
Alexander et al. 1980b; Rand et al. 1982a (monkeys; 14 weeks)	Yes	Yes	Yes	Yes	High
Clark 1981 (rats; 30 weeks)	Yes	Yes	Yes	Yes	High
NTP 1994 (rats; 13 weeks)	Yes	Yes	Yes	Yes	High
NTP 1994 (mice; 13 weeks)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for Hexachlorocyclopentadiene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
NTP 1994 (rats; 13 weeks; special hematology study)	Yes	Yes	Yes	Yes	High
NTP 1994 (mice; 13 weeks; special hematology study)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
NTP 1994 (rats; 104 weeks)	Yes	Yes	Yes	Yes	High
NTP 1994 (mice; 104 weeks)	Yes	Yes	Yes	Yes	High
Outcome: Renal effects (oral only)					
Oral acute exposure					
Treon et al. 1955 (rats; single dose)	No	Yes	Yes	No	Low
Treon et al. 1955 (rabbits; single dose)	No	No	Yes	No	Very Low
Oral intermediate exposure					
Abdo et al. 1984; Velsicol 1981b (rats; 13 weeks)	Yes	Yes	Yes	Yes	High
Abdo et al. 1984; Velsicol 1981a (mice; 13 weeks)	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-15.

Table C-15. Initial Confidence Rating for Hexachlorocyclopentadiene Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects (inhalation only)		
Inhalation acute exposure		
Human studies		
Morse et al. 1979	Low	Low
Kominsky et al. 1980	Low	

Table C-15. Initial Confidence Rating for Hexachlorocyclopentadiene Health Effects Studies

	Initial study confidence	Initial confidence rating
Animal studies		
Alexander et al. 1980a; Rand et al. 1982a (rats; 1–2 weeks)	High	High
Treon et al. 1955 (rats, mice, rabbits, guinea pigs; ≤5 days)	Very Low	
OxyChem 1972 (rats; 4 hours)	Low	
Jackson and Hardy 1986 (rats; 1 hour)	Moderate	
Jackson and Hardy 1986 (rats; 4 hours)	Moderate	
Inhalation intermediate studies		
Animal studies		
Alexander et al. 1980b; Huntingdon Research Centre 1980; Rand et al. 1982a, 1982b (rats; 14 weeks)	High	High
Alexander et al. 1980b; Rand et al. 1982a, 1982b (monkeys; 14 weeks)	High	
Treon et al. 1955 (rats, mice, rabbits, guinea pigs; 6 or 30 weeks)	Very Low	
Clark 1981 (rats; 30 weeks)	High	
NTP 1994 (rats; 13 weeks)	High	
NTP 1994 (mice; 13 weeks)	High	
NTP 1994 (mice; 26 weeks)	High	
NTP 1994 (mice; 33 weeks)	High	
NTP 1994 (mice; 42 weeks)	High	
Inhalation chronic studies		
Animal studies		
NTP 1994 (rats; 104 weeks)	High	High
NTP 1994 (mice; 104 weeks)	High	
Outcome: Gastrointestinal effects (oral only)		
Oral acute studies		
Animal studies		
Dean 1977 (mice, single dose)	Moderate	Moderate
Gardner 1986a (rats, single dose)	Moderate	
Treon et al. 1955 (rats; single dose)	Low	
Treon et al. 1955 (rabbits; single dose)	Very Low	
Oral intermediate studies		
Animal studies		
Abdo et al. 1984; Velsicol 1981b (rats; 13 weeks)	High	High
Abdo et al. 1984; Velsicol 1981a (mice; 13 weeks)	High	

Table C-15. Initial Confidence Rating for Hexachlorocyclopentadiene Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Hematological effects (respiratory only)		
Inhalation acute studies		
Human studies		
Kominsky et al. 1980	Low	Low
Animal studies		
Alexander et al. 1980a; Rand et al. 1982a (rats; 1–2 weeks)	High	High
Inhalation intermediate studies		
Animal studies		
Alexander et al. 1980b; Rand et al. 1982a (rats; 14 weeks)	High	High
Alexander et al. 1980b; Rand et al. 1982a (monkeys; 14 weeks)	High	
Clark 1981 (rats; 30 weeks)	High	
NTP 1994 (rats; 13 weeks)	High	
NTP 1994 (mice; 13 weeks)	High	
NTP 1994 (rats; 13 weeks; special hematology, clinical chemistry, urinalysis study)	High	
NTP 1994 (mice; 13 weeks; special hematology, clinical chemistry, urinalysis study)	High	
Inhalation chronic studies		
Animal studies		
Abdo et al. 1984; Velsicol 1981b (rats; 13 weeks)	High	High
Abdo et al. 1984; Velsicol 1981a (mice; 13 weeks)	High	
Outcome: Renal effects (oral only)		
Oral acute studies		
Animal studies		
Treon et al. 1955 (rats; single dose)	Low	Low
Treon et al. 1955 (rabbits; single dose)	Very Low	
Oral intermediate studies		
Animal studies		
Abdo et al. 1984; Velsicol 1981b (rats; 13 weeks)	High	High
Abdo et al. 1984; Velsicol 1981a (mice; 13 weeks)	High	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory and hematological effects via the inhalation route and gastrointestinal and renal effects via the oral route are presented in Table C-16. If the confidence ratings

for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with HCCPD exposure is presented in Table C-17.

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects (inhalation only)			
Human studies	Low	-1 for risk of bias	Very Low
Animal studies	High	+1 consistency in findings +1 dose-response	High
Outcome: Hematology effects (inhalation only, red blood cell parameters)			
Human studies	Low	-1 for risk of bias	Very Low
Animal studies	High	-1 for unexplained inconsistency	Moderate
Outcome: Hematology effects (inhalation only, white blood cell parameters)			
Human studies	Low	-1 for risk of bias	Very Low
Animal studies	High	-2 for unexplained inconsistency	Low
Outcome: Gastrointestinal effects (oral only)			
Animal studies	High	+1 for consistency in findings +1 dose-response	High
Outcome: Renal effects (oral only)			
Animal studies	High		High

Table C-17. Confidence in the Body of Evidence for Hexachlorocyclopentadiene

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory (inhalation only)	Very Low	High
Hematology (inhalation only, red blood cell parameters)	Very Low	Moderate
Hematology (inhalation only, white blood cell parameters)	Very Low	Low
Gastrointestinal (oral only)	No data	High
Renal (oral only)	No data	High

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
  - No downgrade if most studies are in the risk of bias first tier

- Downgrade one confidence level if most studies are in the risk of bias second tier
- Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
  - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
  - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
  - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
  - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
  - No downgrade if none of the factors are considered indirect
  - Downgrade one confidence level if one of the factors is considered indirect
  - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for HCCPD, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome

- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for HCCPD is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for Hexachlorocyclopentadiene

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects (inhalation)	Very Low	Health effect	Inadequate
Hematology effects (red blood cell parameters, inhalation)	Very Low	Health effect	Inadequate
Hematology effects (white blood cell parameters, inhalation)	Very Low	Health effect	Inadequate
Animal studies			
Respiratory effects (inhalation)	High	Health effect	High
Hematology effects (red blood cell parameters, inhalation)	Moderate	Health effect	Moderate
Hematology effects (white blood cell parameters, inhalation)	Low	Health effect	Low
Gastrointestinal effects (oral)	High	Health effect	High
Renal effects (oral)	High	Health effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

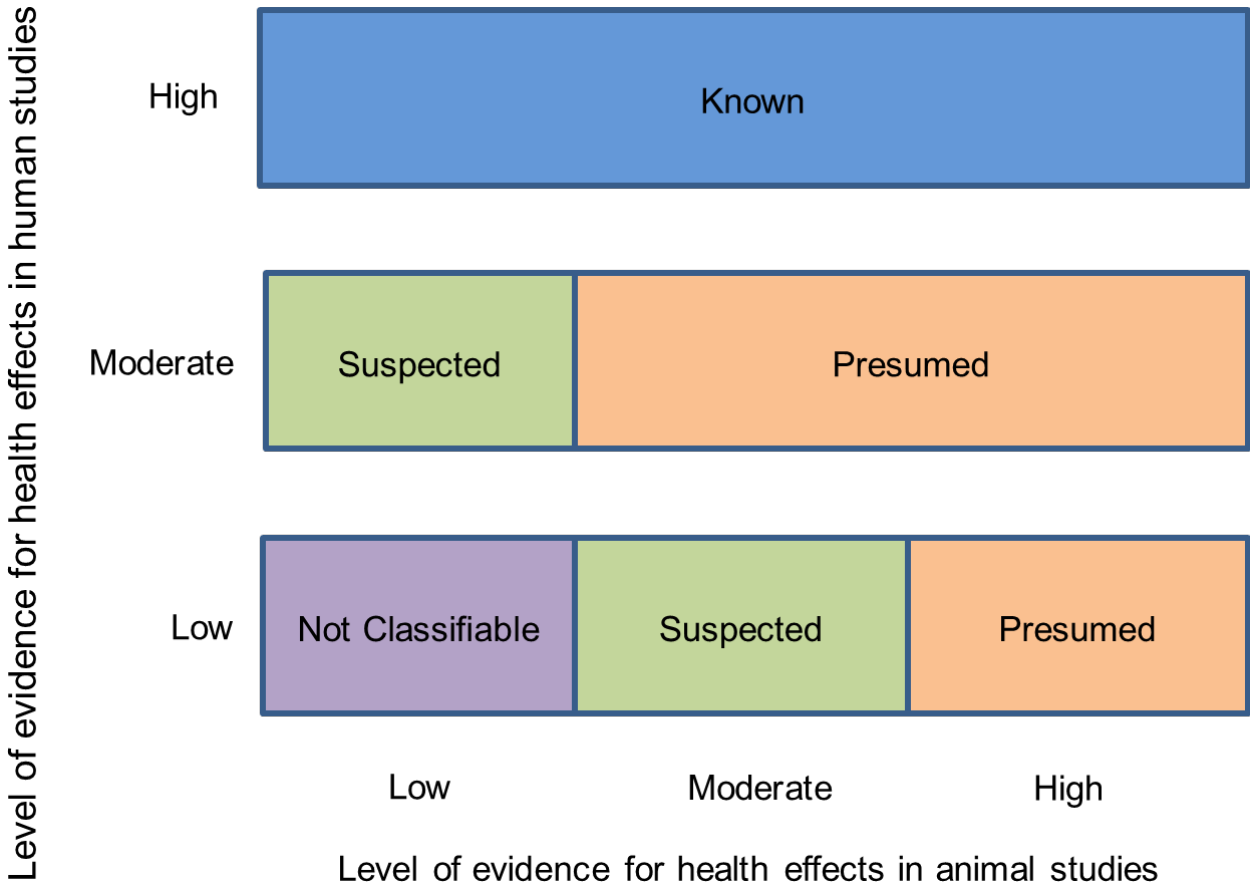
The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.

- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Figure C-1. Hazard Identification Scheme



Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for HCCPD are listed below and summarized in Table C-19.

Presumed Health Effects

- Respiratory effects (inhalation only)
  - Available data in humans (clinical signs from case series) provide inadequate evidence of respiratory effects in workers exposed to HCCPD (Kominsky et al. 1980; Morse et al. 1979).
  - Animal data provide a high level of evidence of respiratory tract damage in rats and mice following intermediate- and chronic-duration inhalation exposures (Clark 1981; NTP 1994).
  - Mechanistic data support portal-of-entry reactivity for HCCPD, which is consistent with effects to the respiratory tract following inhalation exposures.
- Gastrointestinal effects (oral only)
  - No oral data in humans.
  - Animal data provide a high level of evidence of gastrointestinal damage (epithelial hyperplasia and focal inflammation of the forestomach) in rats and mice following intermediate-duration exposure (Abdo et al. 1984; Velsicol 1981a, 1981b), supported by reports of diarrhea in single-dose oral studies (Dean 1977; Gardner 1986a).
  - Mechanistic data support portal-of-entry reactivity for HCCPD, which is consistent with effects to the gastrointestinal tract following oral exposures.
- Renal effects (oral only)
  - No oral data in humans.
  - Animal data provide a high level of evidence for renal damage in rats and mice following intermediate-duration oral exposures (Abdo et al. 1984; Velsicol 1981a, 1981b).
  - HCCPD and/or its metabolites accumulate in the kidneys of orally-exposed rats and mice (Dorough and Ranieri 1984; El Dareer et al. 1983; Lawrence and Dorough 1981, 1982; Yu and Atallah 1981). Increased sensitivity of rats is supported by toxicokinetic data indicating that concentrations of HCCPD and/or its metabolites are highest in the kidneys of rats and livers of mice after oral exposure.

Suspected Health Effects

- Hematology effects (red blood cell parameters, inhalation only)
  - Available data in humans (no alterations in blood parameters from case series) provide inadequate evidence in workers exposed to HCCPD (Kominsky et al. 1980).
  - Animal data provide a moderate level of evidence for altered red blood cell parameters in mice and rats following intermediate-duration inhalation exposure (Clark 1981; NTP 1994); however, there is some inconsistency between species and sexes in the database. Notably, special 13-week hematology studies conducted by NTP (1994) were not able to reproduce results consistent with those observed in the main 13-week toxicity study and hematological effects were not seen in the 2-year bioassays.
  - Due to the lack of measured food and water intake for some studies (NTP 1994), it is not clear if the altered red blood cell parameters could be explained by hemoconcentration following decreased water intake.

- The lack of treatment-related effects on bone marrow histopathology suggests that the altered red blood cell parameters may be due to compromised gas exchange following respiratory toxicity.

Not Classifiable Effects

- Hematology effects (white blood cell parameters, inhalation only)
  - Available data in humans (no alterations in blood parameters from case series) provide inadequate evidence in workers exposed to HCCPD (Kominsky et al. 1980).
  - Animal data provide a low level of evidence for altered white blood cell parameters in mice and rats following intermediate-duration inhalation exposure, with inconsistent findings across studies for specific parameters affected and the magnitude of effect (Alexander et al. 1980b; Clark 1981; NTP 1994; Rand et al. 1982a). No effects were noted in chronic-duration studies (NTP 1994).
  - No clear mechanism is available for altered white blood cells, since no effects on organs involved in white blood cell maturation or function (lymph nodes, spleen, thymus) were identified in animals following inhalation exposures (Clark 1981; NTP 1994; Rand et al. 1982a).

Table C-19. Hazard Identification Conclusions for Hexachlorocyclopentadiene

Outcome	Hazard identification
Respiratory effects	Presumed health effect
Hematological (red blood cell) effects	Suspected health effect
Hematological (white blood cell) effects	Not classifiable
Gastrointestinal effects	Presumed health effect
Renal effects	Presumed health effect

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX D

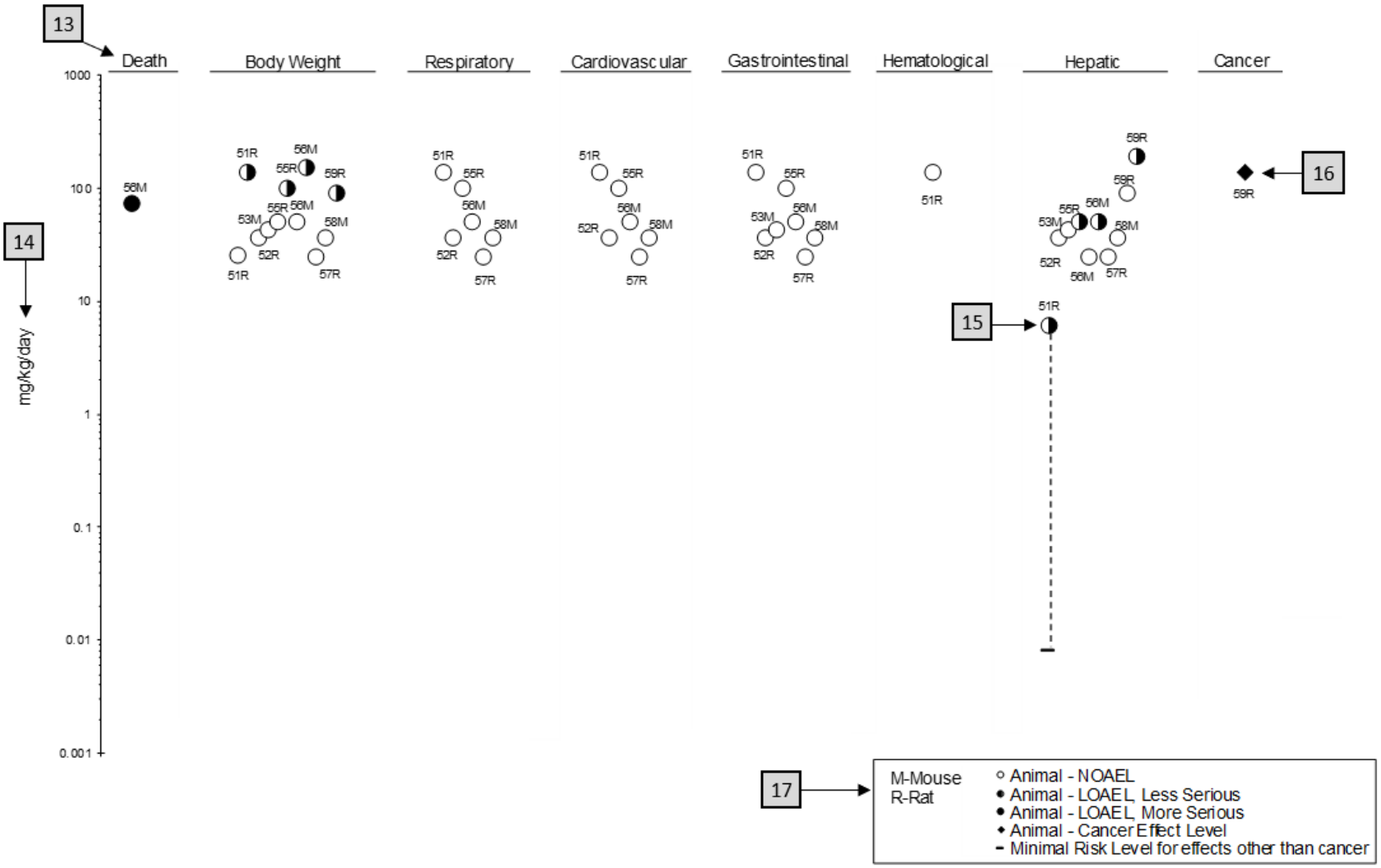
Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). (11)
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX D

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/environmental-medicine/hcp/emhsis/index.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://wwwn.cdc.gov/TSP/ToxFAQs/ToxFAQsLanding.aspx).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at https://www.pehsu.net/.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or malignant tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The exposure level of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this exposure level, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
ALP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result