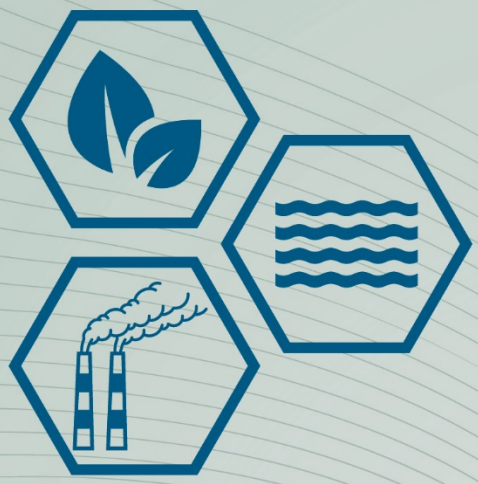

Toxicological Profile for Pentachlorophenol

April 2022

ATSDR
U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

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 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 levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; 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.

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 was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

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.

VERSION HISTORY

Date	Description
April 2022	Final toxicological profile released
July 2021	Toxicological profile released for public comment
August 2012	Addendum to toxicological profile released
September 2001	Final toxicological profile released
October 1994	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Pure pentachlorophenol exists as colorless crystals that are poorly soluble in water, but dissolve in organic solvents such as alcohol, ether, and benzene. Typically, technical-grade pentachlorophenol is 86–90% pure. Contaminants generally consist of other polychlorinated phenols, chlorinated dibenzo-*p*-dioxins (CDDs), and chlorinated dibenzofurans (CDFs), which are formed during the manufacturing process and can impart a darker color to the crystals. To increase its water solubility, pentachlorophenol has often been manufactured and marketed as a sodium salt. Pentachlorophenol was, in the past, one of the most heavily used pesticides in the United States, but it is now regulated as a restricted-use pesticide and is no longer contained in wood-preserving solutions or in insecticides or herbicides available for home and garden use. Its use is restricted to the treatment of utility poles, railroad ties, and wharf pilings. Pentachlorophenol is found in all environmental media as a result of its past widespread use; current releases to the environment are more limited as a result of changing use patterns. In addition, a number of other environmental contaminants, including hexachlorobenzene, pentachlorobenzene, pentachloronitrobenzene, and hexachlorocyclohexane isomers, are known to be metabolized to pentachlorophenol.

Humans may be exposed to pentachlorophenol in occupational settings through inhalation of contaminated workplace air and dermal contact with the compound or with wood products treated with the compound. General population exposure may occur through contact with contaminated environmental media, particularly in the vicinity of wood treatment facilities and hazardous waste sites. Important routes of exposure appear to be inhalation of contaminated air, inhalation exposure to pentachlorophenol that has volatilized from treated wood surfaces, ingestion of contaminated groundwater used as a source of drinking water, ingestion of contaminated food, and dermal contact with contaminated soils or wood products treated with the compound. Children are likely to be exposed to pentachlorophenol by the same routes as adults. In addition, small children are generally more likely than adults to have significant contact with soil and have less concern with hygiene than adults. ATSDR believes that the primary route of human exposure to pentachlorophenol at hazardous waste sites is ingestion of contaminated media, and to a lesser extent, inhalation and dermal contact with contaminated media.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of pentachlorophenol primarily comes from oral studies in laboratory animals. These studies have evaluated a wide range of potential endpoints following acute, intermediate, or chronic exposure. More limited information comes from observational studies in humans examining workers at manufacturing facilities, pesticide applicators, sawmill workers, individuals living in log homes treated with pentachlorophenol, and the general populations. Almost half of the human studies are case reports and most studies provide no or limited information on exposure.

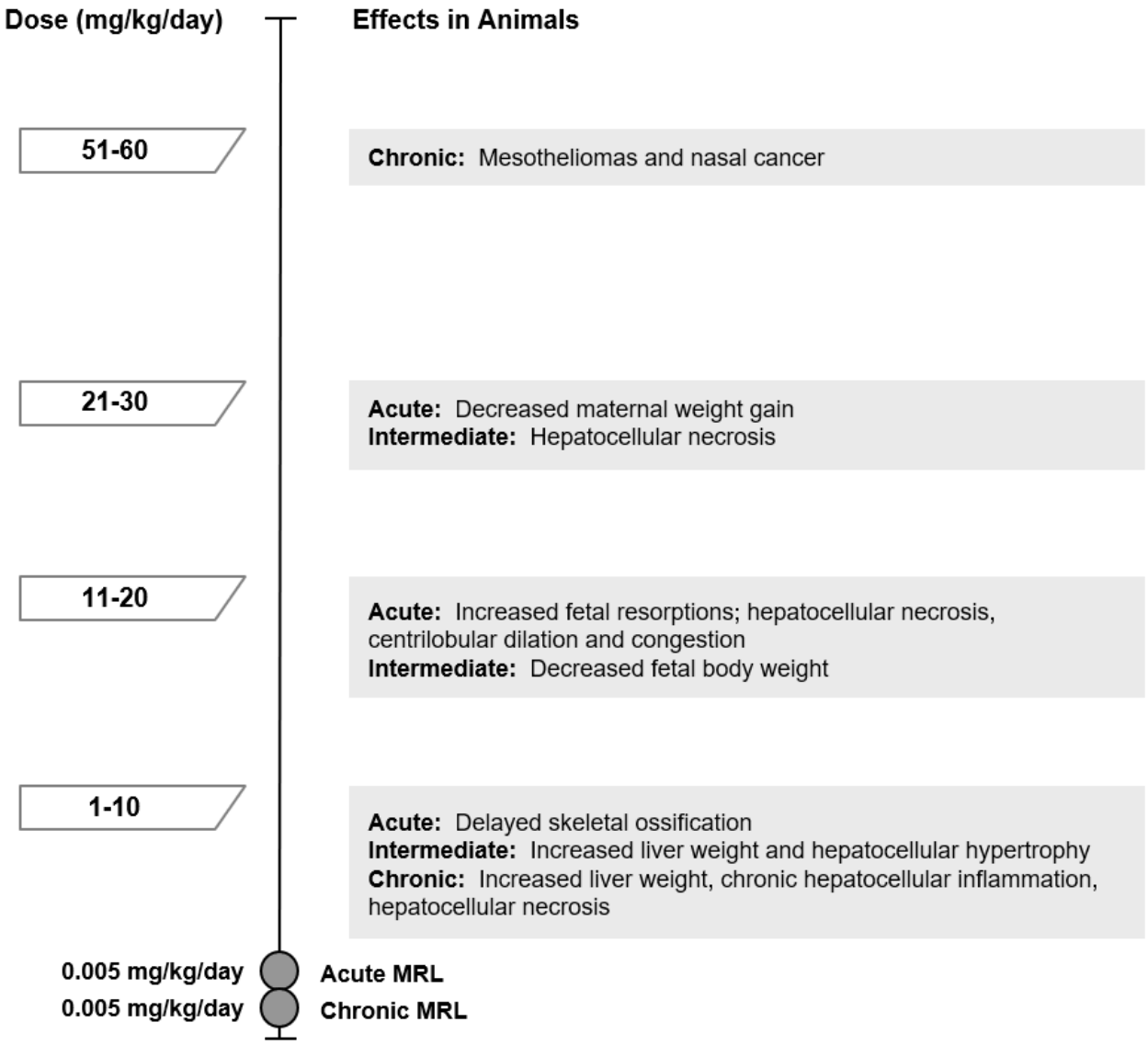
Human studies evaluating the health effects of exposure to pentachlorophenol typically involve exposure to technical-grade pentachlorophenol which contains approximately 85–90% pentachlorophenol and a number of contaminants including other chlorophenols, CDDs, CDFs, hexachlorobenzene, and chlorophenoxy compounds. Studies in laboratory animals have evaluated health effects associated with exposure to pure pentachlorophenol, technical-grade pentachlorophenol, or commercial-grade pentachlorophenol (see Section 2.1 for additional information on the chemical composition of the different grades of pentachlorophenol). Some of the health effects that have been observed in humans and animals have been attributed to the contaminants present in technical-grade and commercial-grade pentachlorophenol rather than the pentachlorophenol itself. The discussion of health effects in this section of the profile excludes health outcomes that have been shown to be due to contaminants.

As illustrated in Figure 1-1, the most sensitive effects in animals appear to be liver damage and developmental toxicity. A systematic review of these endpoints results in the following hazard identification conclusions:

- Hepatic effects are a presumed health effect for humans
- Developmental effects are a presumed health effect for humans

Hepatic Effects. Studies in humans and laboratory animals have identified the liver as a sensitive target of pentachlorophenol toxicity. Inhalation and/or dermal exposures to pentachlorophenol have resulted in alterations in porphyrin excretion (Cheng et al. 1993; Hryhorczuk et al. 1998), liver enlargement (Armstrong et al. 1969; Gordon 1956; Robson et al. 1969; Smith et al. 1996), increased serum liver enzyme levels (Colosio et al. 1993b; Klemmer et al. 1980), and centrilobular degeneration (Bergner et al. 1965) in pentachlorophenol production workers, herbicide sprayers, workers at wood treatment plants, or infants exposed to contaminated diapers and bed linens. These studies provided limited exposure

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



information. Acute- (Bekhouche et al. 2019; Umemura et al. 1996), intermediate- (Bernard et al. 2002; Greichus et al. 1979; Kerkvliet et al. 1982; Kimbrough and Linder 1978; Knudsen et al. 1974; NTP 1989, 1999; Umemura et al. 1996, 2006), and chronic- (EPA 1997; NTP 1989, 1999; Schwetz et al. 1978) duration oral studies in several laboratory animal species provide strong support for identifying the liver as a target tissue. The effects include alterations in serum liver enzyme levels, increases in liver weight, and hepatocellular hypertrophy, degeneration, fibrosis, and necrosis. These effects were observed after exposure to pure pentachlorophenol, technical-grade pentachlorophenol, and commercial-grade pentachlorophenol.

Developmental Effects. Several epidemiological studies evaluated potential developmental effects in the offspring of male sawmill workers (Dimich-Ward et al. 1996) and the general population (Berghuis et al. 2018; Chen et al. 2013b; Meijer et al. 2008; Roze et al. 2009); however, the results are not consistent across studies. Studies in laboratory animals have reported increases in fetal/neonatal mortality (Bernard and Hoberman 2001; Bernard et al. 2002; Exon and Koller 1982; Schwetz et al. 1974, 1978; Welsh et al. 1987), skeletal malformations (Bernard and Hoberman 2001; Schwetz et al. 1974; Welsh et al. 1987), and decreases in growth (Bernard and Hoberman 2001; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1974).

Cancer Effects. A number of epidemiological cohort and case-control studies have evaluated the potential associations between pentachlorophenol and cancer. In separate evaluations of the available epidemiological data, the Department of Health and Human Services (HHS) (NTP 2016), U.S. Environmental Protection Agency (EPA) (IRIS 2010), and International Agency for Research on Cancer (IARC 2019) concluded that the data suggested an association between pentachlorophenol exposure and increased risk of non-Hodgkin lymphoma based on the consistent findings across epidemiological studies. The data for other cancer types were considered inadequate. In rats, oral exposure to pure pentachlorophenol resulted in increases in the incidence of meostheliomas and nasal squamous cell carcinomas (NTP 1999). Oral exposure to a commercial-grade pentachlorophenol (Dowicide EC-7) or technical-grade pentachlorophenol resulted in hepatocellular adenomas/carcinomas, adrenal pheochromocytomas, and hemangiosarcomas in mice (NTP 1989). Other oral studies have not found increases in tumor incidences in rats exposed to the Dowicide EC-7 commercial-grade pentachlorophenol (NCI 1968; Schwetz et al. 1978).

HHS has categorized pentachlorophenol as “reasonably anticipated to be a human carcinogen” (NTP 2016) and EPA has categorized it as “likely to be carcinogenic to humans” (IRIS 2010). IARC (2019) concluded that pentachlorophenol is “carcinogenic to humans” (Group 1).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was not considered adequate for deriving inhalation MRLs. The oral database was considered adequate for derivation of acute- and chronic-duration oral MRLs for pentachlorophenol (see Table 1-1). As presented in Figure 1-2, the liver effects and developmental effects were the most sensitive outcomes.

Figure 1-2. Summary of Sensitive Targets of Pentachlorophenol – Oral

The liver and developing fetuses are the most sensitive target of pentachlorophenol 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. Minimal Risk Levels (MRLs) for Pentachlorophenol[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	0.005 (5 µg/kg/day)	Delayed skeletal ossification in rat fetuses	5 (LOAEL)	1,000	Schwetz et al. 1974
Intermediate	Insufficient data for MRL derivation				
Chronic	0.005 (5 µg/kg/day)	Chronic inflammation of the liver in dogs	1.5 (LOAEL)	300	EPA 1997

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level

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 pentachlorophenol. 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 effect. 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 pentachlorophenol, 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 pentachlorophenol was also conducted; the results of this review are presented in Appendix C.

Animal oral studies are presented in Table 2-2 and Figure 2-2; no inhalation or dermal data were identified for pentachlorophenol.

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. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects (SLOAELs) 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. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of pentachlorophenol are indicated in Table 2-2 and Figure 2-2.

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

The production of pentachlorophenol introduces a number of contaminants; typical contaminants found in technical-grade and commercial-grade pentachlorophenol include other chlorophenols, CDDs, CDFs, hexachlorobenzene, and chlorophenoxy compounds. Pure pentachlorophenol is typically ≥98% pure with very low levels of CDDs and CDFs.

Technical-grade pentachlorophenol typically contains 85–90% pentachlorophenol. Two commonly used commercial-grade pentachlorophenols, Dowicide EC-7 (EC-7) and Dow PCP DP-2 (DP-2), are typically 90% pentachlorophenol and contain lower levels of CDDs and CDFs than technical-grade pentachlorophenol. A number of animal studies evaluated potential differences in the toxicity of pure pentachlorophenol, technical-grade pentachlorophenol, and/or commercial-grade pentachlorophenol. These studies demonstrate that some of the effects observed for technical-grade pentachlorophenol are due to the contaminants rather than the pentachlorophenol and that the contaminant may influence pentachlorophenol potency. NTP (1989) analyzed the samples of pure pentachlorophenol, technical-grade pentachlorophenol, EC-7, and DP-2; the results of these analyzes are presented in Table 2-1.

Table 2-1. Analysis of Impurities Present in Pentachlorophenol Used in NTP (1989) Studies

Contaminant	Pure	Technical grade	EC-7[a]	DP-2
Dichlorophenol	–	–	–	0.0013%[b]
Trichlorophenol	<0.01%	0.01%	0.007%[c]	0.044%[d]
Tetrachlorophenol	1.4%	3.8%	9.4%	7.0%[e]
Hexachlorobenzene	10 ppm	50 ppm	65 ppm	15 ppm
Tetrachlorodibenzodioxin	<0.08 ppm	–	<0.04 ppm	–
Hexachlorodibenzodioxin	<1 ppm	10.1 ppm	0.19 ppm	0.59 ppm
Heptachlorodibenzodioxin	–	296 ppm	296 ppm	28 ppm
Octachlorodibenzodioxin	<1 ppm	1,386 ppm	1,386 ppm	173 ppm
Pentachlorodibenzofuran	–	1.4 ppm	1.4 ppm	–
Hexachlorodibenzofuran	–	9.9 ppm	9.9 ppm	12.95 ppm
Heptachlorodibenzofuran	–	88 ppm	88 ppm	172 ppm
Octachlorodibenzofuran	–	43 ppm	43 ppm	320 ppm
Heptachlorohydroxydiphenyl ether	0.01%	0.11%[f]	0.11%	0.05%[f]
Octachlorohydroxydiphenyl ether	0.09%	1.91%	1.91%	1.41%
Nonachlorohydroxydiphenyl ether	0.21%	3.56%	3.56%	2.21%
Hexachlorohydroxydibenzofuran	0.11%	0.16%	0.16%	0.07%
Heptachlorohydroxydibenzofuran	0.22%	0.47%	0.47%	0.31%
Hexachlorohydroxybiphenyl and heptachlorohydroxybiphenyl	--	--	--	Detected[g]

[a]Four unidentified impurities with concentrations of 0.14, 0.057, 0.045, and 0.035 ppm were also detected.
[b]Probably the 2,4-isomer.
[c]Identified as the 2,3,6-siomer; another isomer was believed to be present but not identified.
[d]Probably the 2,4,5-isomer.
[e]Probably the 2,3,4,6-isomer.
[f]Includes octachlorodiphenyl ether.
[g]Two isomers each of hexachlorohydroxybiphenyl and heptachlorohydroxybiphenyl.

Source: NTP 1989

The health effects of pentachlorophenol have been evaluated in epidemiological and laboratory animal studies. As illustrated in Figure 2-1, most of the health effects data come from oral exposure studies in animals and inhalation studies in humans. Animal data are available for most health effect categories (no dermal effects data are available) and all exposure duration categories. The most examined endpoints were body weight (approximately 60% of the animal studies examined this endpoint), hepatic (approximately 40%), and immunological (approximately 30%). One inhalation exposure study and one dermal exposure study in experimental animals were identified. A number of observational epidemiological studies examined most endpoints. Interpretation of many of the human studies is limited by the small number of subjects (many are case reports of individuals), poor exposure information, and

exposure to other chemicals. Some studies have suggested associations between pentachlorophenol exposure and an adverse health outcome; most of the studies are cross-sectional in design and do not establish causality.

The human and animal studies suggest several sensitive targets of pentachlorophenol toxicity (see Appendix C for details on the systematic review):

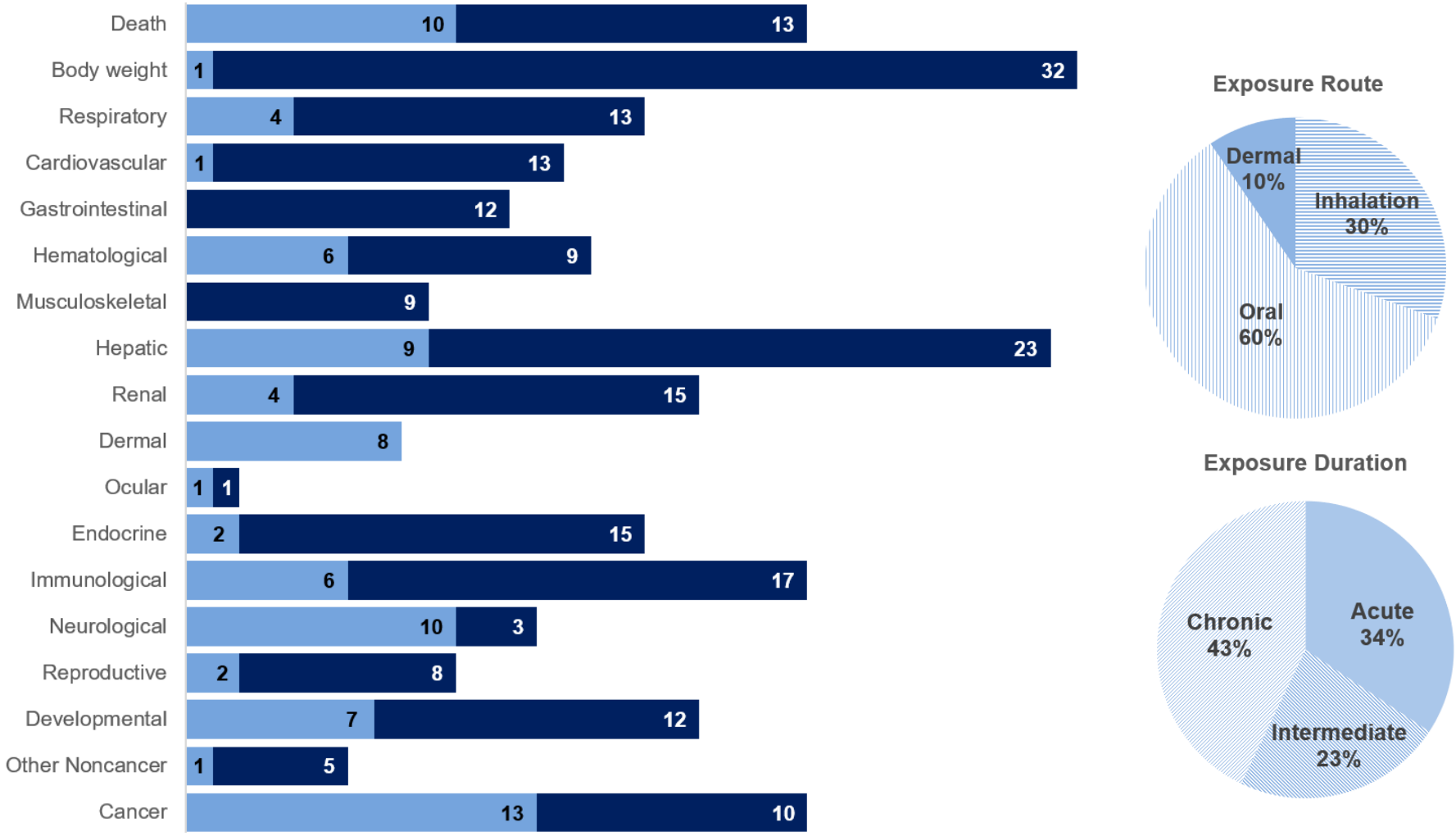
- **Hepatic Endpoints:** Hepatic effects are a presumed health effect for humans based on limited evidence in humans and strong evidence in rats, mice, and dogs exposed to pure pentachlorophenol, commercial-grade pentachlorophenol, and/or technical-grade pentachlorophenol. The observed effects include increases in liver weight, hepatocellular hypertrophy, hepatocellular degeneration and necrosis, and chronic inflammation.

- **Developmental Endpoints:** Developmental effects are a presumed health effect for humans based on limited evidence in humans and strong evidence in animals in rats. Developmental effects include increased resorptions, decreases in litter size, and decreases in fetal/pup body weight in animals exposed to pure pentachlorophenol or technical-grade pentachlorophenol.

Other adverse effects have been reported including gastrointestinal irritation, hematological alterations, and impaired immune responses. However, these effects have not been consistently observed across studies or were attributed to exposure to pentachlorophenol contaminants.

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

Most studies examined the potential body weight, hepatic, and immunological effects of pentachlorophenol
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 100 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Bekhouche et al. 2019									**Purity not reported**
1	Rat (Wistar) 6F	2 weeks (GW)	0, 20	BC, BI, HP	Hepatic		20		Increased serum AST and ALT; hepatocellular necrosis, binucleated and pyknotic hepatocytes, dilation and congestion of the centrilobular vein and sinusoids
Bernard and Hoberman 2001									**Tech (89%)**
2	Rat (Sprague-Dawley) 25F	GDs 6–15 (GO)	0, 10, 30, 80	CS, BW, FI, DX	Bd wt	30	80		Decreased maternal body weight (21% lower than controls on GDs 6–16)
					Develop	30		80	Increased resorptions, decreased fetal body weights and increased incidences of soft tissue (slight to moderate dilation of the kidneys) and skeletal ossification, malformations and variations
Deichmann et al. 1942									**Tech (purity not reported)**
3	Rat (Wistar) 60NS	Once (GO)	NS	LE, CS	Death			78	LD_{50}
Deichmann et al. 1942									**Tech NaPCP**
4	Rat (Wistar) 60NS	Once (G)	NS	LE, CS	Death			210.6	LD_{50}
Schwetz et al. 1974									**Pure (>98%)**
5	Rat (Sprague-Dawley) 15–33F	GDs 6–15 (GO)	0, 5, 15, 30, 50	BW, DX	Bd wt	15		30	74% decrease in maternal weight gain
					Develop		5[b]	30	Delayed ossification of skull at 5 mg/kg/day; increased incidence of subcutaneous edema and skeletal anomalies at ≥15 mg/kg/day; increased incidence of fetal resorptions (97% of fetuses resorbed) and marked decrease in fetal body weights at ≥30 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Schwetz et al. 1974									**Pure (>98%)**
6	Rat (Sprague-Dawley) 16F	GDs 8–11 (GO)	0, 30	BW, DX	Bd wt			30	67% decrease in maternal body weight gain on GDs 6-21
					Develop			30	Increased incidence fetal resorptions (64% of litters affected); skeletal and soft tissue anomalies; 42% decreased fetal body weight
Schwetz et al. 1974									**Pure (>98%)**
7	Rat (Sprague-Dawley) 20F	GDs 12–15 (GO)	0, 30	BW, DX	Bd wt	30			
					Develop		30		Soft tissue and skeletal anomalies; decreased fetal body weight and crown-rump length
Schwetz et al. 1974									**Tech (88.4% pure)**
8	Rat (Sprague-Dawley) 15–19F	GDs 6–15 (GO)	0, 5, 15, 30, 50	BW, DX	Bd wt	15		30	Decreased maternal body weight gain (25 and 45% in the 30 and 50 mg/kg/day groups, respectively)
					Develop	5		15	Fetal resorptions (64% of litters affected), subcutaneous edema, lumbar spurs
Schwetz et al. 1974									**Tech (88.4% pure)**
9	Rat (Sprague-Dawley) 19F	GDs 8–11 (GO)	0, 30	BW, DX	Bd wt		30		27% decrease in maternal weight gain on GDs 6-21
					Develop			30	Increased incidence of fetal resorptions; skeletal and soft tissue anomalies; 25% decreased fetal body weight
Schwetz et al. 1974									**Tech (88.4% pure)**
10	Rat (Sprague-Dawley) 17F	GDs 12–15 (GO)	0, 30	BW, DX	Bd wt	30			
					Develop		30		Increased incidence of sternebrae variations

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
St. Omer and Gadusek 1987									**Tech (purity not reported)**
11	Rat (Sprague-Dawley) 45–75B	Once (G)	31-449	LE, CS	Death			50	Age-specific LD_{50} values: 50 mg/kg at age 10 days, 108 mg/kg at 20 days, 220–230 mg/kg at 25–50 days, 120 mg/kg at 70 days, 80 mg/kg at 127–134 days
Borzelleca et al. 1985									**Pure (approx. 99%)**
12	Mouse (ICR) NS B	Once (G)	NS	LE, CS	Death			117 F 177 M	LD_{50}
Chen et al. 2013a									**Pure (>99%)**
13	Mouse (BALB/c) 4–5F	7 or 14 days 3 times/week (GO)	0, 6	BW, OW, IX	Bd wt	6			
					Immuno		6		Increased IL-2, IL-5, and IL-10 levels and decreased OVA-specific antibodies (IgG and IgM)
Holsapple et al. 1987									**EC-7 (90.4% pure)**
14	Mouse (B6C3F1) 8F	14 days (GO)	100	IX	Immuno	100			
Holsapple et al. 1987									**Tech (purity not reported)**
15	Mouse (B6C3F1) 8F	14 days (GO)	10, 30, 100	IX	Immuno		10[c]		Decreased response to sRBC
Kerkvliet et al. 1985a									**Tech (86% pure)**
16	Mouse (C57BL/6) 6 NS	1–2 days (GO)	15, 30, 60	OW, CS, IX	Immuno		83[c]		50% decrease in splenic response to sRBC
Kerkvliet et al. 1985a									**Pure (>99%)**
17	Mouse (C57BL/6) 6 NS	1–2 days (GO)	0, 15, 30, 60	OW, IX	Immuno	60			

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Renner et al. 1986									**Pure (99%)**
18	Mouse (NMRJ) 10M, 10F	Once (GO)	NS	LE, CS	Death			134 F 129 M	LD_{50}
Umemura et al. 1996									**Pure (98.6%)**
19	Mouse (B6C3F1) 30M	2 weeks (F)	0, 41, 86, 200	BC, BI, HP	Hepatic		41		Increased liver weight and severe hepatocyte swelling
White and Anderson 1985									**Tech (90.4% pure)**
20	Mouse (B6C3F1) NS F	14 days (GO)	0, 10, 30, 100	IX	Immuno	30	100[c]		Inhibition of compliment activity
White and Anderson 1985									**EC-7 (90.4% pure)**
21	Mouse (B6C3F1) NS F	14 days (GO)	0, 100	IX	Immuno	100			
Bernard et al. 2001									**Tech (88-89% pure)**
22	Rabbit (New Zealand) 20F	GD 6–18 (GO)	0, 7.5, 15, 30	BW, DX	Bd wt	7.5	15	30	Transient decrease in maternal body weight gain on GDs 9–12 at 15 mg/kg/day and maternal weight loss at 30 mg/kg/day
					Develop	30			
INTERMEDIATE EXPOSURE									
Bernard et al. 2002									**Tech (89% pure)**
23	Rat (Sprague-Dawley) 30M, 30F	P0: 70 days premating, and through gestation and lactation (GO)	0, 10, 30, 60	CS, BW, FI, HP, RX, DX	Bd wt		60		Decreased body weight gain 10-12% in P0 and 28–29% in F1
					Hepatic		10		Increased absolute and relative liver weight and hepatocellular hypertrophy ≥10 mg/kg/day; hepatocellular necrosis at ≥30 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Repro	60 F			
						10 M	30 M		Decreased average testicular spermatid counts in F1 males; decreased fertility at 60 mg/kg/day
					Develop		10	60	Decreased pup body weight on LDs 1 and 4 in F1 pups at 10 mg/kg/day and LDs 1, 4, and 28 at 30 and 60 mg/kg/day; decreased pup litter size and survival at 60 mg/kg/day
Blakley et al. 1998									**Pure (>99%)**
24	Rat (Fischer-344) 10M	28 days 2 times/week (GO)	0, 2.0	BW, IX, OW	Immuno		2		Enhanced lymphocyte blastogenesis, suppressed antibody response against sRBC
Exon and Koller 1982									**Tech (85% pure)**
25	Rat (Sprague-Dawley) 12–14F	10 week premating throughout gestation and lactation (F)	0, 0.5, 5, 50	BW, BC, HE, DX	Bd wt	50			
					Hemato	50			
					Develop		50		Decreased litter size
Jekat et al. 1994									**Tech (85-90% pure)**
26	Rat (Wistar) 8F	28 days (G)	0, 3, 30	BW, OW, BC	Endocr		3		Decreased serum free T4 (50%) and TSH (30%) levels and serumT4:T3 ratio (60%); decreased serum T3 (50%) and free T3 (55%) levels at 30 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Kimbrough and Linder 1978									**Tech (85% pure)**
27	Rat (Sherman) 10M, 10F	8 months (F)	M: 0, 1, 6, 32 F: 0, 1, 7, 48	BW, OW, FI, GN, HP, CS, BI	Bd wt	6 M	32 M		Decreased body weight in males at 32 mg/kg/day (15%) and females at 48 mg/kg/day (17%)
					Resp	32 M			
					Cardio	32 M			
					Hepatic		1[c]		Centrilobular hepatocyte hypertrophy in males and females at ≥1 mg/kg/day and periportal fibrosis at 32/48 mg/kg/day
					Repro	32 M			
Kimbrough and Linder 1978									**Pure (>99%)**
28	Rat (Sherman) 10M, 10F	8 months (F)	M: 0, 1, 6, 36 F: 0, 1, 7, 45	BW, OW, FI, GN, HP, CS, BI	Bd wt	6 M	36 M		10% decreased body weight in males at 36 mg/kg/day and females at 45 mg/kg/day
					Resp	36 M			
					Cardio	36 M			
					Gastro	36 M			
					Hepatic	6 M	36 M		Centrilobular hepatocyte hypertrophy in males at 36 mg/kg/day and females at 45 mg/kg/day
					Renal	36 M			
					Endocr	36 M			
					Repro	36 M			
Knudsen et al. 1974									**Tech (purity not reported)**
29	Rat (NS) 10M, 10F	12 weeks (F)	M: 0, 1.5, 3, 12 F: 0, 2.4, 4.8, 19	BW, OW, FI, GN, HP, BC, BI, OF	Bd wt	12 M			
					Resp	12 M			
					Cardio	12 M			
					Gastro	12 M			
					Hemato	19 F			
						1.5 M	3 M		Decreases in hemoglobin and RBC levels in males

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic	19 F			
						1.5 M	3 M		Centrilobular vacuolization in males
					Renal	2.4 F	4.8 F		Decreased calculi at corticomedullary junction in females
						12 M			
					Endocr	12 M			
					Neuro	12 M			
					Repro	12 M			
NTP 1999; Chhabra et al. 1999									**Pure (99%)**
30	Rat (Fischer-344) 10M, 10F	28 days (F)	0, 20, 40, 75, 150, 270	BW, CS, FI, GN, HP, OW	Death			270	3/20 animals died
					Bd wt	75		150	35 and 70% decrease in body weight gain in males and females, respectively; weight loss at 270 mg/kg/day
					Resp	270			
					Cardio	270			
					Gastro	270			
					Musc/skel	270			
					Hepatic	20 M	40 M		Increased liver weight and incidence of hepatocyte degeneration in males ≥40 mg/kg/day and in females at ≥75 mg/kg/day
					Renal	270			
					Endocr	270			
Schwetz et al. 1978									**EC-7 (90.4% pure)**
31	Rat (Sprague-Dawley) 10M, 20F	62 days premating, during mating, gestation, and lactation (F)	0, 3, 30	BW, RX, DX	Bd wt	3 F	30 F		10% decrease in maternal body weight
						30 M			
					Develop	3		30	Decreased litter size and neonatal survival; decreased neonatal body weight and growth

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Welsh et al. 1987									**Pure (>99%)**
32	Rat (Sprague-Dawley) 20M, 20F	181 days pre-mating, during mating, and through GD 20 (F)	0, 4, 13, 43	BW, RX, DX	Bd wt	13 F		43 F	76% decrease in maternal weight gain
					Repro	43			
					Develop	4	13	43	Decreased fetal body weight and crown-rump length, increased skeletal variations; increased resorptions at 13 mg/kg/day; fetal lethality at 43 mg/kg/day
Kerkvliet et al. 1982									**Tech (86% pure)**
33	Mouse (C57BL/6) NS M	10–12 weeks (F)	0, 9, 90	CS, BW, HP, IX	Bd wt	90			
					Hepatic		90		Necrosis
					Renal	90			
					Endocr	90			
					Immuno	9	90		Altered immune response
Kerkvliet et al. 1982									**Pure (>99%)**
34	Mouse (C57BL/6) NS M	10–12 weeks (F)	0, 9, 90	CS, BW, HP, IX	Bd wt	90			
					Hepatic		90		Necrosis
					Renal	90			
					Endocr	90			
					Immuno	90			
Kerkvliet et al. 1985a									**Tech (86% pure)**
35	Mouse (B6C3F1) NS	6 weeks (F)	0, 1.8, 45	BW, OW, IX	Immuno		1.8[c]		Decreased antibody response to sRBC
Kerkvliet et al. 1985a									**Tech (86% pure)**
36	Mouse (DBA/2) 6 NS	6 weeks (F)	0, 1.8, 45	BW, OW, CS, IX	Immuno	1.8	45[c]		Decreased response to sRBC

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Kerkvliet et al. 1985b									**Tech (86% pure)**
37	Mouse (C57BL/6) 12F	8 weeks (F)	0, 20, 50, 100	BW, OW, IX	Immuno		50		Decreased lymphocyte proliferative response to alloantigen
NTP 1989									**Tech (90.4% pure)**
38	Mouse (B6C3F1) 19M, 15F	30 days (F)	M: 0, 4, 20, 100, 530, 4400; F: 0, 5, 30, 140, 640, 3600	CS, BW, BC, HE, UR, OW, HP	Death			3,600 F 4,400 M	Deaths in 14/19 males at 4,400 mg/kg/day and 7/15 females at 3,600 mg/kg/day
					Bd wt	640 F		3,600 F	Weight loss; body weights 38.5% and 28.4% in males at 4,400 mg/kg/day and females at 3,600 mg/kg/day
					Hepatic	20 M	100 M		liver lesions (cytomegaly, karyomegaly, nuclear atypia, degeneration, or necrosis) in males at 100 mg/kg/day and females at 140 mg/kg/day
					Other noncancer	100 M	530 M		Decreased body temperature in males at 530 mg/kg/day and females at 640 mg/kg/day
NTP 1989									**EC-7 (90.4% pure)**
39	Mouse (B6C3F1) 19M, 15F	30 days (F)	M: 0, 4, 20, 100, 1020, 3000; F: 0, 6, 30, 140, 850, 4000	CS, BW, BC, HE, UR, OW, HP	Death			850 F 1,020 M	Deaths in 47% males at 1,020 mg/kg/day and 20% females at 850 mg/kg/day
					Bd wt	100 M	1,020 M		13% lower terminal body weight
					Hepatic	140 F	850 F		Liver lesions (cytomegaly, karyomegaly, nuclear atypia, degeneration, or necrosis) in males at 1,020 mg/kg/day and females at 850 mg/kg/day
					Other noncancer	140 F	850 F		Decreased body temperature in males at 1,020 mg/kg/day and females at 850 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1989									**Pure (98.6%)**
40	Mouse (B6C3F1) 19M, 15F	30 days (F)	M: 0, 4, 23, 100, 600, 3000; F: 0, 6, 30, 140, 850, 4500	CS, FI, BW, BC, HE, UR, OW, HP	Death			4,500 F 3,000 M	100% mortality in males at 3,000 mg/kg/day and females at 4,500 mg/kg/day
					Bd wt	600 M			
					Hepatic	23 M	100 M		Liver lesions (cytomegaly, karyomegaly, nuclear atypia, degeneration, or necrosis) in males at 100 mg/kg/day and females at 140 mg/kg/day
					Other noncancer	100 M	600 M		Decreased body temperature in males at 600 mg/kg/day and females at 850 mg/kg/day
NTP 1989									**Tech (90.4% pure)**
41	Mouse (B6C3F1) 25M, 10F	6 months (F)	M: 0, 50, 380, 550; F: 0, 70, 200, 760	CS, FI, BW, BC, HE, UR, OW, HP, IX, NX	Death			760 F 550 M	100% mortality in males at 550 mg/kg/day and females at 760 mg/kg/day
					Bd wt	200 F			
					Resp	550 M			
					Cardio	550 M			
					Gastro	550 M			
					Hemato	550 M			
					Musc/skel	550 M			
					Hepatic		50 M		Hepatocytomegaly, pigmentation, nuclear alterations, necrosis in males at 50 mg/kg/day and females at 70 mg/kg/day
					Renal	550 M			
					Endocr	550 M			
					Immuno		50 M		Decreased response to sRBC in males at 50 mg/kg/day and females at 70 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Neuro				Dose-related increases in motor activity and startle response were observed in male and female mice after 26 weeks of exposure; investigators did not provide dose-response data
					Repro	550 M			
NTP 1989									**EC-7 (90.4% pure)**
42	Mouse (B6C3F1) 25M, 10F	6 months (F)	M: 0, 50, 150, 330; F: 0, 64, 200, 500	CS, FI, BW, BC, HE, UR, OW, HP, IX, NX	Bd wt	150 M	330 M		Lower terminal body weights in males (13%) at 330 mg/kg/day and females (11%) at 500 mg/kg/day
					Resp	50 M	150 M		Nasal mucosal metaplasia/goblet cell hyperplasia in males at 150 mg/kg/day and females at 200 mg/kg/day
					Cardio	330 M			
					Hemato	330 M			
					Musc/skel	330 M			
					Hepatic		50 M		Hepatocytomegaly, pigmentation, nuclear alterations, necrosis in males at 50 mg/kg/day and females at 64 mg/kg/day
					Renal	330 M			
					Endocr	330 M			
					Immuno	330 M			
					Neuro				Dose-related increases in motor activity and startle response were observed in female mice after 26 weeks of exposure; investigators did not provide dose-response data
					Repro	330 M			
NTP 1989									**DP-2 (91.6% pure)**
43		6 months (F)		CS, FI, BW, BC, HE, UR,	Death			580 M	2/10 deaths
					Bd wt	380 F			

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
	Mouse (B6C3F1) 25M, 10F		M: 0, 50, 140, 580; F: 0, 70, 200, 380	OW, HP, IX, NX	Resp	380 F			
					Cardio	380 F			
					Gastro	380 F			
					Hemato	380 F			
					Musc/skel	380 F			
					Hepatic		50 M		Hepatocytomegaly, pigmentation, nuclear alterations, necrosis in males at ≥50 mg/kg/day and females at ≥70 mg/kg/day
					Renal	380 M			
					Endocr	380 M			
					Immuno	200 F	380 F[c]		Decreased response to sRBC in females at 380 mg/kg/day and 580 mg/kg/day in males
					Neuro				Dose-related increases in motor activity and startle response were observed in female mice after 26 weeks of exposure; investigators did not provide dose-response data
					Repro	380 F			

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1989									**Pure (98.6%)**
44	Mouse (B6C3F1) 25M, 10F	6 months (F)	M: 0, 110, 230, 380; F: 0, 67, 170, 540	CS, FI, BW, BC, HE, UR, OW, HP IX, NX	Bd wt	380 M			
					Resp	230 M 540 F	380 M		Nasal mucosal metaplasia/goblet cell hyperplasia in males
					Cardio	380 M			
					Gastro	380 M			
					Hemato	380 M			
					Musc/skel	380 M			
					Hepatic		67 F		Hepatocytomegaly, pigmentation, nuclear alterations, necrosis in males at ≥110 mg/kg/day and females at ≥67 mg/kg/day
					Renal	380 M			
					Endocr	380 M			
					Immuno	380 M			
					Neuro				Dose-related increases in motor activity and startle response were observed in female mice after 26 weeks of exposure; investigators did not provide dose-response data
					Repro	380 M			
Umemura et al. 1996									**Pure (98.6%)**
45	Mouse (B6C3F1) 30M	4 weeks (F)	41, 86, 200	BC, BI, HP	Hepatic		41		Increased liver weight and severe hepatocyte swelling
Umemura et al. 2006									**Pure (98.6%)**
46	Mouse (ICR) 5M	4 weeks (F)	0, 30, 60, 120, 240	BC, OW, HP	Hepatic		30		Moderate cytoplasmic hyperplasia at ≥30 mg/kg/day; increases in serum ALT and AST and slight to moderate necrosis at ≥120 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Beard et al. 1997									**Purity not reported**
47	Mink (NS) 10F	3 weeks pre-breeding through weaning 1 time/day (F)	1	BC, BW, DX GN, HP, RX	Repro		1		Increased severity of cystic uteri, decreased acceptance of second mating, decreased birth rate
CHRONIC EXPOSURE									
NTP 1999; Chhabra et al. 1999									**Pure (99%)**
48	Rat (Fischer-344) 50M, 50F	105 weeks (F)	0, 10, 20, 30	CS, BW, FI, GN, HP	Bd wt	20	30		10 and 14% decrease in body weight gain in males and females, respectively
					Resp	30			
					Cardio	30			
					Gastro	30			
					Musc/skel	30			
					Hepatic	30 F			
						10 M	20 M		Cystic hepatocyte degeneration
					Renal	30			
					Endocr	30			
NTP 1999; Chhabra et al. 1999									**Pure (99%)**
49	Rat (Fischer-344) 60M, 60F	52 weeks followed by 52 week recovery period (F)	0, 60	CS, BW, FI, GN, HP	Bd wt		60		17 and 22% decrease in body weight gain in males and females, respectively, at end of exposure period
					Resp	60			
					Cardio	60			
					Gastro	60			
					Musc/skel	60			
					Hepatic	60 F	60 M		Centrilobular hepatocyte hypertrophy and hepatocyte cytoplasmic vacuolization (males only)
					Renal	60			

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Endocr	60			
					Cancer			60 M	Mesotheliomas and nasal squamous cell carcinomas
Schwetz et al. 1978									**EC-7 (90.4% pure)**
50	Rat (Sprague-Dawley) 25M, 25F	22–24 months (F)	0, 1, 3, 10, 30	BW, OW, FI, GN, HP, BC, CS, UR	Bd wt	10 F 30 M	30 F		12% decrease in body weight gain in females
					Hepatic		10		Elevated ALT
					Renal	30			
NTP 1989									**Tech (90.4% pure)**
51	Mouse (B6C3F1) 50M,50F	2 years (F)	M: 0, 18, 35; F: 0, 17, 35	CS, FI, BW, OW, GN, HP	Bd wt	17 F 35 M	35 F		5–13% lower body weights in females
					Resp	35			
					Cardio	35			
					Hemato		18 M		Diffuse hematopoietic cells in spleen in males at ≥18 mg/kg/day and females at 35 mg/kg/day
					Musc/skel	35			
					Hepatic		17 F		Inflammation, necrosis, pigmentation in males at ≥18 mg/kg/day and females at ≥17 mg/kg/day
					Renal	35			
					Endocr	35 F	18 M		Adrenal gland hyperplasia in males
					Repro	35			
					Other noncancer	17 F	35 F		Cystic hyperplasia in mammary gland
					Cancer			18 M	Hepatocellular adenomas and adrenal pheochromocytoma in males at ≥18 mg/kg/day; hepatocellular carcinoma, and hemangiosarcomas in the liver and spleen in males at 35 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1989									**EC-7 (90.4% pure)**
52	Mouse (B6C3F1) 50M, 50F	2 years (F)	M: 0, 18, 37, 118; F: 0, 17, 34, 114	CS, FI, BW, OW, GN, HP	Bd wt	17 F 118 M	34 F		Decreases in body weight female mice at 34 mg/kg/day (6–12%) and 114 (17–22%) mg/kg/day
					Resp	34 F	114 F		Inflammation of nasal mucosa and focal metaplasia of olfactory epithelium in males at 118 mg/kg/day and females at 114 mg/kg/day
					Cardio	114 F			
					Gastro	114 F			
					Hemato	114 F			
					Musc/skel	114 F			
					Hepatic		17 F		Inflammation, necrosis, pigmentation in males at ≥18 mg/kg/day and females at ≥17 mg/kg/day
					Renal	114 F			
					Endocr	114 F	18 M		Adrenal gland hyperplasia in males at 18 and 37 mg/kg/day
					Repro	114 F			
					Cancer			37 M	Hepatocellular adenomas and adrenal pheochromocytoma in males at ≥37 mg/kg/day, hepatocellular carcinoma in males at 118 mg/kg/day, and hemangiosarcomas in the liver and spleen and hepatocellular adenomas in females at 114 mg/kg/day

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
EPA 1997									**Tech (90.9%)**
53	Dog (Beagle) 4M, 4F	1 year (C)	0, 1.5, 3.5, 6.5	CS, BW, FI, OP, HE, BC, UR, GN, HP	Resp	6.5			
					Cardio	6.5			
					Gastro		1.5		Lymphocytic mucosal inflammation in the stomach
					Hemato	3.5 F 1.5 M	6.5 F 3.5 M		Decreased RBC count in males at 3.5 mg/kg/day and decreased hemoglobin at 6.5 mg/kg/day; in females, decreased RBC count, hemoglobin, and hematocrit at 6.5 mg/kg/day
					Hepatic		1.5 [d]		Increases in liver weight and minimal chronic inflammation; cytoplasmic vacuolation at ≥3.5 mg/kg/day and minimal necrosis at 6.5 mg/kg/day
					Renal	6.5			
					Ocular	6.5			
					Endocr	6.5			
					Neuro	6.5			
					Repro	6.5			

Table 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Beard and Rawlings 1998									**Purity not reported**
54	Mink (NS) F0: NS; F1: 8F, 6M; F2: 10F, 8M	3 generations (F)	1	BC, BW, CS, DX, GN, HP, RX	Bd wt	1			
					Endocr		1		Decreased serum thyroxine levels
					Repro	1			

[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 gender are presented.
[b]Used to derive an acute-duration oral MRL of 0.005 mg/kg/day; LOAEL divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).
[c]Effects are likely due to a contaminant rather than pentachlorophenol.
[d]Used to derive al chronic-duration oral MRL of 0.005 mg/kg/day; LOAEL divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Principal studies for the MRLs.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; B = both sexes; BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; (C) = capsule; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental effects; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; FX = fetal toxicity; (G) = gavage; (GO) = gavage in oil; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; IX= immune function; LD = lactation day; LD_{50} = dose producing 50% death; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NX = neurological function; NS = not specified; OF = organ function; OP = ophthalmology; OW = organ weight; RBC = red blood cell; Repro = reproductive; Resp = respiratory; RX = reproductive function; sRBC = sheep red blood cell; UR = urinalysis

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

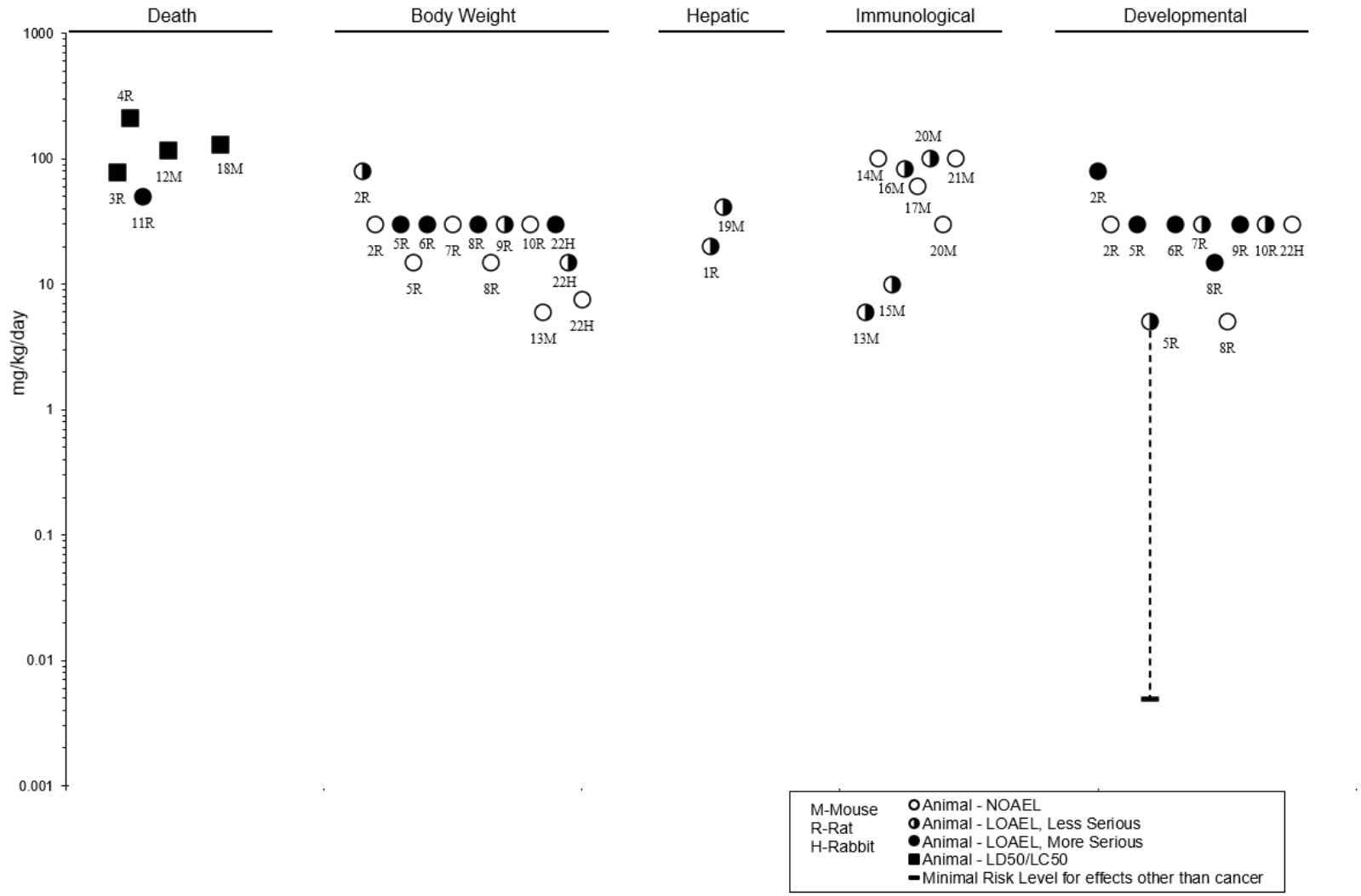


Figure 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral
Intermediate (15-364 days)

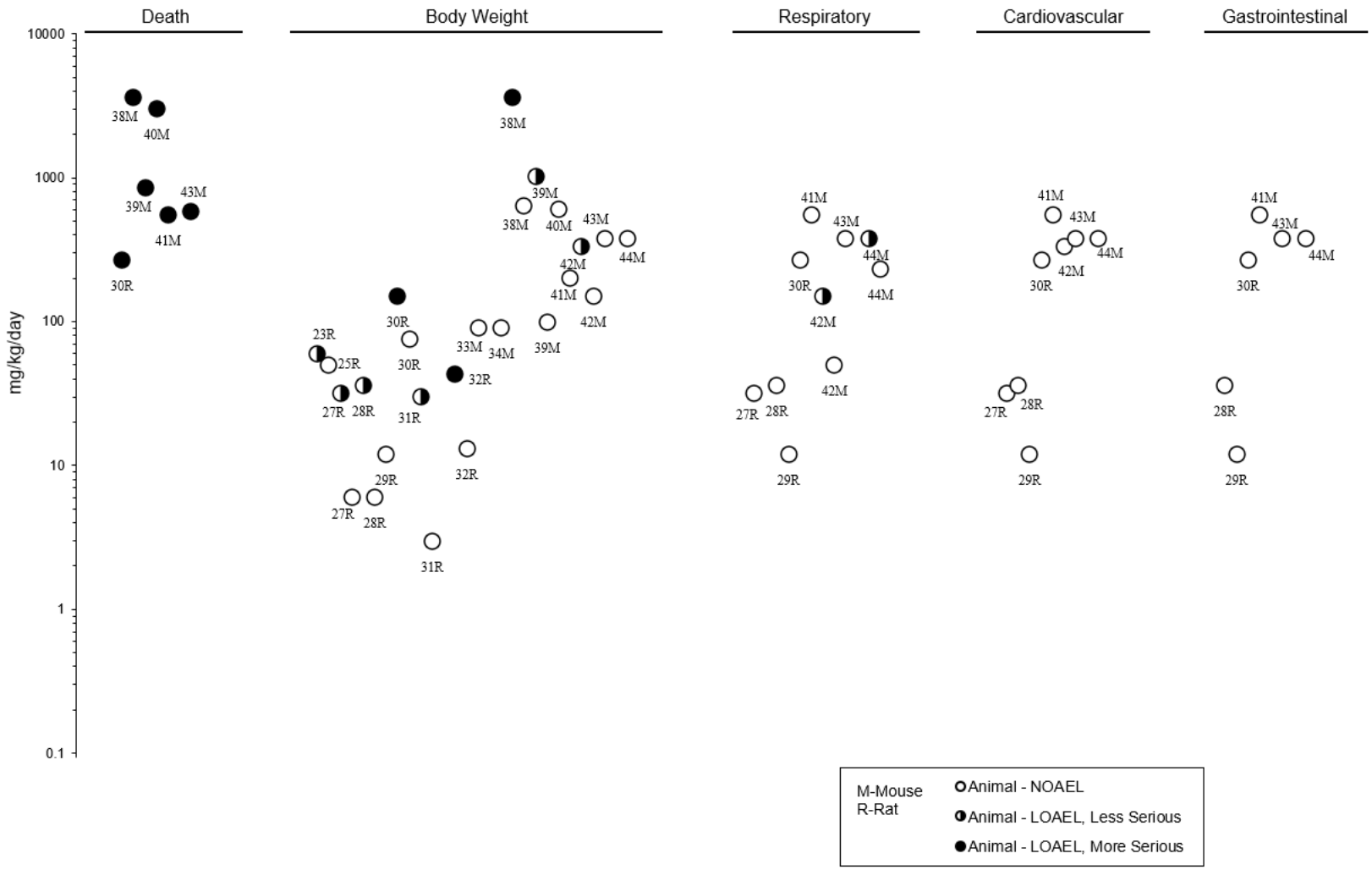


Figure 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral
Intermediate (15-364 days)

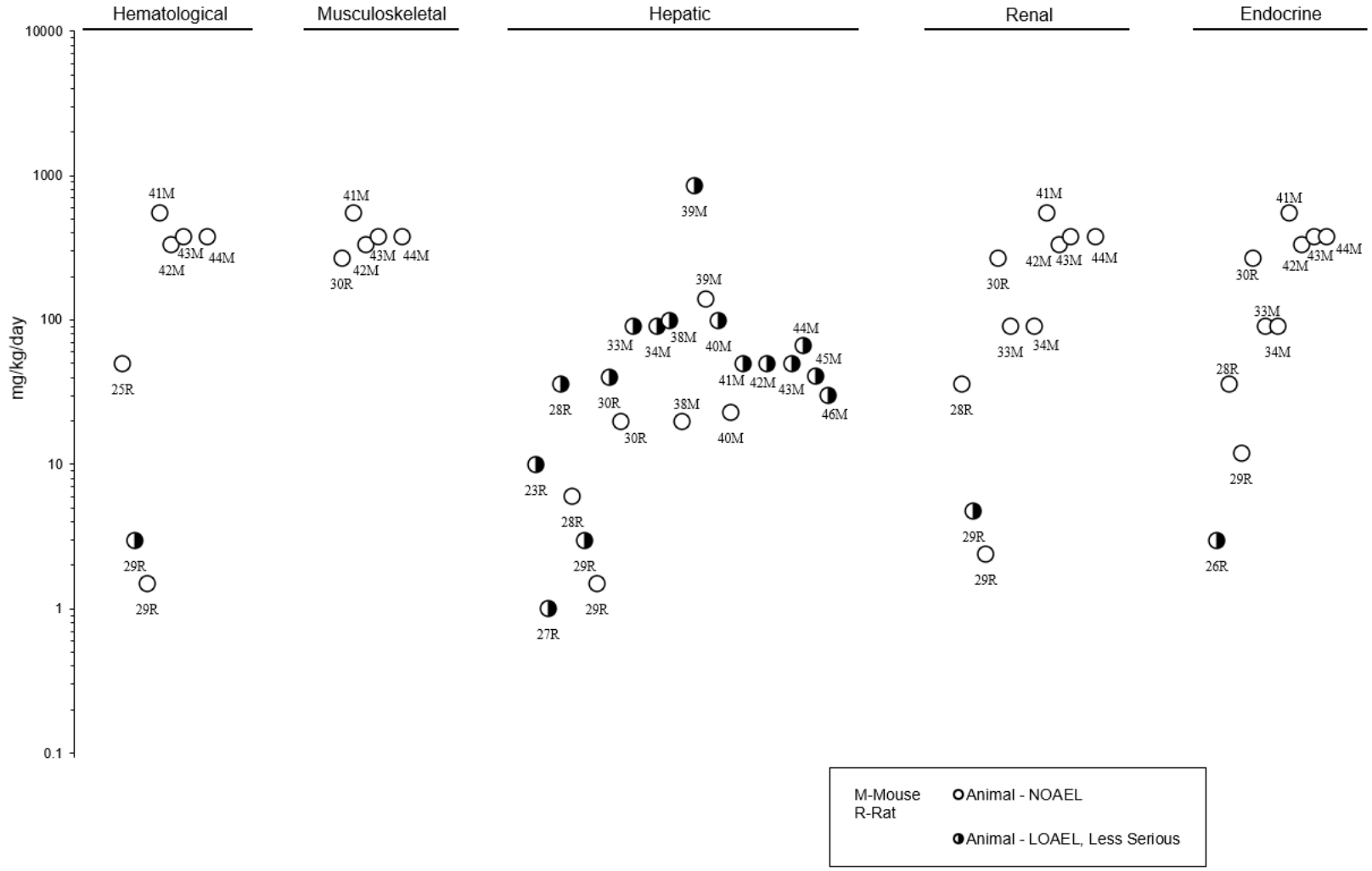


Figure 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral
Intermediate (15-364 days)

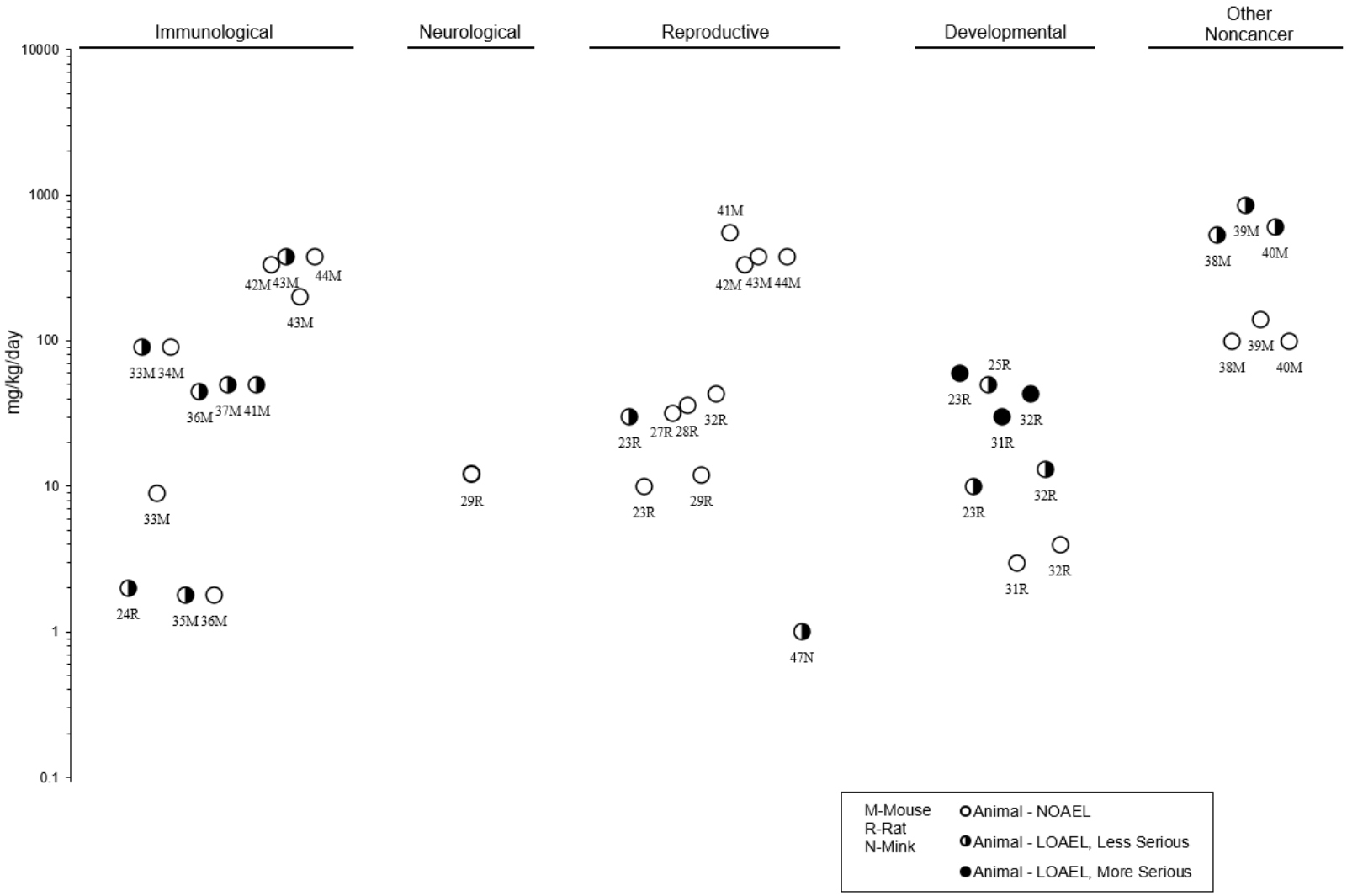


Figure 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral
Chronic (≥365 days)

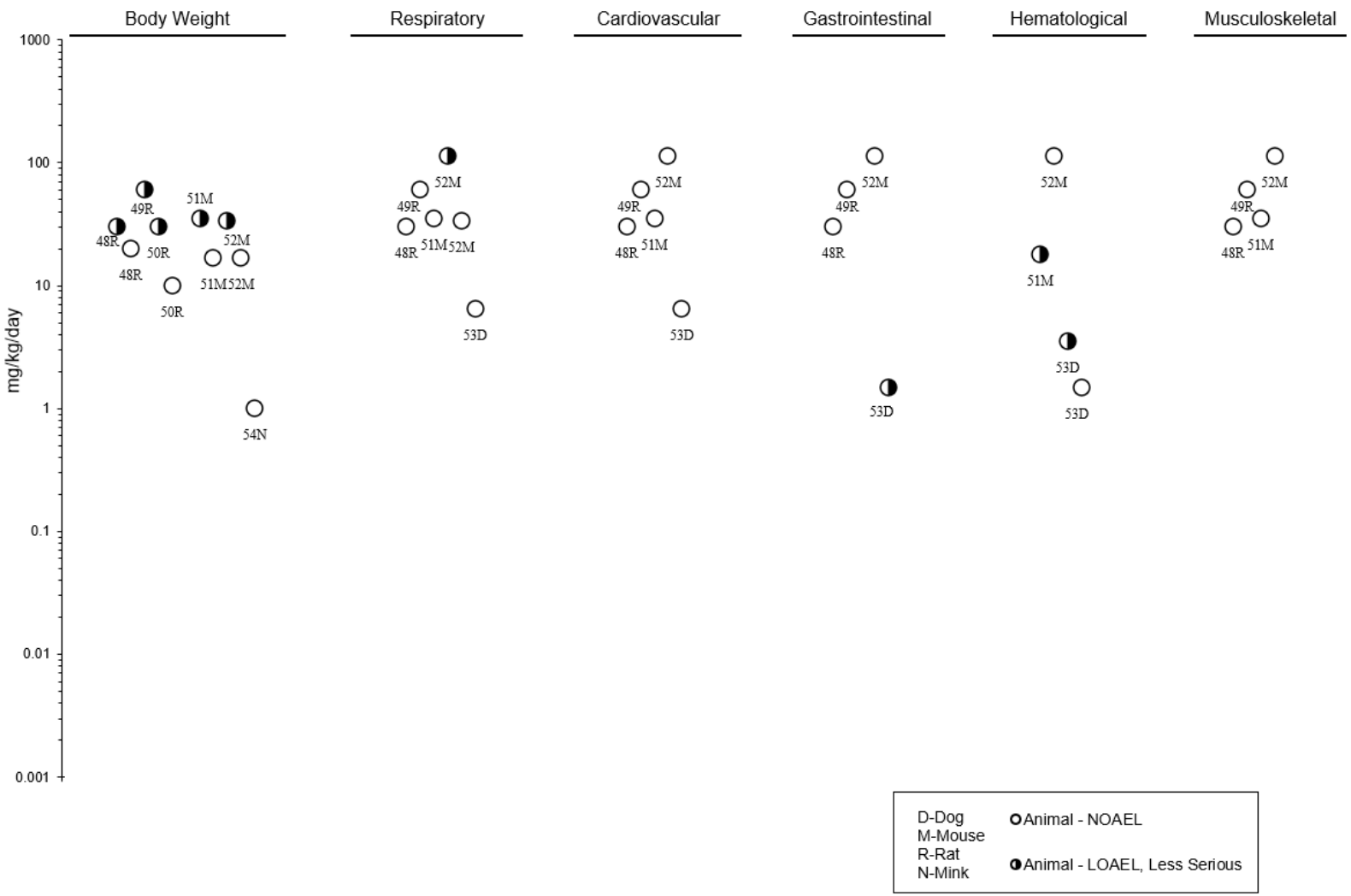
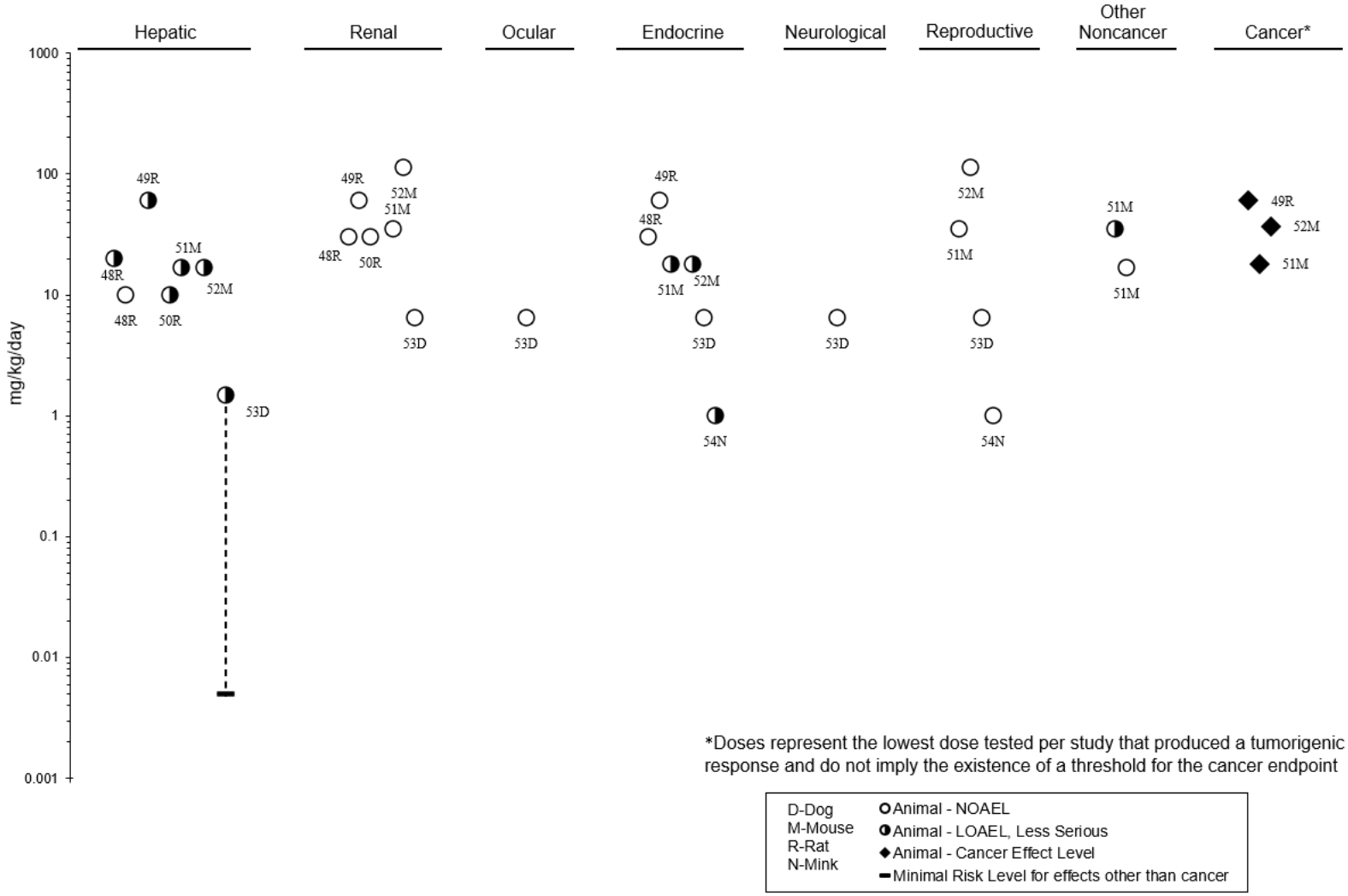


Figure 2-2. Levels of Significant Exposure to Pentachlorophenol – Oral
Chronic (≥365 days)



2.2 DEATH

Deaths have been reported in case reports of occupational exposure to pentachlorophenol dust (Gray et al. 1985). There are also reports of mixed dermal/inhalation exposure to formulations containing pentachlorophenol (Gordon 1956; Gray et al. 1985; Roberts 1963, 1981, 1983, 1990; Smith et al. 1996). Two deaths were reported in a case report of nine newborns exposed to pentachlorophenol in a mixture of synthetic phenolic derivatives used in the hospital laundry as an antimildew agent; pentachlorophenol was found in freshly laundered diapers and in the serum and urine of the infants (Smith et al. 1996). At autopsy, both infants showed fatty metamorphosis of the liver and one showed fatty vacuolar changes in the renal tubules. Several investigators reported examining a wood preserver, herbicide sprayers, or sawmill workers with a reported cause of death of hyperthermia, which presumably resulted from the uncoupling of oxidative phosphorylation by pentachlorophenol (Bergner et al. 1965; Gray et al. 1985; Menon 1958).

Studies in laboratory animals have reported deaths after single or multiple inhalation, oral, or dermal exposures. An LC_{50} of 14 mg/m^3 was reported in rats exposed to sodium pentachlorophenate aerosol for 45 minutes (Hoben et al. 1976b). Oral LD_{50} studies have found similar values across species but did find age-related differences. The LD_{50} values of 77.9–211 mg/kg in rats (Deichmann et al. 1942; St. Omer and Gadusek 1987) and 117–177 mg/kg in mice (Borzelleca et al. 1985; Renner et al. 1986) have been reported. Pre-weaned and mature rats have been reported to have lower oral LD_{50} values for technical-grade pentachlorophenol than juvenile rats (25–50 days old) (St. Omer and Gadusek 1987). The LD_{50} values were 50, 108, 220–230, 120, and 80 mg/kg in 10-, 20-, 25–50-, 70-, and 127–134-day-old rats, respectively.

Deaths were also seen in a 30-day oral range-finding study in mice (NTP 1989), a 28-day oral range-finding study in rats with highly purified pentachlorophenol (NTP 1999), and a 6-month oral study in mice (NTP 1989). At the highest dietary concentration tested (12,500 ppm) in the 30-day study in mice (NTP 1989), incidences of deaths were higher in animals fed pure pentachlorophenol (98.6% pure with <0.0002% CDDs and CDFs) and the purified EC-7 pentachlorophenol preparation (90% pure with <0.0002% CDDs and CDFs) than in animals fed technical-grade pentachlorophenol (90% pure with 0.18% CDDs and CDFs).

One report of death following dermal exposure in experimental animals was found in the reviewed literature (Deichmann et al. 1942). Eight out of 20 rabbits administered dermal applications of 4%

pentachlorophenol (purity not indicated) in fuel oil for 6–61 weeks died of unspecified causes. The vehicle contained other known toxic substances (e.g., polyaromatic hydrocarbons), which may have contributed to the lethal effects observed.

2.3 BODY WEIGHT

In a survey of 127 current and former timber sawmill workers, Walls et al. (1998) reported increases in weight loss in workers exposed to high levels of pentachlorophenol. The workers were assigned into three exposure categories based on duration of pentachlorophenol exposure, type of work, use of personal protection, and intensity of exposure; no air monitoring data were reported.

Decreases in body weight gain have not been consistently observed in oral exposure studies in laboratory animals. Significant (10%) decreases in body weight gain were observed in several oral exposure studies in which rats or mice were administered ≥32 mg/kg/day pure pentachlorophenol, EC-7, or technical-grade pentachlorophenol for intermediate or chronic durations to rats or mice (Kimbrough and Linder 1978; NTP 1989, 1999; Schwetz et al. 1978).

Decreases in maternal body weight gain were observed in rats administered 30 mg/kg/day pure pentachlorophenol or technical-grade pentachlorophenol on gestation days (GDs) 6–15 or 8–11, but not on GDs 12–15 (Schwetz et al. 1974) or 80 mg/kg/day technical-grade pentachlorophenol on GDs 6–15 (Bernard and Hoberman 2001); or in rabbits administered 15 mg/kg/day on GDs 6–18 (Bernard et al. 2001). Decreases in maternal body weight gain were also observed in rats exposed to ≥43 mg/kg/day pure pentachlorophenol prior to mating through GD 20 (Bernard et al. 2002; Welsh et al. 1987) or to 30 mg/kg/day EC-7 prior to mating and during gestation and lactation (Schwetz et al. 1978).

2.4 RESPIRATORY

In humans, chronic high-dose occupational exposure to pentachlorophenol causes inflammation of the upper respiratory tract and bronchitis (Baader and Bauer 1951; Klemmer et al. 1980). The purity of pentachlorophenol in these cases was not specified, and inhalation of pentachlorophenol contaminants (CDDs and CDFs) and other compounds (such as dieldrin, chromium, fluorine, arsenic, copper, boron, and tin compounds) present in workplace air was likely and may have contributed to the respiratory response observed. Furthermore, the inflammation observed may have also been the result of physical irritation from the inhalation of particulate matter. A study of workers at four U.S. pentachlorophenol production facilities reported an increased risk of death from chronic obstructive pulmonary disease

(standardized mortality ratio [SMR] 1.71, 95% confidence interval [CI] 1.28–2.24) (Ruder and Yiin 2011).

In a case report, nine infants in a small nursery for newborns exhibited increased respiratory rate and labored breathing from exposure to pentachlorophenol in a mixture of synthetic phenolic derivatives in diapers and linens from the hospital laundry (Smith et al. 1996). It is likely that these effects were secondary to hyperthermia rather than a direct effect on the respiratory tract.

No animal studies evaluated potential respiratory effects following inhalation exposure to pentachlorophenol. In a 6-month dietary study (NTP 1989) with four different preparations of pentachlorophenol (technical-grade, EC-7, DP-2 formulation, and pure) in B6C3F1 mice, increased incidences of nasal mucosal metaplasia/goblet cell hyperplasia were seen in male mice exposed to 150 mg/kg/day EC-7 (90% pure) or 380 mg/kg/day pure pentachlorophenol. No significant increases were observed in female mice or in male or female mice exposed to DP-2 or technical-grade pentachlorophenol. In a chronic study, inflammation of the nasal mucosa and metaplasia of the olfactory epithelium were observed in male and female mice exposed to EC-7 in the diet at doses of 118 and 114 mg/kg/day, respectively.

No respiratory effects were observed in dietary exposure studies in rats. No alterations in the lungs were observed in rats exposed to 36 mg/kg/day pure pentachlorophenol or 32 mg/kg/day technical-grade pentachlorophenol in the diet for 8 months (Kimbrough and Linder 1978) or in the respiratory tract of rats exposed to 270 mg/kg/day pure pentachlorophenol for 28 days (NTP 1999). Chronic dietary exposure to 30 mg/kg/day pure pentachlorophenol for 2 years (NTP 1999) or 60 mg/kg/day pure pentachlorophenol for 1 year followed by a 1-year recovery period (NTP 1999) did not result in respiratory tract alterations. Similarly, no respiratory effects were observed in dogs administered technical-grade pentachlorophenol via capsules for 1 year (EPA 1997).

2.5 CARDIOVASCULAR

Tachycardia was reported in an adult male intentionally ingesting an estimated 4–8 ounces of weed killer containing 12% pentachlorophenol, 1.5% other chlorinated phenols, 82% aromatic hydrocarbons, and 4.5% inert ingredients (Haley 1977). This effect is possibly the result of pentachlorophenol's ability to uncouple oxidative phosphorylation, leading to hyperthermia and tachycardia.

One early report described the occurrence of extensive vascular damage and heart failure in rats, rabbits, guinea pigs, and dogs following a single oral administration (dose not specified) of pentachlorophenol of unidentified purity (Deichmann et al. 1942). However, most rat and mouse studies have not reported histological alterations of the heart following intermediate-duration exposure to 36–380 mg/kg/day pure pentachlorophenol (Kimbrough and Linder 1978; NTP 1989, 1999), 330 mg/kg/day EC-7 (NTP 1989), 380 mg/kg/day DP-2 (NTP 1989), or 12–550 mg/kg/day technical-grade pentachlorophenol (Knudsen et al. 1974; NTP 1989). Similarly, no cardiovascular effects were found in rats or mice exposed to 30 or 60 mg/kg/day pure pentachlorophenol (NTP 1999), 114 mg/kg/day EC-7 (NTP 1989), or 35 mg/kg/day technical-grade pentachlorophenol (NTP 1989) or in dogs administered 6.5 mg/kg/day technical-grade pentachlorophenol for 1 year (EPA 1997).

2.6 GASTROINTESTINAL

Human data on the potential gastrointestinal effects are limited to anecdotal reports of abdominal pain, nausea, and vomiting in humans occupationally exposed to pentachlorophenol of undefined purity and doses (Gordon 1956; Menon 1958).

No histological alterations were observed in gastrointestinal tissues in rats and mice exposed to pure or technical-grade pentachlorophenol, EC-7, or DP-2 in the diet for intermediate or chronic durations (NTP 1989, 1999). Lymphocytic mucosal inflammation was observed in the stomachs of dogs exposed to capsules containing ≥1.5 mg/kg/day technical-grade pentachlorophenol for 1 year (EPA 1997).

2.7 HEMATOLOGICAL

In a chronic occupational exposure study, increased numbers of immature leukocytes and basophils were observed in workers exposed to technical-grade pentachlorophenol; however, these parameters were still within normal limits (Klemmer et al. 1980). Incidents of fatal hematological disorders were found in case reports following exposure (level and duration not specified) to technical-grade pentachlorophenol or pentachlorophenol of undefined purity as a result of predominantly dermal exposure. Fifteen cases of aplastic anemia, pure red blood cell aplasia, or severe pancytopenia with abnormal marrow have been reported in individuals using pentachlorophenol-containing wood preservative products, 10 of which resulted in death (Roberts 1981, 1983, 1990). Aplastic anemia was also diagnosed in an individual using pentachlorophenol in the renovation of an old home (Rugman and Cosstick 1990). A case of intravascular hemolysis was attributed to use of an insecticide containing pentachlorophenol (Hassan et al. 1985).

Various hematologic changes of questionable biological significance have been reported in animal studies. Decreases in the number of erythrocytes, hemoglobin level, and packed cell volume were observed in rats fed technical-grade pentachlorophenol (85–90% pentachlorophenol) for 90 days; no hematological alterations were observed in rats fed pure pentachlorophenol (Johnson et al. 1973). This study provided minimal information on the study design and the results. Conflicting findings over time were reported in rats fed a purified pentachlorophenol preparation, which contained no tetrachloro-dibenzo-*p*-dioxin (2,3,7,8-TCDD) and <0.03% of the other CDDs, for 12 weeks. Increased hemoglobin and hematocrit were observed after 6 weeks of treatment, followed by a decrease in hemoglobin and erythrocytes at study termination (Knudsen et al. 1974). A decrease in white blood cell counts was observed in pigs administered purified pentachlorophenol via capsule for 30 days (Greichus et al. 1979). Decreases in erythrocyte counts were observed in dogs exposed to 3.5 mg/kg/day for 1 year; decreases in hemoglobin and hematocrit levels were observed at 6.5 mg/kg/day (EPA 1997).

No hematological alterations were observed in intermediate-duration dietary studies in which mice were exposed to 330–550 mg/kg/day pure pentachlorophenol, technical-grade pentachlorophenol, EC-7, or DP-2 (NTP 1989) or in a developmental toxicity study in which rat dams were exposed to 50 mg/kg/day (Exon and Koller 1982). In chronic-duration oral studies, diffuse hematopoietic cells were observed in the spleen of mice exposed to 18 mg/kg/day technical-grade pentachlorophenol in the diet (NTP 1989); no alterations were observed in mice exposed to 114 mg/kg/day EC-7 in the diet for 2 years (NTP 1989).

2.8 MUSCULOSKELETAL

There are limited data on potential musculoskeletal effects. No histological alterations were observed in musculoskeletal tissues in rats and mice exposed via the diet to pure pentachlorophenol (NTP 1989, 1999), technical-grade pentachlorophenol (NTP 1989), EC-7 (NTP 1989), or DP-2 (NTP 1989) for intermediate durations or to pure pentachlorophenol (NTP 1999), technical-grade pentachlorophenol (NTP 1989), or EC-7 (NTP 1989) for chronic durations.

2.9 HEPATIC

In a study of male and female pentachlorophenol-production workers, higher urinary excretion of coproporphyrins, compared with unexposed controls, was associated with workers with chloracne involved in the production of pentachlorophenol (Hryhorczuk et al. 1998). In another epidemiological

study, Cheng et al. (1993) found elevated urinary porphyrin and delta-amino levulinic acid concentrations among male workers who produced technical-grade pentachlorophenol, but there were no differences in these parameters between the workers with chloracne and those without.

No studies were located regarding hepatic effects in humans after oral exposure to pentachlorophenol. Most of the studies reviewed concerning hepatic effects of dermal exposure to pentachlorophenol in humans described case reports of individuals exposed either occupationally or in the home following the use of pentachlorophenol-containing solutions by individuals who did not employ appropriate precautionary measures. It is noted that these reports involved exposure to multiple chemicals, and it is not known if pentachlorophenol was the causative agent. Hepatic enlargement has been observed in herbicide sprayers (Gordon 1956) and in neonates exposed for a short time via contaminated diapers and bed linen in a hospital nursery (Armstrong et al. 1969; Robson et al. 1969; Smith et al. 1996). Autopsy findings in those affected individuals who died revealed fatty infiltration of the liver (in the neonates) and severe centrilobular congestion with hepatocellular fat accumulation (in the chemical worker). Centrilobular degeneration was also observed in a liver specimen from a worker who dipped wood in a preservative that contained 4.1% pentachlorophenol every day for 1 week (Bergner et al. 1965). In an epidemiologic study of male factory workers who brushed technical-grade pentachlorophenol onto wood strips, sometimes without gloves, serum biliary acid concentrations were elevated in the high-exposure group, but not the low-exposure group, as compared with controls. Exposure was assessed by measurement of pentachlorophenol concentrations in plasma and urine (Colosio et al. 1993b). Evidence of liver damage was also seen in an epidemiological study of adult males occupationally exposed to pentachlorophenol in wood-treatment plants or as farmers or pest control operators in Hawaii (Klemmer et al. 1980). This evidence consisted of elevated levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) following chronic, predominantly dermal exposure to technical-grade pentachlorophenol or pentachlorophenol of undefined purity.

Studies in laboratory animals provide strong evidence that the liver is a target of pentachlorophenol-induced toxicity. Evidence of biochemical (alterations in hepatic enzyme activities), gross (increased liver weight), and histopathological (hypertrophy, vacuolization, hyperplasia, fibrosis, necrosis, and degeneration) effects have been reported in acute, intermediate, and chronic oral exposure studies in rats, mice, and dogs.

At low dosages, the observed liver effects are characteristic of enzyme induction. Exposure to pure pentachlorophenol resulted in increases in liver weight, hepatocellular hypertrophy, and/or vacuolization

in mice exposed to 41 mg/kg/day for 2 weeks (Umemura et al. 1996), in rats exposed to 36 mg/kg/day for 8 months (Kimbrough and Linder 1978), in mice exposed to 30 or 41 mg/kg/day for 4 weeks (Umemura et al. 1996, 2006), and in pigs exposed to 10 mg/kg/day for 30 days (Greichus et al. 1979). Similar effects were observed following oral exposure to technical-grade pentachlorophenol in rats exposed to 1–10 mg/kg/day for an intermediate duration (Bernard et al. 2002; Kimbrough and Linder 1978; Knudsen et al. 1974) and in dogs chronically exposed to 1.5 mg/kg/day (EPA 1997). Alterations in serum ALT and/or AST were observed in rats exposed to 20 mg/kg/day methodological-grade pentachlorophenol (purity unspecified) for 2 weeks (Bekhouche et al. 2019); in mice exposed to 120 mg/kg/day pure pentachlorophenol for 4 weeks (Umemura et al. 2006), 50 mg/kg/day technical-grade pentachlorophenol for 6 months (NTP 1989), or 30 mg/kg/day for 22–24 months (Schwetz et al. 1978); and in dogs exposed to 3.5 mg/kg/day for 1 year (EPA 1997).

In general, the severity of the liver damage increased with increasing exposure concentrations. Acute-duration exposure to 20 mg/kg/day methodological-grade pentachlorophenol resulted in hepatocellular necrosis, binucleated and pyknotic hepatocytes, and dilation and congestion of the centrilobular vein and sinusoids (Bekhouche et al. 2019). Intermediate-duration exposure to doses of 7–48 mg/kg/day pure or technical-grade pentachlorophenol resulted in necrosis, periportal fibrosis, and/or hepatocellular degeneration in rats (Bernard et al. 2002; Kimbrough and Linder 1978; NTP 1999) and multifocal necrosis and hepatocellular degeneration in mice exposed to 50–90 mg/kg/day pure or technical-grade pentachlorophenol, EC-7, or DP-2 (Kerkvliet et al. 1982; NTP 1989). Hepatocellular degeneration was observed in rats exposed to 10–60 mg/kg/day pure pentachlorophenol in the diet for 52 or 104 weeks (NTP 1999). Chronic inflammation and minimal necrosis were observed at 3.5 and 6.5 mg/kg/day, respectively, in dogs administered technical-grade pentachlorophenol via capsule for 1 year (EPA 1997).

The results of the Kimbrough and Linder (1978) study suggests that the impurities found in technical-grade pentachlorophenol may influence its toxicity. The liver effects observed in this study included centrilobular hepatocyte hypertrophy at 1 mg/kg/day, periportal fibrosis at 7 mg/kg/day, and periportal fibrosis and bile duct proliferation at 48 mg/kg/day in rats exposed to technical-grade pentachlorophenol in the diet for 8 months. In contrast, minimal liver effects (centrilobular hepatocyte hypertrophy) were observed at the highest tested dose (32 mg/kg/day) of pure pentachlorophenol. It is possible that the tetrachlorophenol, hexachloro-*p*-dibenzodioxin, heptachloro-*p*-dibenzodioxin (HpCDD), octachloro-*p*-dibenzodioxin (OCDD), hexachlorodibenzofuran, pentachlorodibenzofuran, and tetrachlorodibenzofuran present in the technical-grade pentachlorophenol influenced its hepatotoxicity. However, other

studies that compared the hepatotoxicity of pure and technical-grade pentachlorophenol did not find differences in potency or the type of liver effects (Kerkvliet et al. 1982; NTP 1989).

2.10 RENAL

No studies regarding renal effects in humans after inhalation or oral exposure to pentachlorophenol were identified. Four reports were found that described renal toxic effects following dermal exposure to pentachlorophenol in humans. All involved either occupational exposure or accidental poisoning with the predominant route of exposure being dermal, but the possibility of inhalation exposure cannot be excluded. In one instance, a 3-year-old girl was exposed to pentachlorophenol of undefined composition via a pesticide-contaminated domestic water supply. Transient disruption of acid-base equilibrium and metabolic balance as evidenced by acidosis, aminoaciduria, and ketonuria suggested the occurrence of renal dysfunction in this child (Chapman and Robson 1965). In a case study of nine infants, metabolic acidosis, proteinuria, and increased blood urea nitrogen (BUN) were found following exposure of the infants to pentachlorophenol of undefined composition in diapers and bedding at a hospital that used pentachlorophenol in the hospital laundry as an antimildew agent. Fatty vacuolar changes in the renal tubules were noted in one of the two infants that died (Smith et al. 1996). An autopsy conducted on a worker who dipped wood in a preservative that contained 4.1% pentachlorophenol every day for 1 week revealed mild renal tubular degeneration (Bergner et al. 1965). Finally, evidence for pentachlorophenol-induced impaired glomerular filtration and tubular function was reported in 18 workers employed at a wood-treatment facility (Begley et al. 1977). These findings consisted of depressed creatinine clearance and phosphorus reabsorption. Considerable improvement in these symptoms was seen following a 20-day absence from work, although creatinine clearance was still depressed in 6 of the 18 workers and phosphorus reabsorption was depressed in 3 of 18 workers. These data suggest that the renal toxicant effects of technical-grade pentachlorophenol are reversible. The extent to which contaminants of technical-grade pentachlorophenol are responsible for the effects discussed above is not known. Hyperthermia may also be a mechanism of renal injury in individuals that are acutely overexposed to pentachlorophenol.

The available data from laboratory animals do not suggest that the kidney is a sensitive target of pentachlorophenol toxicity. Although a number of studies have reported increases in kidney weights, most did not find histological evidence of damage; thus, the alterations in organ weight were not considered biologically relevant. Biochemical changes indicative of renal toxicity have been reported in

pentachlorophenol-treated animals. For example, after 15 days of oral exposure to purified pentachlorophenol at 10 or 15 mg/kg/day, young pigs exhibited statistically significant increased levels of BUN, but this effect was no longer significant after 30 days of treatment (Greichus et al. 1979). Proximal tubular alkaline phosphatase activity was decreased after 1 month of twice-weekly gavage doses (40–160 mg/kg/day) of 90% pentachlorophenol (sodium salt; impurities not identified) administered to rats, but this effect was no longer evident after 3 months of treatment (Nishimura et al. 1980). The biological significance of these apparently transient renal effects with regard to long-term toxicity is not known. One study reported histological alterations: decreases in calculi at the corticomedullary junction were observed in rats exposed to 4.8 mg/kg/day technical-grade pentachlorophenol for 12 weeks (Knudsen et al. 1974). Other intermediate- and chronic-duration studies with pure, technical-grade, or commercial-grade pentachlorophenol did not report histological alterations in the kidneys (Kerkvliet et al. 1982; Kimbrough and Linder 1978; Knudsen et al. 1974; NTP 1989, 1999; Schwetz et al. 1978).

2.11 DERMAL

Occupationally-exposed workers at a wood-treatment plant exhibited a statistically significant increase in low-grade inflammation of skin and subcutaneous tissue, and severe eruptions of the skin. However, it is possible these symptoms resulted from exposure to contaminants in pentachlorophenol (e.g., CDDs, CDFs) and other materials such as dieldrin, chromium, fluorine, arsenic, copper, boron, and tin compounds (Baader and Bauer 1951; Klemmer et al. 1980). EPA (1986b) reported the presence of skin abnormalities (type not specified) in some residents of log homes treated with pentachlorophenol (purity not indicated).

Numerous occupational exposure studies have reported chloracne, characterized by extensive cysts and pus forming abscesses on the face, chest, abdomen, and proximal part of the extremities in sodium pentachlorophenate (Sehgal and Ghorpade 1983) and pentachlorophenol (Cheng et al. 1993; Hryhorczuk et al. 1998; O'Malley et al. 1990) production workers. It is likely that these workers were also exposed to CDDs and CDFs, which are known to induce chloracne in humans.

Transient localized redness and pain subsequent to immersion of the hands in a 0.4% pentachlorophenol solution for 10 minutes were exhibited by an adult male (Bevenue et al. 1967). Two cases of pemphigus vulgaris and one of chronic urticaria (both examples of severe skin lesions) attributed to nonoccupational chronic pentachlorophenol exposure (i.e., via contact with wood treated with pentachlorophenol) have

been described (Lambert et al. 1986). It is not known whether these effects were due to pentachlorophenol or from impurities.

Pentachlorophenol-induced toxic effects on the skin of experimental animals have also been reported. A single application of pentachlorophenol of unspecified purity (1,111 mg/kg in 95% ethyl alcohol or 150 mg/kg in pale paraffin oil) resulted in gross changes such as pronounced edema and inflammation leading to wrinkling, cracking, desquamation, and hair loss. Microscopic changes observed include widespread foci of atrophy and necrosis, thinning and disappearance of upper skin layers, and hyperkeratinization and hypertrophy of hair follicles (Deichmann et al. 1942). Single dermal applications of 250 mg/kg of a 10% aqueous solution of sodium pentachlorophenate of unspecified purity to rabbits did not result in dermal irritation. Repeated application of lower doses of pentachlorophenol (40 mg/kg in mineral oil) to rabbits for 21 days induced no irritation, whereas daily application of 10–50 mg/kg of a 4% solution of pentachlorophenol in fuel oil for 6–61 weeks resulted in pronounced dermal effects, and daily application of 63 mg/kg of an aqueous sodium pentachlorophenate solution for 32 days was without effect (Deichmann et al. 1942). No evidence of histologic changes in the epidermis or pilosebaceous unit were noted after application of 0.036 mg of sodium pentachlorophenate of unspecified purity to a 9 cm^2 area of the dorsal skin of hairless dogs once daily for 7 days. The toxic effects of dermal exposure to pentachlorophenol appear to be most severe following high-dose, acute exposure to pentachlorophenol in fuel oil.

Acne was observed in rabbits following application of technical-grade pentachlorophenol to the ear; acne was not observed following application of pure pentachlorophenol (Johnson et al. 1973), suggesting that the effects were due to contaminants rather than the pentachlorophenol.

2.12 OCULAR

Inflammation of the conjunctival membrane of the eyes was observed in workers exposed to technical-grade pentachlorophenol at a wood treatment plant (Klemmer et al. 1980). As discussed in Section 2.17, congenital eye cataracts were reported in the offspring of chlorophate workers (Dimich-Ward et al. 1996). No ocular alterations were observed in ophthalmologic examination of dogs administered 6.5 mg/kg/day technical-grade pentachlorophenol for 1 year (EPA 1997).

2.13 ENDOCRINE

Three human studies evaluated potential associations between pentachlorophenol exposure and thyroid disease or function. In a case-control study including 35 cases of hypothyroidism, 44 cases of hyperthyroidism, and 160 matched controls (2 controls/case), no associations were observed between blood pentachlorophenol levels and thyroid disease (Dufour et al. 2020). When analyzed together with 54 other persistent organic pollutants using a weighted quantile sum regression, pentachlorophenol was associated with lower odds for hyperthyroidism. Gerhard et al. (1998) examined several endocrine endpoints among 89 women with repeated miscarriages. An inverse correlation was found between triiodothyronine (T3) levels and pentachlorophenol levels. It should be noted that this is a preliminary study; study design limitations include (1) lack of a matched control group, (2) lack of control for other confounding factors, (3) the fact that only 15% of the women had pentachlorophenol levels that were above the reference level of 25 μg/L, (4) lack of information on possible sources of exposure to pentachlorophenol, and (5) elevated levels of other chlorinated hydrocarbons (e.g., polychlorinated biphenyls [PCBs], dichlorodiphenyltrichloroethane [DDT]) in some of the women. In another study by Gerhard et al. (1999) of a group of women with gynecological and/or endocrinological disorders, a decrease in T3 levels was found in women with elevated pentachlorophenol serum levels (median level of 3.59 μg/L); although the levels were lower than levels found in age-, geographical region-, and condition-matched controls, the mean and median T3 levels were within the normal range. An euthyroid goiter was also observed in 50% of these subjects as compared to 30% in the controls. Other statistically significant alterations in endocrine hormones included an increase in adrenocorticotropic hormone (ACTH)-stimulated cortisol levels and decreases in follicle stimulating hormone, testosterone, hydroepiandrosterone, hydroepiandrosterone sulfate, 17-hydroxypregnenolone, and 17-hydroxy-progesterone levels. As with the T3 levels, the hormone levels were within the normal range. The source of pentachlorophenol was wood ceilings that were treated with wood preservatives; it is likely that these women were also exposed to other chemicals in the wood preservative.

Significant alterations in thyroid hormone levels have been observed in laboratory animals. Gavage administration of 3 mg/kg/day pure pentachlorophenol to young adult female rats for 28 days produced decreases in serum free thyroxine (T4) levels (50%), serum thyroid stimulating hormone levels (30%), and serum T4:T3 ratio (60%) (Jekat et al. 1994). Decreases in serum T3 (50%) and free T3 (55%) were also observed at 30 mg/kg/day. In a multigeneration study in mink, significant decreases in serum T4 levels were observed in the F1 males (18%) and the F2 males (20%) and females (16%) exposed to

1 mg/kg/day pentachlorophenol (purity not reported) (Beard and Rawlings 1998). A decrease in relative thyroid weight (28%) was also observed in the F2 female mink.

Alterations in thyroid hormone levels were also observed in a series of studies in sheep. A significant decrease in T4 levels was observed in female sheep administered 2 mg/kg/day pure pentachlorophenol by gavage twice weekly for 36 days (Rawlings et al. 1998). Exposure of female sheep to 1 mg/kg/day pentachlorophenol (purity not reported) for 5 weeks premating and throughout gestation and lactation resulted in significant decreases in serum T4 levels in the mothers (Beard et al. 1999a), in the ram lambs that were also exposed for 20 weeks post weaning (Beard et al. 1999b), and in the ewe lambs also exposed for 67 weeks post weaning (Beard and Rawlings 1999). No alterations in thyroid stimulating hormone levels or the response to thyroid releasing hormone were observed in the female offspring. However, in response to thyroid stimulating hormone, there were reductions in the magnitude and duration of the T4 response and in the maximum T3 level and net T3 increase.

Studies in animals have shown that acute (single-dose, intraperitoneal injection) pentachlorophenol administration causes a marked, statistically significant decrease in serum total T4 levels in rats (van Raaij et al. 1991b). This decrease peaked 6–24 hours after administration, and T4 levels slowly returned to control values within 96 hours after administration. Further *in vitro* studies by these investigators revealed that the likely mechanism of action for this anti-thyroid effect was competition for serum protein T4 binding sites (van Raaij et al. 1991a).

Adrenal gland hyperplasia was observed in mice chronically exposed to ≥18 mg/kg/day technical-grade pentachlorophenol or EC-7 in the diet.

Other intermediate- and chronic-duration studies in rats and mice have not reported histological alterations in endocrine tissues (Kerkvliet et al. 1982; Kimbrough and Linder 1978; Knudsen et al. 1974; NTP 1989, 1999).

2.14 IMMUNOLOGICAL

In an epidemiological study, McConnachie and Zahalsky (1991) evaluated 18 lymphocyte phenotype frequencies, proliferative responses of peripheral lymphocytes to mitogens and allogenic stimulator lymphocytes, serum immunoglobulin levels, and autoantibody levels in 38 people ages 8–60 years (21 males) and 9–60 years (17 females) from 10 families who had been exposed to pentachlorophenol

(purity not indicated) in their pentachlorophenol-treated log homes for periods of 1–13 years. Fifteen of the individuals were children ages 8–18 years. The mean serum concentration of pentachlorophenol in the individuals who still lived in log homes at the time of the study was 884 μg/L; this was higher than the mean of 420 μg/L found in another study of people living in log homes and a mean level of 40 μg/L reported for members of the general public with no known exposure to pentachlorophenol (Cline et al. 1989). Comparison of the pentachlorophenol-exposed individuals with controls indicated that the exposed individuals had activated T-cells, autoimmunity, immunosuppression, and B-cell dysregulation. T-cell activation was indicated by statistically significant increases of >50% in the proportion of lymphocytes with T-cell activation markers, as detected by monoclonal antibodies, in pentachlorophenol-exposed individuals compared with controls. Autoantibodies were detected in 8 of 38 pentachlorophenol-exposed subjects, and there was increased expression of a monoclonal-antibody-detected marker associated with autoimmunity in the pentachlorophenol-exposed group. Functional immunosuppression was indicated by statistically-significant decreases of 24–41% in the proliferative response of peripheral lymphocytes of pentachlorophenol-exposed individuals, compared with controls, to three different mitogens and to allogeneic stimulation in mixed-lymphocyte culture. A statistically significant increase in natural killer cell function was also reported in pentachlorophenol-exposed women compared with women of the control group. This study is limited by the absence of reported serum pentachlorophenol concentrations in members of the control group and the lack of control for potential confounders such as smoking, hypertension, and alcohol use. Gerhard et al. (1991) reported “immunological disorders” (no further details were given) in 15 of 22 women attending a clinic for reproductive and/or endocrinological disorders. The women were exposed to pentachlorophenol by the outgassing of wood products in the home.

Two cases of pemphigus vulgaris and one of chronic urticaria (skin diseases with an immunologic etiology) have been attributed to nonoccupational exposure to pentachlorophenol (Lambert et al. 1986). Immune function was examined in 188–190 individuals exposed to pesticides containing pentachlorophenol (Daniel et al. 1995, 2001) and 32 workers treating wood with pentachlorophenol (Colosio et al. 1993b). Daniel et al. (1995) found that the likelihood of having an impaired response to at least one lymphocyte-stimulating agent was increased among individuals with blood pentachlorophenol levels of ≥10 μg/L. Impaired responses were observed in 50, 65, and 71% of subjects with blood pentachlorophenol levels of ≤10, 11–20, and >20 μg/L, respectively. In the Daniel et al. (2001) study, inverse associations were found between blood pentachlorophenol levels and several cellular and humoral immune parameters including total lymphocyte count, specific lymphocyte subpopulations (CD3+, CD4+, CD16+, CD19+, DR+, and CD4/CD8 ratio), interleukin levels (IL-2, IL-2R, IL-6, IL-10), interferon

gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and IgM-antiFab. An association was also found between pentachlorophenol blood levels and the number of impaired stimulation assays per person. Similar to the Daniel et al. (1995) study, individuals with blood pentachlorophenol levels of >10 μg/L were more likely to have blood lymphocyte counts and subpopulation counts that were below the mean level of healthy controls. In the Colosio et al. (1993b) study of workers who brushed technical-grade pentachlorophenol onto wood strips, a significant reduction in the lymphocyte response to phytohemagglutinin was observed among the highly exposed workers, as compared to controls.

A number of oral exposure studies in laboratory animals evaluated the immunotoxicity of pentachlorophenol. These studies found that exposure to technical-grade pentachlorophenol and commercial-grade pentachlorophenol affected a wide range of immune functions, such as humoral and cellular immunity, susceptibility to tumor induction, and complement activity (Holsapple et al. 1987; Kerkvliet et al. 1982, 1985a, 1985b; NTP 1989; White and Anderson 1985). Most studies of pure pentachlorophenol did not find immune effects (Kerkvliet et al. 1982, 1985a; NTP 1989), suggesting that the majority of the immunotoxic effects may be related to the level of impurities in the technical-grade product (e.g., CDDs and CDFs) (Kerkvliet et al. 1982, 1985a; NTP 1989; White and Anderson 1985). Two studies of pure pentachlorophenol reported immune effects (Blakley et al. 1998; Chen et al. 2013a). Studies that compared effects of technical-grade to pure pentachlorophenol are reviewed below in an attempt to illustrate immunotoxic effects attributable to pentachlorophenol.

Several studies evaluated effects on humoral immunity, in particular the response to sheep red blood cells (sRBC). Blakley et al. (1998) reported a decreased response to sRBC in rats administered via gavage 2 mg/kg 2 times per week for 28 days. This conflicts with the findings of Kerkvliet et al. (1985a) and NTP (1989), which found no significant alterations in the response to sRBC in mice administered pure pentachlorophenol at 60 mg/kg/day via gavage for 1–2 days or 380 mg/kg/day via the diet for 6 months, respectively. Studies of technical-grade pentachlorophenol found decreases in the response to sRBC in mice administered 10 or 83 mg/kg/day for acute durations (Holsapple et al. 1987; Kerkvliet et al. 1985a) or 1.8–50 mg/kg/day for intermediate durations (Kerkvliet et al. 1985a; NTP 1989). Studies with commercial-grade pentachlorophenol identified a higher LOAEL for impaired response to sRBC (NOAEL of 200 mg/kg/day and LOAEL of 300 mg/kg/day for mice exposed to DP-2) (NTP 1989) or did not find a significant response (NOAELs of 100 mg/kg/day [Holsapple et al. 1987] and 330 mg/kg/day [NTP 1989] in mice exposed to EC-7). A study in mice found that oral administration of 6 mg/kg pure pentachlorophenol 3 times/week for 1–2 weeks resulted in suppressed immune response to ovalbumin antigen, as evidenced by decreased levels of IgG and IgM (Chen et al. 2013a).

A series of studies conducted by Kerkvliet et al. (1985a) investigated the immunotoxicity of pentachlorophenol contaminants. Exposure to chlorinated dioxin/furan fraction isolated from technical pentachlorophenol resulted in immunosuppression; this was not seen when mice were administered the chlorinated diphenyl ethers fraction or the chlorinated phenoxyphenol fraction at doses expected to be found in technical pentachlorophenol. Co-administration of HpCDD, one of the most prevalent CDD impurities in technical-grade pentachlorophenol, with pure pentachlorophenol resulted in an immunosuppressive response that was similar in magnitude to that seen with technical-grade pentachlorophenol or HpCDD alone (Kerkvliet et al. 1985a). These results provide good evidence that impurities (particularly HpCDD) are responsible for some of the immunotoxic effects attributed to technical-grade pentachlorophenol. In another series of experiments conducted by Kerkvliet et al. (1985a), technical-grade pentachlorophenol was fed to both C57BL/6 mice and DBA/2 mice for 6 weeks. The C57BL/6 strain has a high-affinity aryl hydrocarbon (Ah) receptor and the DBA/2 strain a low-affinity Ah receptor. The ability of CDD and CDF congeners to bind to this receptor correlates with their toxicity and their ability to induce cytochrome P-450 monooxygenase activity. Antibody response to sRBC was suppressed by 28 and 72% in C57BL/6 mice exposed to 10 or 250 ppm technical-grade pentachlorophenol in the diet, as opposed to 0 and 45% in corresponding groups of DBA/2 mice. Based on these results, the investigators concluded that the immunosuppressive effect of technical-grade pentachlorophenol was probably mediated by contaminant CDDs and CDFs via interaction with the Ah receptor. This finding is supported by the results of the NTP (1989) 6-month study, which found immunosuppression in mice exposed to technical-grade pentachlorophenol or DP-2, but not in mice exposed to EC-7 or pure pentachlorophenol; EC-7 has very low levels of CDDs and CDFs, as compared to the other tested formulations.

Impurities also appear to be the causative agent for other immunological effects observed in animals exposed to technical-grade pentachlorophenol. In a test of resistance to syngeneic tumor growth, an indication of an organism's state of immunosurveillance, technical-grade pentachlorophenol induced a significant dose-independent enhancement of susceptibility to methylcholanthrene-induced sarcoma 1412 tumor growth, whereas the pure pentachlorophenol had no effect on this parameter (Kerkvliet et al. 1982). In another test of immunocompetence, an increase in mortality and secondary tumor susceptibility was observed in mice exposed to technical-grade pentachlorophenol and inoculated with Maloney sarcoma virus (MSV) to examine resistance to secondary tumor growth (Kerkvliet et al. 1982). These effects were not observed in similarly inoculated mice exposed to pure pentachlorophenol. In a third test designed to evaluate macrophage competence, resistance to encephalomyocarditis virus (EMCV), no effect was seen on susceptibility in mice exposed to technical-grade or pure pentachlorophenol (Kerkvliet et al. 1982).

The investigators concluded that immunomodulatory effects observed with pentachlorophenol were due primarily, but not exclusively, to contaminants present in the technical-grade preparation.

Studies evaluating the effect of technical-grade pentachlorophenol on T-cell, macrophage, and natural killer cell activity found that T-cell and macrophage-mediated (cell-mediated) immunocompetence is relatively resistant to technical-grade pentachlorophenol. (Kerkvliet et al. 1985b). The only statistically significant change seen was a reduction in lymphoproliferative response in mixed lymphocyte culture. This finding contrasts with marked effects that technical-grade pentachlorophenol has on antibody-mediated immunity. NTP (1989) notes that a marked effect on humoral immunity and an absence of an effect on cell-mediated immunity is also found in mice exposed to TCDD.

The complement component of the immune system in mice has also been found to be affected by exposure to technical-grade pentachlorophenol, but not EC-7 (White and Anderson 1985). In this study, technical-grade pentachlorophenol inhibited functional activity of all aspects of complement in a dose-dependent manner. This suppression was still seen up to 30 days after termination of treatment.

2.15 NEUROLOGICAL

There are limited data on the neurotoxicity of inhaled pentachlorophenol in humans. Signs of central nervous system toxicity (lethargy and tachypnea) and cerebral edema with focal swelling of the myelin sheath was observed in a worker exposed to pentachlorophenol dust (Gray et al. 1985; Walls et al. 1998). It is likely that these effects were secondary to hyperthermia, which resulted from pentachlorophenol-induced uncoupling of oxidative phosphorylation.

A study by Peper et al. (1999) examined neurotoxicity in individuals exposed to wood preserving chemicals used to treat wood ceilings and wood paneling. An increase in subjective symptoms (increased fatigue, distractibility, attenuated motivation, and depressed mood) and impaired performance on several objective tests of neurobehavioral performance (paired-associated learning with a distracting condition, verbal memory test with distraction, visual short term memory, and incidental learning of visual objects) were observed in 15 women with elevated pentachlorophenol (mean of 43.6 μg/L) and γ-hexachloro-cyclohexane (0.085 μg/L) blood levels, as compared to a sex-, age-, education-, and intelligence-matched control group. Additionally, the results of the reading speed, naming speed, paired associated learning, and visual short-term memory tests were significantly associated with pentachlorophenol blood levels. Although this study provides some suggestive evidence of the neurotoxic potential of pentachlorophenol,

interpretation of the results is complicated by co-exposure to high levels of γ-hexachlorocyclohexane (lindane) and other solvents and the small number of subjects. Sawmill workers reported an increased number of symptoms in a questionnaire assessing higher brain functions (no additional information was provided) (Walls et al. 1998); see Section 2.3 for more information on this survey study.

A reduction in median motor nerve conduction velocity was seen in male pentachlorophenol production workers, as compared to matched controls (Cheng et al. 1993). However, the reduction was only statistically significant in the subgroup of pentachlorophenol workers in the trichlorobenzene tank area where the highest levels of CDDs were also found. In contrast, Triebig et al. (1987) did not find significant alterations in motor or sensory nerve conduction velocities in the ulnar and/or median nerve in workers exposed to low levels (0.0003–0.18 mg/m^3) of technical-grade pentachlorophenol.

In a case-control study of patients with Parkinson's disease, Seidler et al. (1996) found significant associations of Parkinson's disease with long-term (>15 years) exposure to wood paneling in the home, contact with wood preservatives in free time, and contact with wood preservatives at work. However, the association of Parkinson's disease with exposure to pentachlorophenol is uncertain because the patients were more likely than control subjects to have used organochlorines and alkylated phosphates/ carbamates, and the patients reported more frequent exposure to heavy metals, solvents, exhaust fumes, and carbon monoxide than the control group.

One report describing effects of ingestion of pentachlorophenol in humans was found in the literature (Haley 1977). In this case, an adult male intentionally ingested an estimated 4–8 ounces of weed killer that contained 12% pentachlorophenol, 1.5% other chlorinated phenols, 82% aromatic petroleums, and 4.5% inert ingredients. Clinical signs observed upon subsequent hospital admission included pyrexia, diaphoresis, hyperkinesis, muscle twitching, tremors, epigastric tenderness, leg pain, tachypnea, and tachycardia. These neurologic symptoms may be the result of pentachlorophenol's ability to uncouple oxidative phosphorylation (including the resultant increase in body temperature, tachycardia, and tachypnea) rather than a direct toxic effect of pentachlorophenol on the central or peripheral nervous systems.

Numerous signs of central nervous system toxicity have been reported in case reports of individuals exposed to high levels of pentachlorophenol via dermal contact and inhalation exposure. The observed effects include intermittent delirium and convulsions (Chapman and Robson 1965) and irritability

(Robson et al. 1969; Smith et al. 1996). It is likely that these are effects secondary to hyperthermia due to pentachlorophenol-induced uncoupling of oxidative phosphorylation.

Results from animal studies demonstrate that the central nervous system is adversely affected by pentachlorophenol, possibly as a result of hyperthermia induced by uncoupling of oxidative phosphorylation. At the neurochemical level, transient changes in activity of some brain enzymes and decreased glial glutathione levels were seen in rats administered technical-grade pentachlorophenol in drinking water for 14 weeks (Savolainen and Pekari 1979). These findings suggest another biochemical component to technical-grade pentachlorophenol neurotoxicity. The possibility and extent of the role of technical-grade contaminants in producing these effects are not known, although the study authors concluded that the neurochemical changes were most likely associated with the body burden of chlorophenols. Inhibition of the uptake of T4 into the cerebrospinal fluid, as demonstrated in rats following intraperitoneal injection of pentachlorophenol, is another possible component of pentachlorophenol neurotoxicity.

A 6-month dietary study conducted by NTP (1989) reported neurobehavioral alterations in mice exposed to technical-grade pentachlorophenol, DP-2, EC-7, and pure pentachlorophenol. After 5 weeks of exposure, dose-related decreases in motor activity and rotarod performance were only observed in mice exposed to technical-grade pentachlorophenol. After 26 weeks of exposure, dose-related increases in both motor activity and startle response were observed in female mice exposed to each of the four mixtures. These alterations were also observed in male mice exposed to technical-grade pentachlorophenol. Because NTP (1989) did not provide actual dose-response data, LOAELs cannot be identified for these effects. The study did not find consistent alterations in other tests of neurotoxicity (pinna, corneal, or righting reflexes, visual placement, grip strength, or rotarod test performance).

No histological alterations were observed in the brain or spinal cord of mice exposed to 330–550 mg/kg/day technical-grade pentachlorophenol, DP-2, EC-7, and pure pentachlorophenol in the NTP (1989) 6-month study, rats exposed to 12 mg/kg/day in the 12 week study by Knudsen et al. (1974), or dogs exposed to 6.5 mg/kg/day technical-grade pentachlorophenol for 1 year (EPA 1997). Degenerative changes in 10% of the Types A and B fibers consisting of breaks in the myelin sheath of sciatic nerves and a variable loss of neurotubules, neurofilaments, and other axoplasmic components were observed in male rats administered 38 mg/kg/day pentachlorophenol (purity not reported) in drinking water for 90 days or 114 mg/kg/day for 120 days (Villena et al. 1992). Type C fibers were unaffected. These changes were more marked in the rats receiving the higher dose. No effects were observed in rats

exposed to 11.4 mg/kg/day for 60 days or 38 mg/kg/day for 60 days. While these results suggest that pentachlorophenol can cause neurotoxic changes in the morphology of peripheral nerves, since the purity of the pentachlorophenol tested was not specified, it is not possible to determine whether these changes were due to pentachlorophenol itself or impurities present in technical-grade pentachlorophenol. Other limitations associated with this study include a lack of protocol details (e.g., number of animals per group) and a lack of quantitative incidence data.

2.16 REPRODUCTIVE

In a brief report, Gerhard et al. (1991) noted that elevated blood levels of pentachlorophenol (>25 μg/L) and/or lindane (>100 ng/L) were found in 22 of 90 women with histories of habitual abortion, unexplained infertility, menstrual disorders, or the onset of menopause. Exposure duration was 4.6–10 years, and exposure occurred via off gassing (from wooden ceiling and wall panels and from carpets and leather upholstery treated with wood preservatives) as well as via dermal contact with these treated materials. Pentachlorophenol blood levels were highest in the women with infertility (mean=73 μg/L) and lower in those with menstrual dysfunction (42 μg/L). Seventeen of the 22 women also exhibited adrenocortical insufficiency, and 6 of these women had thyroid dysfunction as assessed by measurement of thyroid stimulating hormone (no further details were provided). However, a causal relationship between pentachlorophenol exposure and the effects is uncertain because of concurrent exposures to other chemicals, absence of matched controls, and lack of control for other confounding factors. Gerhard et al. (1999) also examined a group of 65 women with gynecological and/or endocrinological alterations and elevated serum pentachlorophenol levels (median level was 35.9 μg/L). Statistically significant decreases in follicle stimulating hormone and testosterone levels were found, as compared to age-, geographical-, region-, and condition-matched controls. Although the hormone levels were lower than in the control group, they were within the normal range of values. The women were exposed to pentachlorophenol via outgassing of wood ceilings treated with wood preservatives. It is likely that the women were also exposed to other components of the wood preservatives.

A second epidemiological study examined fertility in approximately 24,000 men who worked for at least 1 year in 1 of 11 sawmills (Heacock et al. 1998); the men were exposed to chlorophenates (compounds not specified) and contaminants. A decrease in fertility was observed among the chlorophenate-exposed workers, as compared to controls. However, there was no relationship between cumulative exposure and fertility when adjusted for time since first hire.

A number of animal studies have examined the reproductive toxicity of pentachlorophenol. The available data suggest that long-term exposure to technical-grade pentachlorophenol can decrease fertility. In a 2-generation study, decreased fertility (significant decreases in the number of rats mated and in the ratio of pregnant rats to the number of rats in cohabitation) was observed in the first generation of rats exposed to 60 mg/kg/day technical-grade pentachlorophenol administered by gavage (Bernard et al. 2002). No alterations in fertility were observed in the F1 generation exposed to 10 or 30 mg/kg/day or in the parental generation. The only other reproductive effects observed in this study were decreases in testicular spermatid count, decreases in absolute testes weight and the ratio of testes weight to brain weight, and focal/multifocal mononuclear cell infiltrate in the epididymis in the F1 rats administered 30 or 60 mg/kg/day. However, no alterations in the average number of motile or nonmotile sperm, epididymal or testicular sperm counts, or sperm morphology were observed in either generation. No alterations in reproductive tissues were observed in the female rats. Significant increases in the average day of preputial separation and vaginal patency were observed in the F1 generation, suggesting that *in utero* exposure to pentachlorophenol disrupted the normal development of the reproductive system. No adverse reproductive effects were observed in another multigeneration study in which mink were fed a diet containing 1 mg/kg/day pentachlorophenol (purity not reported) (Beard and Rawlings 1998). A single-generation mink study also conducted by this group reported significant decreases in the proportion of mated females accepting a second mating and the proportion of mink that whelped, although no effect on the proportion of mink that accepted the first mating or the proportion of mink with visible implantation sites were found (Beard et al. 1997). In both studies, the minks were exposed to 1 mg/kg/day pentachlorophenol (purity not reported) in the diet for 3 weeks prior to mating. Additionally, no significant alterations in mating response, ovulation rate, follicle and corpus luteum size, gestation length, pregnancy rate, lambing rate, and lamb birth rate were observed in sheep exposed to 1 mg/kg/day pentachlorophenol in the diet for 5 weeks premating and throughout the gestation and lactation periods (Beard et al. 1999a). No effect on fertility was observed in the offspring of these sheep, later mated to unexposed males (Beard and Rawlings 1999).

Several reproductive toxicity studies and general toxicity studies have reported histological alterations in reproductive tissues. Minimal to marked germinal epithelial degeneration and lack of spermatozoa in the seminiferous tubules were observed in rats exposed to 270 mg/kg/day pure pentachlorophenol in the diet for 28 days (effects may have been secondary to poor condition of animals) (NTP 1999). Effects observed in sheep include focal degeneration of the seminiferous tubules and decreased sperm density in the epididymis body (but not in caput or cauda epididymis) at 1 mg/kg/day pentachlorophenol (purity not reported) in the diet during gestation, lactation, and for 20 weeks postnatally (Beard et al. 1999b),

increased severity of oviductal intraepithelial cysts at 2 mg/kg/day pure pentachlorophenol administered by gavage twice weekly for 43 days (Rawlings et al. 1998), and lymphocyte infiltration into the endometrium at 1 mg/kg/day pentachlorophenol (purity not reported) in the diet for 5 weeks premating and during the gestation and lactation periods (Beard et al. 1999a). In mink, increased severity of cystic uterine glands was observed at 1 mg/kg/day pentachlorophenol (purity not reported) administered in the diet prior to mating and during gestation and lactation periods (Beard et al. 1997). No histological alterations in reproductive tissues were observed in male or female mice exposed to 330–550 mg/kg/day technical pentachlorophenol, DP-2, EC-7, or pure pentachlorophenol for 6 months (NTP 1989), male or female rats chronically exposed to 30 mg/kg/day pure pentachlorophenol in the diet for 2 years (NTP 1999), male or female mice exposed to technical-grade pentachlorophenol or EC-7 for 2 years (NTP 1989), or male or female dogs exposed to technical-grade pentachlorophenol for 1 year (EPA 1997). Additionally, no alterations in reproductive hormones (estradiol, testosterone, progesterone, follicle stimulating hormone, and/or luteinizing hormone levels) have been observed in mink (Beard et al. 1997) or sheep (Beard et al. 1999b).

Because no studies compared the effect on reproductive function of technical-grade pentachlorophenol and pure pentachlorophenol or did not report the purity, it is difficult to assess whether the observed reproductive effects are due to pentachlorophenol or one or more of the impurities. Studies on CDDs and CDFs have reported reproductive effects in laboratory animals, including decreases in fertility and histological alterations in the seminiferous tubules (ATSDR 1994, 1998).

2.17 DEVELOPMENTAL

Information on the developmental toxicity of pentachlorophenol in humans is limited. In a study of over 9,500 male sawmill workers exposed to chlorophenate (a mixture of the sodium salts of pentachlorophenol and tetrachlorophenol) and contaminants such as CDDs, a significant correlation between presumed exposure to chlorophenate and an increased incidence of congenital eye cataracts were observed in the workers' children (Dimich-Ward et al. 1996). Because there were no data on exposure level, exposure to chlorophenate was estimated by 10 experienced workers based on each cohort member's job title.

Several general population studies evaluated potential neurodevelopmental effects. No associations between maternal pentachlorophenol levels and cognitive and motor outcomes were observed in children 18 months of age (Meijer et al. 2008; Ruel et al. 2019) or 13–15 years of age (Berghuis et al. 2018). A

study of children 5–6 years of age found associations between maternal pentachlorophenol levels and motor, cognitive, and behavioral performance (Roze et al. 2009); it should be noted that this study also found associations with other organohalogens including brominated diphenyl ethers and PCBs.

A case-control study of 70 couples with a history of spontaneous abortions found an association between paternal blood pentachlorophenol levels and the risk of spontaneous abortions (odds ratio of 2.09, 95% confidence interval of 1.05–4.14 for 31 couples with high paternal pentachlorophenol exposure); no association was found with maternal pentachlorophenol levels (Chen et al. 2013b). An evaluation of the association between maternal pentachlorophenol levels and reproductive development in 90 mother-infant pairs found that maternal pentachlorophenol levels influenced follicle-stimulating hormone levels in boys and girls at 3 months, but no significant relationships were found with other reproductive hormone levels, testes volume, or penile length (Meijer et al. 2008). In a prospective birth cohort, no associations between maternal or child urinary levels of pentachlorophenol and body weight, height, weight-for-height, body mass index, or head circumference of children at 3 years of age (Guo et al. 2019).

A number of animal studies have examined the developmental toxicity of pentachlorophenol and provide evidence that gestational exposure can result in fetal/neonatal mortality, malformation/variations, decreased growth, and possibly functional deficits in rats exposed to pure pentachlorophenol or technical-grade pentachlorophenol. No developmental effects have been observed in rabbits administered up to 30 mg/kg/day technical-grade pentachlorophenol by gavage on GDs 6–18 (Bernard et al. 2001). Significant increases in post-implantation resorptions or embryo lethality were observed in rats administered 30 mg/kg/day pure pentachlorophenol or 15 mg/kg/day technical-grade pentachlorophenol by gavage on GDs 6–15 (Schwetz et al. 1974), in rats administered 80 mg/kg/day technical-grade pentachlorophenol by gavage on GDs 6–15 (Bernard and Hoberman 2001), and in the rats exposed to 46 mg/kg/day pure pentachlorophenol in the diet during mating and gestation (Welsh et al. 1987). An increase in the number of litters having more than two resorptions was also observed in rats exposed to 13 mg/kg/day pure pentachlorophenol (Welsh et al. 1987). Decreases in litter size and decreases in neonatal survival were observed in offspring of rats exposed for 77 days prior to gestation and throughout the gestation and lactation periods to 30 mg/kg/day EC-7 in the diet (Schwetz et al. 1978), rats exposed to 48 mg/kg/day technical-grade pentachlorophenol in the diet for 10 weeks prior to mating and throughout gestation and lactation (Exon and Koller 1982), and F1 and F2 rat pups exposed to 60 mg/kg/day technical-grade pentachlorophenol (Bernard et al. 2002).

The occurrence of malformations and variations has been reported in a small number of studies. An increase in the incidence of delayed ossification of the skull was observed in the fetuses of rats administered 5 mg/kg/day pure pentachlorophenol on GDs 6–15 (Schwetz et al. 1974). Soft tissue (subcutaneous edema) and skeletal (lumbar spurs, rib, vertebrae, and sternebrae) anomalies were observed in the offspring of rats exposed by gavage to 15 mg/kg/day of technical-grade pentachlorophenol or pure pentachlorophenol (Schwetz et al. 1974), skeletal (variations in vertebral, sternal, and pelvic ossification, increased rib pairs, delays in sternal forelimb and hindlimb ossification) and soft tissue (diaphragmatic hernia, slight to moderate dilation of the kidneys) malformations and variations have been observed in rat offspring administered 80 mg/kg/day technical-grade pentachlorophenol on GDs 6–15 (Bernard and Hoberman 2001), and skeletal variations were observed in the fetuses of rats exposed to 13 mg/kg/day pure pentachlorophenol prior to mating and through GD 20 (Welsh et al. 1987).

Decreases in growth have been reported in a number of developmental toxicity studies. Statistically significant decreases in fetal body weights were observed in the offspring of rats administered pure or technical-grade pentachlorophenol by gavage at doses of ≥30 mg/kg/day (Bernard and Hoberman 2001; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1974). Decreases in pup weight have been observed in the offspring of rats administered 14 mg/kg/day pure pentachlorophenol in the diet (Welsh et al. 1987), in rats in a 2-generation study administered 10 mg/kg/day technical-grade pentachlorophenol in the diet (Bernard et al. 2002), and in sheep fed 1 mg/kg/day pentachlorophenol (purity not reported) in the diet (Beard et al. 1999a).

There is some limited evidence that gestational/lactational exposure to pentachlorophenol may impair the development of the reproductive system. Significant increases in the average day of vaginal patency in F1 females exposed to 60 mg/kg/day and preputial separation in F1 males exposed to 60 mg/kg/day technical-grade pentachlorophenol (Bernard et al. 2002). Decreased fertility was also observed in the F1 generation.

Schwetz et al. (1974) examined the differences in the developmental toxicity between pure and technical-grade pentachlorophenol. The pure pentachlorophenol was slightly more toxic than the technical-grade pentachlorophenol in terms of maternal body weight gain, fetal resorptions, fetal body weight, and occurrence of fetal anomalies. The study authors estimated that the maternal dose that would be lethal to one half of the embryos was 16 mg/kg/day pure pentachlorophenol versus 44 mg/kg/day for technical-grade pentachlorophenol.

In many of the oral developmental toxicity studies, decreases in maternal body weight were observed at the same doses as the developmental effects in rats (Bernard and Hoberman 2001; Courtney et al. 1976; Schwetz et al. 1974). However, in other rat studies (Bernard et al. 2002; Welsh et al. 1987), the LOAEL for maternal toxicity was higher than the LOAEL for developmental effects (decreased fetal or pup body weight), suggesting that developmental toxicity can occur in the absence of maternal toxicity.

2.18 OTHER NONCANCER

A study of sawmill workers reported an increased incidence of nausea and fever/sweating among workers exposed to high levels of pentachlorophenol (Walls et al. 1998); see Section 2.3 for more information on this survey study.

There are limited data on the metabolic toxicity of pentachlorophenol. Nishimura et al. (1980) reported significant increases in blood glucose levels and decreases in hepatic glycogen levels in rats administered 40 mg/kg/day technical-grade sodium pentachlorophenate by gavage twice weekly for 1–3 months.

In the intermediate-duration studies conducted by NTP (1989), granular eosinophilic pigment was observed in the epithelial cells of the urinary bladder of rats exposed to technical-grade pentachlorophenol, EC-7, DP-2, and pure pentachlorophenol; the increase in pigment was not accompanied by inflammation.

2.19 CANCER

A number of epidemiological studies have evaluated the possible carcinogenicity of pentachlorophenol. Early studies conducted in the 1970s and 1980s have limited value in assessing carcinogenicity due to the use of broad occupational groups (such as wood workers or chlorophenols workers), small cohort size, follow-up periods too short to detect an excess cancer risk, mortality due to competing causes of death, and brief exposure periods. Additionally, many studies did not provide pentachlorophenol-specific exposure data. Because these studies provide limited information on the association between pentachlorophenol exposure and carcinogenicity, they are not discussed in this toxicological profile. Cohort studies (Collins et al. 2009; Demers et al. 2006; Ramlow et al. 1996; Ruder and Yiin 2011) and case-control studies (Hardell and Eriksson 1999; Hardell et al. 1994, 1995, 2002; Kogevinas et al. 1995; Pearce et al. 1986a, 1986b; Ward et al. 2009; Yang et al. 2021a) providing pentachlorophenol exposure information are summarized in Table 2-3.

Table 2-3. Summary of Select Epidemiological Studies Evaluating Possible Associations Between Cancer Outcomes and Pentachlorophenol

Reference and study population	Exposure	Measures of association (95% confidence interval)
Collins et al. 2009 Cohort study of 773 male workers at Dow manufacturing plant in Michigan; 577 of the workers had no exposure to trichlorophenol This is a follow-up to the study conducted by Ramlow et al. (1996)	Exposure estimated based on work history and historical monitoring data Worker had elevated blood levels of several hexaCDD congeners, heptaCDD, and octaCDD; 27% of the cohort developed chloracne indicating exposure to high levels of dioxins	Age and calendar year adjusted SMR (95% CI); Dow regional workers comparison group All cancers Full cohort (94 deaths): 1.0 (0.8–1.2) No trichlorophenol cohort (71 deaths): 1.0 (0.8–1.3) Non-Hodgkin lymphoma Full cohort (8 deaths): 2.4 (1.0–4.7) No trichlorophenol cohort (7 deaths): 2.8 (1.1–5.7) Kidney cancer Full cohort (4 deaths): 1.7 (0.5–4.4) No trichlorophenol cohort (4 deaths): 2.3 (0.6–5.8) Age and calendar year adjusted SMR (95% CI); Dow regional workers comparison group among workers with high cumulative exposure to CDD congeners Non-Hodgkin lymphoma 2,3,7,8-TCDD (3 deaths): 3.1 (0.6–9.1) HexaCDD (5 deaths): 5.3 (1.7–12.4) HeptaCDD (4 deaths): 4.6 (1.3–11.8) OctaCDD (4 deaths): 4.7 (1.3–12.0) TEQ (4 deaths): 4.5 (1.2–11.6)
Demers et al. 2006 Cohort study of 27,464 male sawmill workers from 14 mills in British Columbia Canada; 1,495 cancer deaths and 2,571 incident cancer cases	Exposure estimated based on detailed work history; representative exposures estimated for 3–4 time periods; dermal contact was the primary route of exposure.	Adjusted SIR values (adjusted for age and calendar period). Non-Hodgkin lymphoma incidence (92 cases): 0.99 (0.81–1.21) Multiple myeloma incidence (25 cases): 0.80 (0.52–1.18), Kidney cancer deaths (79 cases): 1.10 (0.88–1.38) See Table 2-4 for dose-response analysis data

Table 2-3. Summary of Select Epidemiological Studies Evaluating Possible Associations Between Cancer Outcomes and Pentachlorophenol

Reference and study population	Exposure	Measures of association (95% confidence interval)
Hardell and Eriksson 1999 Case-control study of Swedish males; 404 cases of non-Hodgkin lymphoma and 741 controls	Self-reported work history	Non-Hodgkin lymphoma Mostly pentachlorophenol exposure (55 cases, 87 controls): OR 1.2 (0.7–1.8)
Hardell et al. 1994 Case-control study of Swedish males; 105 cases of non-Hodgkin lymphoma and 335 controls	Self-reported work history	Non-Hodgkin lymphoma Mostly pentachlorophenol exposure (15 cases, 9 controls): OR 8.8 (3.4–24)
Hardell et al. 1995 Meta-analysis of four case-control studies conducted in Sweden (Eriksson et al. 1981, 1990; Hardell and Eriksson 1999; Hardell and Sandström 1979); total of 434 cases and 948 controls, all males	Self-reported work history	Soft tissue sarcoma Pentachlorophenol workers: OR 2.8 (1.5–5.4)
Hardell et al. 2002 Pooled data from Hardell and Eriksson (1999) and Hardell et al. (1994); 404 cases and 741 controls for non-Hodgkin lymphoma and 111 cases and 400 controls with hairy cell lymphoma, for a total of 515 cases and 1,141 controls	Self-reported work history	Non-Hodgkin lymphoma and hairy cell lymphoma (combined) Pentachlorophenol exposure (64 cases and 101 controls): OR 1.40 (0.99–1.98)

Table 2-3. Summary of Select Epidemiological Studies Evaluating Possible Associations Between Cancer Outcomes and Pentachlorophenol

Reference and study population	Exposure	Measures of association (95% confidence interval)
Kogevinas et al. 1995 Nested case control study of European workers involved in phenoxy herbicide or chlorophenols production and spraying; 32 cases and 158 controls	Company records of job histories; cumulative exposure estimated based on estimated level of exposure and duration of exposure	Non-Hodgkin lymphoma All pentachlorophenol workers (3 cases, 9 controls): OR 2.75 (0.45–17.00) High cumulative pentachlorophenol exposure (lagged 5 years) (3 cases, 5 controls): OR 4.19 (0.59–29.59)
Pearce et al. 1986a Case control study of New Zealand males; 76 cases with multiple myeloma and 315 controls with other cancer types	Self-reported work history	Multiple myeloma Ever worked as a fencer (29 cases, 87 controls) OR 1.6 (0.9–2.7)
Pearce et al. 1986b Case control study of New Zealand males; 83 cases with non-Hodgkin lymphoma and 168 controls with other cancer types	Self-reported work history	Non-Hodgkin lymphoma Ever exposed to fencing as a farmer (33 cases, 43 controls) OR 1.9 (90% CI 1.1–3.0) Ever worked as a fencing contractor (4 cases, 6 controls) OR 1.4 (90% CI 0.5–4.3) All fencing work (37 cases, 49 controls) OR 2.0 (90% CI 1.3–3.0), p=0.01

Table 2-3. Summary of Select Epidemiological Studies Evaluating Possible Associations Between Cancer Outcomes and Pentachlorophenol

Reference and study population	Exposure	Measures of association (95% confidence interval)
Ramlow et al. 1996 Cohort study of 770 male workers at Dow manufacturing plant in Michigan	Exposure estimated based on work history and historical monitoring data	Age and calendar year adjusted (95% CI); Dow regional workers comparison group Any pentachlorophenol exposure All lymphopoietic cancers (7 cases): SMR 1.4 (0.56–2.88) Other and unspecified lymphopoietic cancers (5 cases): SMR 2.0 (0.65–1.67) High cumulative exposure (0-year lag) All lymphopoietic cancers (6 cases): RR 1.91 (0.86–4.24), trend p=0.23 Other and unspecified lymphopoietic cancers (3 cases): RR 2.58 (0.98–6.80), trend p=0.08 Kidney cancer (3 cases): RR 4.16 (1.43–12.09), trend p=0.03 High cumulative exposure (15-year lag) All lymphopoietic cancers (4 cases): RR 2.01 (0.90–4.45), trend p=0.19 Kidney cancer (3 cases): RR 4.27 (1.47–12.39), trend p=0.03
Ruder and Yiin 2011 Cohort mortality study of 1,402 workers at four U.S. pentachlorophenol production facilities (excludes workers at these facilities exposed to trichlorophenol contaminated with 2,3,7,8-TCDD)	Exposure estimated from work histories	Mortality rates compared to the U.S. population All cancers (238 cases): SMR 1.25 (1.09–1.42) Respiratory cancer (105 cases): SMR 1.59 (1.30–1.92) Trachea, bronchus, lung cancer (99 cases): SMR 1.56 (1.27–1.90) Kidney cancer (4 cases): SMR 0.90 (0.25–2.31) Non-Hodgkin lymphoma (9 cases): SMR 1.41 (0.64–2.67) Multiple myeloma (6 cases): SMR 1.84 (0.68–4.00)

Table 2-3. Summary of Select Epidemiological Studies Evaluating Possible Associations Between Cancer Outcomes and Pentachlorophenol

Reference and study population	Exposure	Measures of association (95% confidence interval)
Ward et al. 2009 Case control study of 184 children (0–7 years of age) in California with acute lymphocytic leukemia and 212 matched controls	Children exposed to carpet dust containing six PCB congeners, α- and γ-chlordane, *p,p′*-DDT, *p,p′*-DDE, methoxychlor, and pentachlorophenol Geometric mean pentachloro-phenol concentration in carpet dust was 77.0 ng/g; arithmetic mean was 199.27 ng/g	Acute lymphocytic leukemia (adjusted for age, sex, race/ethnicity, age of home, and breastfeeding duration) Carpet dust concentration, trend p=0.476 2nd quartile (32.2–<75.8 ng/g) (46 cases): OR 1.28 (0.68–2.40) 3rd quartile (75.8–<164.7 ng/g) (47 cases): OR 1.46 (0.78–2.74) 4th quartile (164.7–22,676 ng/g) (31 cases): OR 0.84 (0.43–1.65) Chemical loading[a], trend p=0.045 2nd quartile (32.7–<82.2 ng/g) (50 cases): OR 0.56 (0.29–1.08) 3rd quartile (82.2–<272.5 ng/g) (50 cases): OR 0.78 (0.42–1.47) 4th quartile (≥272.5 ng/g) (50 cases): OR 0.47 (0.24–0.92)
Yang et al. 2021b, 2021c Case control study of 297 cases of thyroid cancer in China and 297 matched controls	Median urinary pentachlorophenol concentration (μg/g creatinine): Cases: 0.62 Controls: 0.39	Risk of thyroid cancer, trend p=0.008 (males p<0.001; females p=0.055) 2nd quartile (0.18–<0.40 μg/g) (60 cases): OR 1.36 (0.72–2.59) 3rd quartile (0.40–<0.95 μg/g) (88 cases): OR 2.46 (1.30–4.64) 4th quartile (≥0.95 μg/g) (111 cases): OR 3.30 (1.71–6.36) Risk of non-metastatic thyroid cancer, trend p=0.060 2nd quartile (0.18–<0.40 μg/g) (35 cases): OR 2.26 (0.82–6.22) 3rd quartile (0.40–<0.95 μg/g) (46 cases): OR 2.98 (1.12–7.87) 4th quartile (≥0.95 μg/g) (35 cases): OR 5.11 (1.67–15.60) Risk of metastatic thyroid cancer, trend p=0.019 2nd quartile (0.18–<0.40 μg/g) (39 cases): OR 0.80 (0.30–2.12) 3rd quartile (0.40–<0.95 μg/g) (25 cases): OR 3.15 (1.18–8.40) 4th quartile (≥0.95 μg/g) (38 cases): OR 4.27 (1.68–10.86) Risk of large tumor thyroid cancer (tumor diameter >1 cm), trend p=0.034 2nd quartile (0.18–<0.40 μg/g) (44 cases): OR 1.62 (0.58–4.44) 3rd quartile (0.40–<0.95 μg/g) (36 cases): OR 2.86 (1.02–8.00) 4th quartile (≥0.95 μg/g) (50 cases): OR 3.24 (1.20–8.76)

Table 2-3. Summary of Select Epidemiological Studies Evaluating Possible Associations Between Cancer Outcomes and Pentachlorophenol

Reference and study population	Exposure	Measures of association (95% confidence interval)
		Risk of unilateral thyroid cancer, trend p=0.088 2nd quartile (0.18–<0.40 µg/g) (48 cases): OR 1.63 (0.78–3.43) 3rd quartile (0.40–<0.95 µg/g) (47 cases): OR 2.54 (1.22–5.22) 4th quartile (≥0.95 µg/g) (34 cases): OR 3.14 (1.39–7.12) Risk of multifocal thyroid cancer, trend p=0.008 2nd quartile (0.18–<0.40 µg/g) (28 cases): OR 1.16 (0.36–3.78) 3rd quartile (0.40–<0.95 µg/g) (23 cases): OR 2.32 (0.60–8.93) 4th quartile (≥0.95 µg/g) (32 cases): OR 5.12 (1.56–16.74) No association with other thyroid cancer subgroups (microcarcinoma [tumor diameter ≤1 cm], bilateral, or unifocal).

[a]Chemical loading is an estimate of the amount of pentachlorophenol per square meter of carpeting.

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; CDD = chlorinated dibenzo-*p*-dioxin; CI = confidence interval; *p,p'*-DDE = *p,p'*-dichlorodiphenyldichloroethylene; *p,p'*-DDT = *p,p'*-dichlorodiphenyltrichloroethylene; hexaCDD = hexachlorodibenzo-*p*-dioxin; heptaCDD = heptachlorodibenzo-*p*-dioxin; octaCDD = octachlorodibenzo-*p*-dioxin; OR = odds ratio; PCB = polychlorinated biphenyl; RR = relative risk; SIR = standardized incidence ratio; SMR = standardized mortality ratio; TEQ = toxic equivalency for 2,3,7,8-TCDD, hexaCDD congeners, heptaCDD congeners, and octaCDD congeners

Table 2-4. Relative Risks for Cancer in Sawmill Workers Dermally Exposed to Pentachlorophenol

	RR (95% CI)[a]			
	1–2 Exposure-years	2–5 Exposure-years	5+ Exposure-years	Trend
Kidney cancer				
Mortality	1.33 (0.51–3.47) (n=6)	2.59 (1.22–5.49) (n=17)	2.30 (1.00–5.32) (n=12)	p=0.02
Incidence	1.03 (0.49–2.18) (n=9)	1.79 (0.99–3.24) (n=22)	1.66 (0.85–3.23) (n=16)	p=0.07
Soft tissue sarcoma				
Incidence	0.64 (0.18–2.20) (n=3)	0.18 (0.04–0.85) (n=2)		p=0.11
Non-Hodgkin's lymphoma				
Mortality	1.21 (0.46–3.15) (n=6)	2.44 (1.17–5.11) (n=18)	1.77 (0.75–4.21) (n=10)	p=0.06
Incidence	1.33 (0.70–2.52) (n=13)	1.88 (1.08–3.28) (n=24)	1.71 (0.91–3.24) (n=17)	p=0.03
Multiple myeloma				
Mortality	3.30 (0.87–12.51) (n=5)	1.58 (0.38–6.63) (n=4)	4.80 (1.39–16.54) (n=10)	p=0.03
Incidence	2.09 (0.57–7.61) (n=4)	1.30 (0.34–4.98) (n=4)	4.18 (1.36–12.9) (n=11)	p=0.02

[a]Adjusted relative risk values (adjusted for age, calendar period, and race)

CI = confidence interval; RR= relative risk

Source: Demers et al. 2006

A meta-analysis, which included the Hardell et al. (1994) and Kogevinas et al. (1995) case-control studies along with three other studies reporting probable exposure to pentachlorophenol, calculated the risk of Hodgkin disease (odd ratio [OR] 1.59, 95% CI 0.51–4.95), non-Hodgkin lymphoma (OR 2.65, 95% CI 1.33–5.27), and all lymphoma (OR 2.57, 95% CI 1.52–4.35) (Zheng et al. 2015).

Exposure to technical-grade and commercial-grade pentachlorophenol can result in concomitant exposure to a number of contaminants, particularly other chlorophenols, CDDs, and CDFs. As discussed in IARC (2019), some of the epidemiological studies (e.g., Collins et al. 2009; Demers et al. 2006) have assessed co-exposure to other chlorophenols and several CDDs and CDFs by using high-quality exposure assessment techniques, including measurement of CDD and CDF serum levels and estimation of cumulative dermal exposure to pentachlorophenol. IARC (2019) and EPA (2010) noted that the types of cancers observed in the pentachlorophenol workers (primarily non-Hodgkin lymphoma) differed from the pattern reported in epidemiological studies of persons highly exposed to dioxins (all cancers combined, lung cancer, soft tissue sarcoma, and non-Hodgkin lymphoma). Additionally, EPA (2010) noted that in

the Kogevinas et al. (1995) study, the association between non-Hodgkin lymphoma and pentachlorophenol was stronger than the associations with CDDs and CDFs. In studies of laboratory animals, the pattern of excess cancers was similar for pure pentachlorophenol, technical-grade pentachlorophenol, and commercial-grade pentachlorophenol.

Based on the results of cohort and case-control studies, HHS (NTP 2016), EPA (IRIS 2010), and IARC (2019) concluded that the available data demonstrated an association between pentachlorophenol and non-Hodgkin lymphoma. IARC (2019) considered the data sufficient to establish a causal relationship; HHS (NTP 2016) considered the data to be suggestive of a causal relationship but noted that it has not been established. Although increases in the risk of other tumor types were observed in some studies, IARC (2019) concluded that the findings for other tumor sites were inconsistent across studies. One case-control study published after the IARC (2019) report suggests an association between thyroid cancer and pentachlorophenol exposure in the general population (Yang et al. 2021b).

The carcinogenicity of pentachlorophenol has been evaluated in several oral exposure studies in rats and mice (NCI 1968; NTP 1989, 1999; Schwetz et al. 1978); these studies evaluated three grades of pentachlorophenol—pure pentachlorophenol, technical-grade pentachlorophenol, and EC-7; a study of transgenic mice also evaluated the carcinogenicity of pure pentachlorophenol (Tasaki et al. 2014). In a 2-year study conducted by NTP (1999), no significant increases in tumor incidence were observed in rats exposed to 30 mg/kg/day pure pentachlorophenol in the diet. However, in rats exposed via the diet to 60 mg/kg/day pure pentachlorophenol for 1 year followed by a 1-year recovery period, increases in the incidence of mesothelioma originating in the tunica vaginalis and nasal squamous cell carcinoma were observed in male rats (NTP 1999); no increases in tumor incidence were observed in the female rats. It is noted that the incidence of nasal carcinoma was not significantly higher than controls but did exceed the incidence in historical controls and the investigators considered them to be chemical-related. In *Nrf2*-deficient mice, dietary exposure to pure pentachlorophenol for 52 weeks resulted in increased incidences of cholangiocarcinomas and hepatocellular adenomas (Tasaki et al. 2014); no increases in tumor incidences were observed in *Nrf2* wild type mice.

Several studies evaluated the carcinogenicity of EC-7, which contains approximately 90% pentachlorophenol and 10% contaminants; 9.4% of the impurities are tetrachlorophenol (NTP 1989). In a preliminary study conducted by NCI (1968; results also reported in Innes et al. 1969), 46.4 mg/kg/day EC-7 in corn oil administered via gavage to mice for 18 months did not result in increases in the incidence of tumors. Schwetz et al. (1978) also reported no increases in tumor incidence in rats exposed

to 30 mg/kg/day EC-7 in the diet for 22–24 months. In contrast, NTP (1989) reported an increased incidence of hepatocellular adenomas and adrenal pheochromocytoma in male mice exposed to ≥37 mg/kg/day EC-7 in the diet for 2 years. Hepatocellular carcinomas were observed in males exposed to 118 mg/kg/day and hemangiosarcomas in the liver and spleen and hepatocellular adenomas were observed in female mice exposed to 114 mg/kg/day.

The carcinogenicity of technical-grade pentachlorophenol was evaluated by NTP (1989). Technical-grade pentachlorophenol was 90.4% pentachlorophenol with tetrachlorophenol, higher CDDs, CDFs, and chlorohydroxydiphenyl ethers as the primary contaminants. Increases in tumor incidences were observed in the liver, adrenal gland, and spleen. Neoplastic liver lesions included hepatocellular adenomas in male mice at ≥18 mg/kg/day and hepatocellular carcinoma in males at 35 mg/kg/day. In the adrenal gland, pheochromocytomas were observed in males in the ≥18 mg/kg/day groups. A significant increase in hemangiosarcomas in the liver and spleen (most observed in the spleen) were observed in female mice exposed to 35 mg/kg/day.

In initiation-promotion studies in mice, pure pentachlorophenol promoted diethylnitrosamine-induced intrahepatic biliary cysts to cholangiomas and cholangiocarcinomas and increased the formation of hepatocellular adenomas (Umemura et al. 1999, 2003a, 2003b). When pentachlorophenol was given as an initiator with phenobarbital, there were no increases in tumor incidence (Umemura et al. 1999).

In a dermal exposure study, a 20% solution of commercial-grade pentachlorophenol in benzene was applied to shaved skin of mice twice a week for 13 weeks. Mice were previously treated with a dose of 0.3% dimethylbenzanthracene (DMBA) in benzene to induce skin cancer (Boutwell and Bosch 1959). No increase in DMBA-induced skin tumors resulted from pentachlorophenol treatment.

In zetaglobin v-Has-ras (Tg·AC) transgenic female mice, dermal exposure to pentachlorophenol in acetone 5 days/week for 20 weeks in the diet for 26 weeks resulted in an increase in the incidence of skin papillomas in mice exposed to 1.5 or 3.0 mg (Spalding et al. 2000).

As reviewed by EPA (2010) and IARC (2019), there is evidence of several carcinogenic mechanisms of action for pentachlorophenol:

- *Oxidative stress.* Increases in reactive oxygen species, oxidative stress markers, and deoxyribonucleic acid (DNA) adducts associated with oxidative stress have been found in *in vitro* studies in human cells and mammalian cells, *in vivo* studies in laboratory animals, and non-mammalian test systems in response to exposure with pentachlorophenol or its metabolites

(tetrachlorohydroquinone [TCHQ] and tetrachlorobenzoquinone [TCBQ]). Several studies in mice have found dose- and time-related increases in 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels in the liver; the cumulative oxidative DNA damage could result in critical mutations.

- *Genotoxicity.* Genotoxic effects (e.g., chromosomal aberrations, sister chromatid exchanges, and single strand breaks) have been observed in *in vitro* mammalian cells exposed to pentachlorophenol or TCHQ. Mixed results have been found in *in vivo* studies for micronuclei formation, chromosomal aberrations, or sister chromatid exchanges in human lymphocytes or in rats or mice exposed to pentachlorophenol.
- *Modulation of receptor-mediated effects.* There are some suggestive data that pentachlorophenol can interact with several nuclear receptor subtypes including estrogen receptors and the Ah receptor.
- *Alterations in cell proliferation or death. In vitro* studies in human cell lines have demonstrated pentachlorophenol- and/or TCHQ-induced alterations in the expression of several genes relevant to apoptosis. *In vivo* mouse studies have demonstrated increased cell proliferation and inhibition of gap junction intercellular communication in hepatocytes.

HHS has categorized pentachlorophenol as "reasonably anticipated to be a human carcinogen" (NTP 2016) and EPA has categorized it as "likely to be carcinogenic to humans" (IRIS 2010). IARC (2019) concluded that pentachlorophenol is "carcinogenic to humans" (Group 1).

2.20 GENOTOXICITY

Numerous *in vivo* and *in vitro* studies have assessed the genotoxic potential of pentachlorophenol, and the results of these studies are presented in Tables 2-5 and 2-6, respectively. Three studies examined the clastogenic activity of pentachlorophenol in workers primarily exposed via inhalation. A marginal increase in chromosomal aberrations was found in the lymphocytes of workers exposed to pentachlorophenol or its sodium salt (Bauchinger et al. 1982). In contrast, studies by Wyllie et al. (1975) and Ziemsen et al. (1987) did not find significant increases in the occurrence of chromosomal aberrations in their studies of workers. The occurrence of sister chromatid exchange was not increased in the lymphocytes of workers (Bauchinger et al. 1982; Ziemsen et al. 1987). No other human *in vivo* genotoxicity studies were located. An increase in DNA adduct formation was observed in the liver of mice orally exposed to pentachlorophenol (Sai-Kato et al. 1995; Umemura et al. 1996, 2003a, 2006), but not in the kidney or spleen (Sai-Kato et al. 1995), and positive results were seen in a coat color spot test in mouse embryos treated transplacentally with pentachlorophenol (Fahrig et al. 1978). Evidence of DNA damage (increased levels of 8-oxodeoxyguanosine in the liver) was observed in rats orally exposed to 60 mg/kg/day pentachlorophenol in the diet for 27 weeks (Lin et al. 2002). However, DNA damage was not observed when the rats were exposed to a single gavage dose of 120 or 60 mg/kg/day for 5 days (Lin et al. 2002). No evidence of genotoxicity was observed in assays of sex-linked recessive lethal mutations in *Drosophila melanogaster* (Fahrig 1974; Fahrig et al. 1978; Vogel and Chandler 1974), micronuclei

formation in rats and mice (NTP 1999), and gene mutations and recombination in a mouse spot test (Fahrig and Steinkamp-Zucht 1996).

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

Species (exposure route)	Endpoint	Results	Reference
Drosophila melanogaster spermatocytes	Sex-linked recessive lethal mutation	–	Fahrig 1974; Fahrig et al. 1978; Vogel and Chandler 1974
Human lymphocytes (occupational exposure)	Chromosomal aberrations	(+)	Bauchinger et al. 1982
		–	Wyllie et al. 1975
		–	Ziemsen et al. 1987
	Sister chromatid exchange	–	Bauchinger et al. 1982
		–	Ziemsen et al. 1987
B6C3F1 mouse (oral exposure)	DNA adduct formation	+	Sai-Kato et al. 1995; Umemura et al. 1996, 2003a, 2006
Fischer 344 rats (oral exposure for 1 or 5 days)	DNA damage	–	Lin et al. 2002
		+	Lin et al. 2002
Mouse bone marrow (intraperitoneal exposure)	Micronuclei	–	NTP 1999
		–	NTP 1999
Mouse embryonic cells (transplacental exposure)	Gene mutation	(+)	Fahrig et al. 1978
Mouse/spot test	Gene mutation	–	Fahrig and Steinkamp-Zucht 1996
	Recombination	–	Fahrig and Steinkamp-Zucht 1996

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

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

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Prokaryotic organisms				
Salmonella typhimurium	Gene mutation	–	–	Donnelly et al. 1998; EPA 1977; Kubo et al. 2002; Markiewicz et al. 1996; Moriya et al. 1983; NTP 1999; Waters et al. 1982
S. typhimurium/spot test	Gene mutation	NT	–	Andersen et al. 1972; Lemma and Ames 1975
S. typhimurium (mouse host-mediated assay)	Gene mutation	–	NT	Buselmaier et al. 1973
Escherichia coli/spot test	Gene mutation	NT	–	Waters et al. 1982
Serratia marcescens/spot test	DNA damage	NT	–	Fahrig 1974

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

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Bacillus subtilis/rec- assay	DNA damage	NT	+	Waters et al. 1982
E. coli pol A	DNA damage	NT	–	Waters et al. 1982
Eukaryotic organisms				
Saccharomyces cerevisiae MP-1	Gene mutation	NT	+	Fahrig et al. 1978
S. cerevisiae aAeZ	Recombination	NT	+	Fahrig 1974
S. cerevisiae MP-1/ intergenic recombination	Recombination	NT	–	Fahrig et al. 1978
S. cerevisiae MP-1/ intergenic recombination	Recombination	NT	+	Fahrig et al. 1978
S. cerevisiae	Recombination	+	+	Waters et al. 1982
Mammalian cells				
Human lymphocytes	Chromosomal aberrations	NT	(+)	Fahrig 1974
Human lymphocytes	DNA damage (single strand breaks)	NT	+	Maheshwari and Mahmood 2020a
Human lymphocytes	DNA damage (single strand breaks)	NT	+	Maheshwari and Mahmood 2020b
Chinese hamster ovary cells	Chromosomal aberrations	(+)	–	NTP 1999
Chinese hamster ovary cells	Sister chromatid exchange	–	(+)	NTP 1999
Human nasal mucosal cells	DNA damage	NT	+	Tisch et al. 2005
Chinese hamster ovary cells	DNA damage	NT	–	Ehrlich 1990
Chinese hamster V79 cells	DNA damage (8-OH-dG adduct)	NT	–	Dahlhaus et al. 1996
Chinese hamster V79 cells	DNA damage (single-strand breaks)	NT	–	Dahlhaus et al. 1996
Mouse embryonic fibroblast cells	DNA damage (single-strand breaks)	(+)	–	Wang and Lin 1995
Chinese hamster ovary cells	DNA repair defect	NT	–	Johansson et al. 2004

+ = positive results; (+) = weakly positive results; – = negative results; DNA = deoxyribonucleic acid; NT = not tested

No alterations in the occurrence of gene mutations (Andersen et al. 1972; Donnelly et al. 1998; EPA 1977; Lemma and Ames 1975; Markiewicz et al. 1996; Moriya et al. 1983; NTP 1999; Waters et al. 1982) or DNA damage (Fahrig 1974; Waters et al. 1982) were observed in bacterial systems, with the exception of one study that reported positive activity in the rec assay using *Bacillus subtilis* (Waters et al. 1982). In yeast, pentachlorophenol induced gene mutations (Fahrig 1974; Fahrig et al. 1978) and genetic recombination (Fahrig et al. 1978; Waters et al. 1982). Weak clastogenic activity was observed in

chromosomal aberration assays in human lymphocyte (Fahrig 1974) and in chromosomal aberration and sister chromatid exchange assays in Chinese hamster ovary cells (NTP 1999). No significant increases in the occurrence of DNA damage (adduct formation or single-strand breaks) were seen in mouse and hamster cell lines (Dahlhaus et al. 1996; Ehrlich 1990; Wang and Lin 1995); however, increased DNA damage was observed in human nasal mucosal cells (Tisch et al. 2005) and lymphocytes (Maheshwari and Mahmood 2020a, 2020b).

2.21 MECHANISMS OF ACTION

It is widely believed that pentachlorophenol exerts its toxic effects, at least in part, by uncoupling mitochondrial oxidative phosphorylation, thereby causing accelerated aerobic metabolism and increased heat production. Pentachlorophenol has been found to bind to purified rat liver mitochondrial protein. This may induce conformational changes in enzymes involved in oxidative phosphorylation (Weinbach and Garbus 1965). The pattern of pentachlorophenol-induced toxicity often seen in humans and animals supports this proposed mechanism of action. A young worker who died following 3 weeks of exposure to pentachlorophenol dust in a chemical plant was found to have cerebral edema and fatty degeneration of liver and lungs at autopsy (Gray et al. 1985). The study authors concluded that these clinical findings are consistent with a hypermetabolic state resulting from a derangement of aerobic metabolism and characterized by hyperthermia, which can lead to tachycardia, tachypnea, hyperemia, diaphoresis, and metabolic acidosis. This is usually followed by death and rapid, profound rigor mortis. Toxicity resulting from uncoupling of oxidative phosphorylation was generally seen prior to death in animals acutely exposed to pentachlorophenol. These included accelerated respiration, hyperemia, cardiac and muscular collapse, asphyxial convulsions, death, and rapid rigor mortis (St. Omer and Gadusek 1987). The ultrastructural changes observed in mitochondria from liver cells of rats treated with technical-grade pentachlorophenol for 15 days are consistent with uncoupling of oxidative phosphorylation (Fleischer et al. 1980).

The cell membrane is apparently a possible site of action for pentachlorophenol. Lipid bilayers of purified and total cell membranes have been reported to destabilize following sublethal pentachlorophenol treatment (Duxbury and Thompson 1987). This was evidenced by a 50% decrease in bulk lipid fluidity attributable to disruption of the bilayer by pentachlorophenol. These authors also found that pentachlorophenol partitions into the hydrophobic interior of the bilayer. Other membrane changes observed by these investigators included a decrease in phospholipid phosphate levels that they believe was a result of a

selective chemical effect on phospholipase C. However, the authors concluded that this was only a sublethal effect since the cells remained viable.

In another investigation of the physicochemical basis of pentachlorophenol membrane effects, membrane toxicity was associated with the pentachlorophenol-induced change in hydrogen ion permeability of the membrane lipid matrix (Smejtek 1987). The onset of toxic effects was correlated with the loss of membrane electrical resistance and a measurable amount of pentachlorophenol binding to the membrane. In human neuroblastoma cells and lymphocytes, *in vitro* exposure to pentachlorophenol or its metabolites, TCBQ and TBHQ, reduced mitochondrial membrane potential, resulting in mitochondrial dysfunction (Fraser et al. 2019; Maheshwari and Mahmood 2020a). These changes were accompanied by oxidative stress (e.g., increased reactive oxidant species, decreased antioxidant enzymes) followed by apoptosis, lysis, and/or necrosis of cells. Fraser et al. (2019) concluded that since mitochondrial dysfunction was observed sooner than oxidative stress, it was a precursor event. However, oxidative stress, heme degradation, and hemolysis were also observed in red blood cells, which lack mitochondria (Maheshwari and Mahmood 2020a, 2020b; Maheshwari et al. 2019)

Studies described above indicate that pentachlorophenol can disrupt membrane structure and function. These effects could conceivably occur throughout the body and could therefore explain the wide range of toxic effects associated with pentachlorophenol, including the uncoupling of oxidative phosphorylation.

Oral and intraperitoneal administration of pentachlorophenol to animals causes adverse effects on thyroid homeostasis (e.g., decreased serum T4) and on the thyroid gland (Beard and Rawlings 1998; Beard et al. 1999a; Jekat et al. 1994; van Raaij et al. 1991b). These effects may occur during gestation, pregnancy, and lactation (Beard and Rawlings 1998; Beard et al. 1999a). Further *in vitro* studies by van Raaij et al. (1991a) revealed that the likely mechanism of action for this anti-thyroid effect of pentachlorophenol was competition for serum protein T4 binding sites. van Raaij et al. (1994) subsequently demonstrated a dose- and time-dependent uptake of pentachlorophenol into the cerebrospinal fluid of rats following single intraperitoneal injections. Since similar doses of pentachlorophenol also significantly decreased the uptake of radiolabeled T4 into cerebrospinal fluid, the study authors suggested that pentachlorophenol may interact with the T4 binding site of transthyretin and compete with T4 for uptake into cerebrospinal fluid (van Raaij et al. 1994). This is a plausible explanation since the affinity of pentachlorophenol for the T4 binding site on transthyretin is 2.5-fold greater than that of T4 itself (den Besten et al. 1991).

Such effects on thyroid parameters, combined with the activity of pentachlorophenol as a potent inhibitor of oxidative phosphorylation (Weinbach 1954), may be expected to have general adverse effects on basal metabolic rate and many critical processes including development, reproduction, nervous system function, and the specific functioning of endocrine and other organs.

In addition, the effects of pentachlorophenol on thyroid homeostasis and the availability of T4 to the central nervous system may have adverse effects on development of the nervous system. Deficiencies in T4 during prenatal and postnatal life can cause decrements in intellectual function in children (Bargagna et al. 1997; Birrell et al. 1983; Kooistra et al. 1994), and hypothyroidism in animals leads to disorders in structural and functional development of the brain (Gould et al. 1990; Neveu and Arenas 1996; Stein et al. 1991; Vega-Nunez et al. 1995). However, testing has not been performed on animals exposed to pentachlorophenol, either prenatally or postnatally, to examine the potential for the anti-thyroid effects of pentachlorophenol to produce adverse effects on neurobehavior. *In vitro*, pentachlorophenol binds microtubule-associated protein in hippocampal neurons, resulting in increased dendritic length; such disturbances in neurite outgrowth during development could result in altered neurological function (Matsunaga et al. 2010).

Recent studies in rats and mice involved the characterization of chlorinated protein adducts arising from pentachlorophenol metabolism following oral administration of pentachlorophenol (Lin et al. 1997; Waidyanatha et al. 1994, 1996). Results from these studies and previously summarized studies suggest that the metabolism of pentachlorophenol can proceed through the quinols, TCHQ and tetrachlorocatechol (Cl_4CAT), via microsomal cytochrome P-450 enzymes and that these quinols can be oxidized via semiquinone intermediates (tetrachloro-1,2-semiquinone [Cl_4-1,2-SQ] and tetrachloro-1,4-semiquinone [Cl_4-1,4-SQ]) into the corresponding quinones (tetrachloro-1,2-benzoquinone [Cl_4-1,2-BQ] and tetrachloro-1,4-benzoquinone [Cl_4-1,4-BQ]). Both the quinones and semiquinones are electrophilic and can bind to cellular macromolecules (Lin et al. 1997). The redox cycling associated with oxidation of TCHQ and reduction of Cl_4-1,4-BQ generates oxygen radicals that caused an increase in 8-hydroxy-2-deoxyguanosine levels in liver DNA in mice that had been fed pentachlorophenol (Sai-Kato et al. 1995; Umemura et al. 1996) or TCHQ (Dahlhaus et al. 1994) in the diet for up to 4 weeks. It is possible that the formation of such adducts is involved in the induction of hepatic neoplasms in mice (NTP 1989). Lin et al. (1997) measured levels of chlorinated protein adducts arising from pentachlorophenol metabolism in the livers of mice and rats administered pentachlorophenol in the diet for up to 4 weeks. After aggregation of the estimated contributions of all quinone species derived from pentachlorophenol metabolism, mice had a 4-fold greater dose to liver nuclei than rats, whereas rats had a

3-fold greater dose to liver cytosol than mice. The increased nuclear dose to mouse liver compared to that of the rat suggests that the mouse is at greater risk to hepatic DNA damage from pentachlorophenol-derived quinones. Using a model to predict quinone and semiquinone production, Lin et al. (1999) estimated that at low doses of pentachlorophenol, the production of semiquinone adducts was proportionally greater in rats than mice; in mice, direct oxidation to quinones and the production of quinone adducts is favored in mice exposed to low doses of pentachlorophenol. These data suggest that both the types and amounts of adducts differ in rats and mice, which may account for the occurrence of liver tumors in mice but not in rats in bioassays conducted by NTP (1989, 1999).

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

3.1 TOXICOKINETICS

- Pentachlorophenol is efficiently absorbed following inhalation, oral, and dermal exposure.
- Pentachlorophenol is distributed throughout the body, with the highest levels in the liver and kidneys. The binding of pentachlorophenol to plasma proteins plays a significant role in the distribution of pentachlorophenol.
- The available human and animal data indicate that metabolism of pentachlorophenol does occur in the liver, and the major pathways are conjugation to form the glucuronide and oxidative dechlorination to form tetrachlorohydroquinone (TCHQ).
- The primary route of pentachlorophenol elimination in all species studied, including humans, is urine, with lesser amounts (around 10%) excreted in the feces. Enterohepatic circulation and plasma protein binding influence the elimination kinetics of pentachlorophenol, but no data are available to assess whether the elimination kinetics of pentachlorophenol are dependent on its concentration in blood.

3.1.1 Absorption

The limited data available on the absorption of inhaled pentachlorophenol suggest that it is readily absorbed. In a study of two volunteers exposed to 0.230 or 0.432 ng/m^3 pentachlorophenol for 45 minutes, 88 and 76%, respectively, was absorbed, based on measurements of respiratory rates during exposure, total urinary pentachlorophenol recovered for up to 1 week postexposure, and tidal volume estimates (Casarett et al. 1969). In rats exposed to pentachlorophenol for 20 minutes, 70–75% of radioactivity was recovered in urine, plasma, liver, and lung by 24 hours postexposure (Hoben et al. 1976a).

Oral absorption of pentachlorophenol (as the sodium salt in water) in humans was determined to be first order, with peak blood levels of 0.248 μg/mL pentachlorophenol being achieved within 4 hours of ingestion of 0.1 mg sodium pentachlorophenate/kg by four healthy male volunteers (Braun et al. 1979). The average half-life of absorption was calculated to be approximately 1.3 hours, indicating that oral absorption of pentachlorophenol in humans is rapid.

Similar results were observed in studies of monkeys, rats, and mice. Following gavage administration of a single dose of pentachlorophenol, peak plasma levels were achieved 1.5–6 hours after administration (Braun and Sauerhoff 1976; Braun et al. 1979; Reigner et al. 1991, 1992b; Yuan et al. 1994), and the half-life of absorption ranged from 0.25 to 1.5 hours (Reigner et al. 1991; Yuan et al. 1994). Absorption efficiencies ranging from 86 to 100% were reported in rats administered pentachlorophenol via gavage (Reigner et al. 1991; Yuan et al. 1994). Yuan et al. (1994) estimated efficiencies of 100% at

9.5 mg/kg/day and 86% at 38 mg/kg/day. In contrast, Pu et al. (2003) found slightly higher bioavailability in rats receiving a single 300 mg/kg dose (87.8%), as compared to a 100 mg/kg dose (75.0%). A somewhat lower absorption efficiency was observed in a dietary exposure study, absorption efficiencies of 52 and 30% were estimated in rats exposed to approximately 21 or 64 mg/kg/day pentachlorophenol, respectively, in the diet for 5 days (Yuan et al. 1994). A 1-week drinking water study in rats found that sodium pentachlorophenate (0.05 mg/kg/day) is almost completely absorbed (Meerman et al. 1983). The available data suggest that pentachlorophenol may interact with dietary constituents, which may decrease its absorption following dietary exposure.

Oral bioavailability of pentachlorophenol in several soil samples were 36–55% and 46–77% at 100 and 200 mg/kg doses, respectively (Pu et al. 2003). The relative bioavailability, as compared to pentachlorophenol in corn oil, were 48–62% at 100 mg/kg and 52–87% at 200 mg/kg. The study did not find any obvious correlations between bioavailability and soil properties.

Using human abdominal skin (dermis and epidermis) obtained at autopsy, it has been demonstrated that 62% of pentachlorophenol in diesel oil solution penetrated skin *in vitro*, while only 16% of an aqueous solution of sodium pentachlorophenate penetrated skin (Hortsman et al. 1989). Thus, it appears that pentachlorophenol is absorbed to a much greater extent in an oily solution than in an aqueous solution following dermal exposure in humans.

Animal studies support the human findings that pentachlorophenol is absorbed across the skin. In a Rhesus monkey study, pentachlorophenol was well absorbed following percutaneous application in soil or in acetone (Wester et al. 1993). Under the conditions of this study (0.7 μg/cm^2 in soil and 0.8 μg/cm^2 in acetone of ^{14}C-pentachlorophenol applied for 24 hours to abdominal skin), 24.4% of the applied dose in soil and 29.2% of the applied dose in acetone were absorbed. In an *in vivo* swine model, 40 μg/cm^2 [^{14}C-UL]-pentachlorophenol was applied occlusively or nonocclusively in a soil-based mixture to a clipped abdominal site of female pigs (Qiao et al. 1997). By 408 hours after dosing, total radiolabel absorption was 29.08% under nonocclusive conditions and 100.72% under occlusive conditions. When antibiotics (neomycin sulfate, bacitracin, and polymyxin B) were co-dosed with occlusively applied [^{14}C-UL]-pentachlorophenol, total radiolabel absorption by 408 hours was 86.21%. If it is assumed that the antibiotics had no direct effect on the dermal absorption of pentachlorophenol, then the inhibition of dermal absorption by the antibiotics suggests that degradation of pentachlorophenol by skin microorganisms may play a role in dermal absorption. The percentage of applied dose present in blood or plasma reached maxima at approximately 96 hours under occlusive conditions (with or without

antibiotics) and 144 hours under nonocclusive conditions. These results indicate that pentachlorophenol is readily absorbed following dermal exposure and is bioavailable from soil. In a second study using an *in vivo* swine model and a prolonged exposure period (264-408 hours) (Qiao and Riviere 2002), 50.15% of the pentachlorophenol was absorbed; pretreatment with benzo[a]pyrene (BaP) increased absorption to 56.77%. The investigators suggested that the increased absorption in pigs pre-exposed to BaP was due to BaP-induced cutaneous cytochrome P-450.

3.1.2 Distribution

There are limited data on the distribution of pentachlorophenol in humans. The distribution of background levels of pentachlorophenol was measured in the urine and tissues collected during the autopsy of 21 humans (Grimm et al. 1981). The highest concentrations of pentachlorophenol were found in the liver (0.067 μg/g), kidneys (0.043 μg/g), brain (0.047 μg/g), spleen (0.019 μg/g), and body fat (0.013 μg/g). The median pentachlorophenol levels in the urine and blood were 0.0044 and 0.033 μg/mL, respectively.

The distribution of pentachlorophenol following a 20-minute inhalation exposure was examined in rats exposed to an aerosol of pentachlorophenol for 1–5 days (Hoben et al. 1976a). Immediately after exposure, 1.8% of the dose was present in the lungs; 24 hours after exposure, approximately 0.7% of the dose was present in the lungs. Shortly after exposure, 35 and 25% of the dose was present in the plasma and liver, respectively; 24 hours post-exposure 8–10% was detected in these tissues. The investigators proposed that the similarity of the clearance rates in the plasma and liver suggests that there is no apparent storage or preferential binding at these sites. Repeated-exposure experiments support the observation that pentachlorophenol does not accumulate in rats following inhalation exposure. By 24 hours after the last (fifth) exposure, 70% of the administered dose was recovered in urine, 5% in plasma, 4% in liver, and 0.3% in lung. It is not clear from these data where pentachlorophenol was distributed immediately following exposure, but high levels in urine suggest that pentachlorophenol was cleared rapidly and did not reach an appreciable body burden following repeated exposure.

Nine days after oral administration of a single dose of 10 mg/kg [^{14}C]-pentachlorophenol in corn oil to rats, the highest levels of radioactivity were found in liver and kidneys (0.315 and 0.045% of the administered dose, respectively) and lower levels are found in the stomach, lungs, testes, ovaries, brain, heart, spleen, and adrenals (0.005% of dose) (Braun et al. 1977). Levels of radioactivity were uniformly higher in plasma and tissues of females as compared to males, although the distribution pattern was

qualitatively the same. In a study of two female monkeys orally administered 10 mg/kg [^{14}C]-pentachlorophenol, the highest concentrations of radioactivity were found in the large intestine, small intestine, and liver (5.00, 2.60, and 1.41% of the administered dose) 15 days post-exposure (Braun and Sauerhoff 1976).

Studies in rats demonstrated that following oral repeated exposure, plasma pentachlorophenol concentrations are proportional to dose (NTP 1999; Yuan et al. 1994). In the NTP (1999) 2-year study, plasma pentachlorophenol concentrations were 24, 44, and 67 µg/mL in females and 17, 36, and 53 µg/mL in males at dietary concentrations of 200, 400, and 600 ppm, respectively. Similar to the findings of Braun et al. (1977), the plasma pentachlorophenol levels were higher in females than in males.

The distribution of radiolabelled pentachlorophenol was examined in female pigs following occlusive application of 40 µg/cm^2 [^{14}C-UL]-pentachlorophenol in a soil-based mixture (Qiao et al. 1997). The distribution of radiolabel 17 days after dosing was as follows (highest to lowest): liver, lung, ovary, gall bladder, kidney, spleen, uterus, urinary bladder, heart, diaphragm, and brain. A large amount of the label was retained in the body, approximately 50–67% of the absorbed label was present in the tissues 17 days after exposure. Similar results were found when the radiolabeled pentachlorophenol was administered in an ethanol vehicle (Qiao and Riviere 2002). After 264 hours, 22% was retained in local skin, fat, and muscle and 18% was found in inner organs of pigs; in the inner organs, the highest levels were found in the liver, ovaries, kidneys, lungs, gall bladder, uterus, and small intestine.

Distribution of radioactivity in mice following intraperitoneal and subcutaneous administration of single doses of [^{14}C]-pentachlorophenol has been reported (Jakobson and Yllner 1971). Only 0.4–6% of the administered dose was found in tissues 96 hours after intraperitoneal injection of 14.8–37.2 mg [^{14}C]-pentachlorophenol/kg body weight. The highest concentrations of radiolabel were found in the gall bladder, liver, stomach wall, and gastrointestinal contents, indicating the occurrence of biliary secretion of pentachlorophenol. Lesser amounts of radiolabel were found in the kidneys, heart, and brain. A similar distribution pattern was observed after subcutaneous administration of 50 mg [^{14}C]-pentachlorophenol/kg body weight. The concentration of radiolabel in the liver remained high 1 week after dosing. These data are similar to those obtained after oral administration of pentachlorophenol. Based on plasma concentrations and clearance rates, the volume of distribution of pentachlorophenol was estimated to be relatively small and approximately correspond to the volume of distribution of albumin and volume of extracellular fluid following intravenous injection of a single dose of 2.5 mg/kg to rats (Reigner et al. 1991). Similar results were obtained in mice (Reigner et al. 1992b). Following intravenous

administration of 5 mg/kg pentachlorophenol (>99% purity) in rats, plasma concentrations tended to be slightly higher in males than in females during the first 12 hours. The volume of distribution was 0.13±0.006 L/kg in males and 0.19±0.04 L/kg in females, but the difference was not statistically significant (Yuan et al. 1994).

Binding of pentachlorophenol to plasma proteins plays a significant role in the distribution of pentachlorophenol. Tissue/plasma ratios and renal clearance rates following oral administration of pentachlorophenol were much lower than would be predicted, based on the octanol/water partition coefficient and glomerular filtration rate (Braun et al. 1977). This could be explained by extensive binding of pentachlorophenol to plasma proteins. The authors subsequently demonstrated that 95% of pentachlorophenol in plasma is protein bound (Braun et al. 1977). In another experiment in rats, 97.1±2.0% of the administered dose of pentachlorophenol was found bound to plasma proteins as compared to plasma lipoproteins (Gómez-Catalán et al. 1991). An inhalation study found that the binding of pentachlorophenol to plasma proteins varies linearly with increasing dose (Hoben et al. 1976c). An *in vitro* study found that the percentage of unbound pentachlorophenol in serum was 1.37 in mice, 0.85 in rats, 0.67 in monkeys, 0.53 in humans, and 0.43 in cows. Percent unbound pentachlorophenol was inversely correlated with serum protein concentrations (Reigner et al. 1993). These data suggest that the distribution of pentachlorophenol may be restricted due to extensive plasma protein binding.

A limited number of studies have evaluated maternal transfer of pentachlorophenol. A general population study of 15 women reported a correlation between maternal plasma pentachlorophenol levels and cord blood plasma levels (Guvenius et al. 2003). The median maternal plasma and cord blood plasma pentachlorophenol levels were 2,830 and 1,960 pg/g, respectively. Pentachlorophenol levels in breast milk were about 100 times lower; the median level was 20 pg/g. Other studies have also reported low levels of pentachlorophenol in breast milk (Gebefugi and Korte 1983; Veningerova et al. 1996). A study of participants in the Northern Norway Mother-Child Contaminant Cohort Study found a correlation between pentachlorophenol levels in infant meconium samples and second trimester maternal serum pentachlorophenol levels (Veyhe et al. 2013). Larsen et al. (1975) administered a single oral dose of 60 mg/kg pentachloro[U-^{14}C]phenol (99.54% radiochemical purity) to rats on GD 15. Tissue distributions, expressed as the percentage of administered dose per gram tissue, were 0.88% in blood serum, 0.20% in placentas, and 0.05% in fetuses at 2 hours after dosing. By 32 hours after dosing, percentages of administered dose were 0.43% in serum, 0.08% in placentas, and 0.04% in fetuses. Peak amounts occurred in serum at 8 hours (1.12%), in placentas at 12 hours (0.28%), and in fetuses at 12 hours (0.08%).

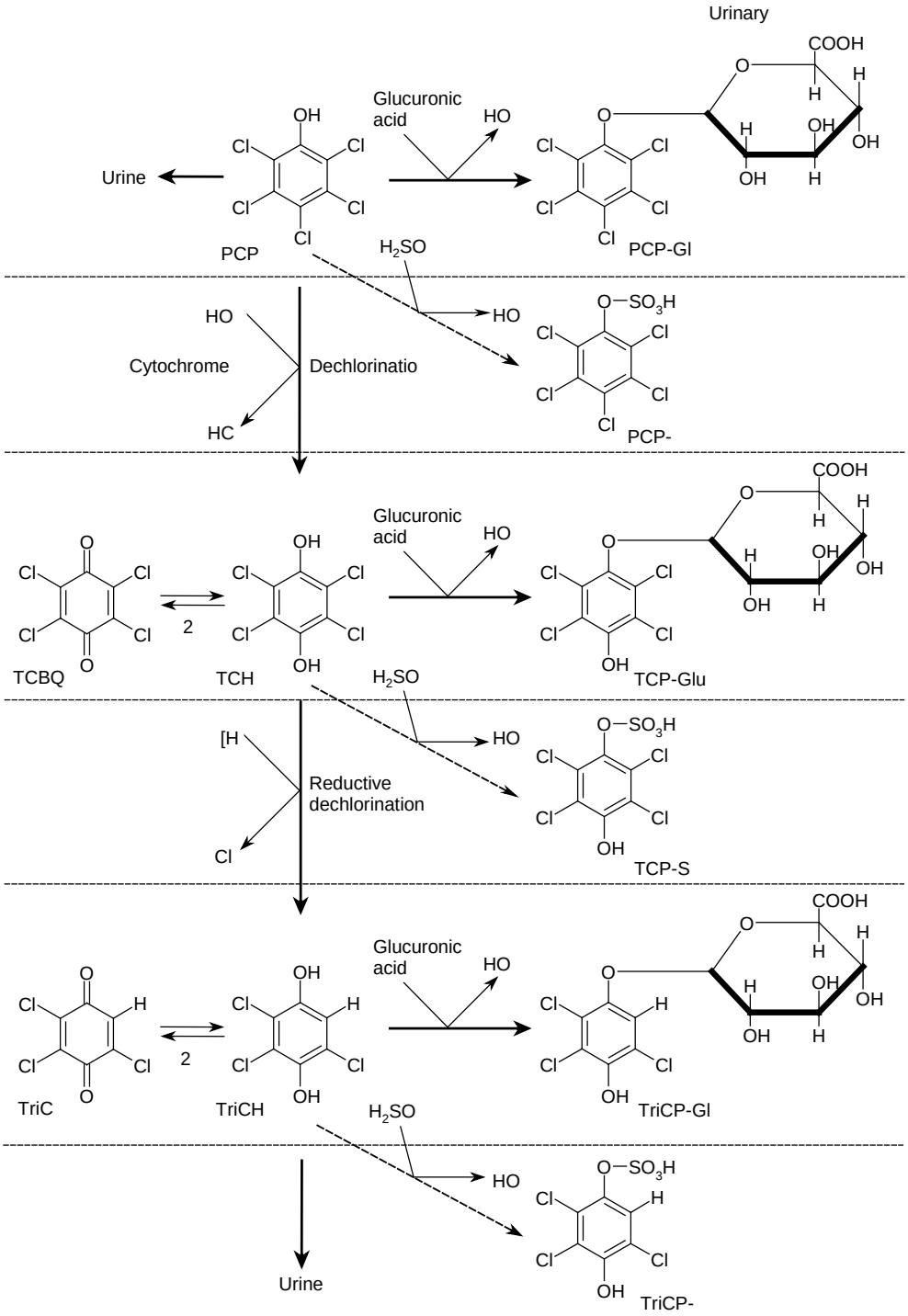
3.1.3 Metabolism

Available human and animal data indicate that metabolism of pentachlorophenol occurs in the liver, and the major pathways are conjugation to glucuronide and oxidative dechlorination to form TCHQ. A summary of possible metabolic pathways for pentachlorophenol is presented in Figure 3-1.

Studies in humans suggest that approximately 80–90% of an administered dose is excreted as unchanged pentachlorophenol or pentachlorophenol glucuronide conjugate in the urine (Reigner et al. 1992a; Uhl et al. 1986), with most excreted as the glucuronide conjugate. Another study reported that 78% of the administered dose was excreted as unchanged pentachlorophenol (Braun et al. 1979); however, the discrepancy may be due to the analytical method used to measure urinary levels, which resulted in hydrolysis of the pentachlorophenol glucuronide to form pentachlorophenol in the urine (Reigner et al. 1992a). A study of two workers exposed via inhalation reported the presence of TCHQ in the urine (Ahlborg et al. 1974); dechlorination is considered to be a minor route of metabolism.

In mice receiving a 20 mg/kg gavage dose, approximately 50% of the pentachlorophenol dose was excreted as glucurono- and sulfo-pentachlorophenol conjugates, 6–9% as unchanged pentachlorophenol, and the remainder as TCHQ or TCHQ conjugates (Reigner et al. 1992b). Studies in rats indicate that most of the administered dose was excreted as pentachlorophenol and TCHQ and their glucurono- and sulfo-conjugates (Ahlborg et al. 1974; Braun et al. 1977; Reigner et al. 1991; Renner 1989; Renner and Hopfer 1990). The following urinary metabolites were recovered and identified by gas chromatography from female Sprague-Dawley rats dosed with pentachlorophenol (>99% pure) for 28 days: 2,3,4,5-tetrachlorophenol; 2,3,4,6-tetrachlorophenol; 2,3,5,6-tetrachlorophenol; Cl_4CAT; trichloro-1,4-benzenediol; tetrachloro1,4-benzenediol; tetrachlororesorcinol; trichlorohydroquinone; TCHQ; and traces of trichloro1,4-benzoquinone and tetrachloro-1,4-benzoquinone. The major metabolite was TCHQ, which was excreted mainly as a glucuronide conjugate (Renner and Hopfer 1990). Based on the urinary metabolites identified, the study authors concluded that the main metabolic pathway for pentachlorophenol in the rat was pentachlorophenol to 2,3,5,6-tetrachlorophenol to TCHQ, with a minor pathway being pentachlorophenol to 2,3,4,6- and 2,3,4,5-tetrachlorophenol to trichlorohydroquinone. Results of studies in rats and mice indicate that metabolism of pentachlorophenol following intraperitoneal injection is similar to that observed following oral exposure (Ahlborg et al. 1978; Jakobson and Yllner 1971).

Figure 3-1. Proposed Metabolic Scheme for Pentachlorophenol



PCP = pentachlorohenol; PCP-Glu = pentachlorophenol-β-glucuronide; PCP-S = pentachlorophenylsulfate; TCHQ = tetrachloro-*p*-hydroquinone; TCP-Glu = tetrachlorophenol-β-glucuronide; TCP-S = tetrachlorophenylsulfate; TCBQ = tetrachlorobenzoquinone; Tri CHQ = trichloro-*p*-hydroquinone; Tri CP-Glu = richlorophenyl-β-glucuronide; Tri CP-S = trichlorophenylsulfate; Tri CQ = trichloro-*p*-quinone

It has been demonstrated that the monkey differs from the rat and mouse in that virtually all radioactivity recovered in urine following oral administration of 10 mg [^{14}C]-pentachlorophenol/kg was associated with pentachlorophenol; no TCHQ or glucuronide conjugates were identified (Braun and Sauerhoff 1976). These data suggest that pentachlorophenol is not metabolized to any great degree by the monkey. As noted previously, the lack of pentachlorophenol conjugates in urine may be due to hydrolysis of urinary pentachlorophenol glucuronide; thus, conclusions regarding the metabolism of pentachlorophenol cannot be drawn from this study.

The rate of pentachlorophenol-glucuronide conjugation in human liver microsomes is reported to be one-third of that found in rat liver microsomes (Lilienblum 1985), although phenobarbital-enhanced dechlorination of pentachlorophenol, phenobarbital, and 3-methylcholanthrene (another microsomal enzyme inducer) had little effect on the conjugation reaction in rat liver microsomes (Ahlborg et al. 1978). This indicated that the extent of glucuronide conjugation was governed by factors other than phenobarbital- and 3-methylcholanthrene-inducible microsomal enzyme activity.

In vitro studies in both human and rat liver homogenates clearly demonstrate that pentachlorophenol is converted to TCHQ (Juhl et al. 1985). Pentachlorophenol was identified as an inducer of cytochrome P450 3A in cultured rat hepatocytes, quail hepatocytes, and human hepatoma (Hep G2) cells (Dubois et al. 1996). Mehmood et al. (1996) provided evidence that human cytochrome P450 3A may metabolize pentachlorophenol to TCHQ in phase I metabolism of pentachlorophenol. In humans, this enzyme has low activity in the first month of life, with approach toward adult levels by 6–12 months of postnatal age; adult activity may be exceeded between 1 and 4 years of age and then activity progressively declines, reaching adult levels at the conclusion of puberty (Leeder and Kearns 1997).

Binding of pentachlorophenol to specific components of liver cells or differential distribution of pentachlorophenol to different cellular organelles can affect its metabolic fate or that of other xenobiotics and ultimately regulate the manifestation of toxic effects. The relative concentration of pentachlorophenol in microsomes was 6 times greater than in mitochondria in rats receiving a single gavage dose of pentachlorophenol (Arrhenius et al. 1977). Since maximum effects on inhibition of microsomal detoxification processes (requiring electron transport from flavin to cytochrome) occur at a pentachlorophenol concentration (100 μM) that is 4 times greater than the concentration of pentachlorophenol required to cause maximum inhibition of oxidative phosphorylation in mitochondria (25 μM), Arrhenius et al. (1977) suggested that inhibition of mitochondrial oxidative phosphorylation and inhibition of microsomal detoxification by pentachlorophenol might be equally important. The possibility that the

presence of pentachlorophenol in microsomes allows this substance to inhibit its own metabolism provides a possible explanation for the relative lack of pentachlorophenol metabolism seen in all species studied. Another possible explanation is that extensive plasma binding of pentachlorophenol limits distribution of pentachlorophenol to the liver for subsequent biotransformation. In either case, any perturbation that increases the level of free circulating pentachlorophenol may result in enhanced toxicity as well as an increased rate of biotransformation and elimination. For individuals living in close proximity to areas of potentially high pentachlorophenol exposure, concomitant exposure to chemicals or intentional ingestion of drugs that compete with pentachlorophenol for protein binding may enhance pentachlorophenol-induced toxicity.

3.1.4 Excretion

Pentachlorophenol is primarily excreted in the urine, with smaller amounts excreted in the feces. Several studies have estimated elimination half-lives using only urinary excretion in workers exposed to airborne pentachlorophenol. The half-lives ranged from 10 to 19–20 days (Barbieri et al. 1995; Begley et al. 1977; Casarett et al. 1969; Pekari et al. 1991). In contrast, a single exposure study estimated a urinary half-life of 10 hours following a 45-minute exposure (Casarett et al. 1969). One study estimated an elimination rate constant using a one-compartment model of 0.044±0.018/day (Pekari et al. 1991). Excretion of pentachlorophenol following inhalation exposure in animals has not been well documented. The elimination half-life of pentachlorophenol following a single 20-minute inhalation exposure to 5.7 mg [^{14}C]-pentachlorophenol/kg was 24 hours (Hoben et al. 1976a). The investigators noted that most of the pentachlorophenol was excreted unchanged.

Two studies have evaluated pentachlorophenol excretion in humans following oral administration of single low doses 0.016–0.31 mg/kg. Uhl et al. (1986) found that pentachlorophenol was excreted slowly, displaying an elimination half-life in both blood and urine of 14 days and a renal clearance of 0.07 mL/minute following ingestion of 0.016–0.31 mg pentachlorophenol/kg in ethanol. The authors concluded that slow elimination could be attributed to extensive plasma protein binding and tubular reabsorption. In contrast, Braun et al. (1979) found that the half-life of elimination of a 0.1 mg/kg dose was 30.2 hours from plasma and 33.1 hours from urine for pentachlorophenol, and 12.7 hours from urine for the glucuronide conjugate. Approximately 74% of the administered dose was eliminated in urine as pentachlorophenol and 12% as pentachlorophenol-glucuronide within 168 hours post-ingestion, and 4% was recovered as pentachlorophenol and pentachlorophenol-glucuronide in feces. These investigators

concluded that pentachlorophenol elimination in humans followed first-order kinetics with enterohepatic recirculation following oral exposure.

Elimination of pentachlorophenol in rats following oral exposure was shown to be rapid and biphasic, with urine being the major route of excretion (Braun et al. 1977). Within 8–9 days of a single dose of 10 mg [^{14}C]-pentachlorophenol/kg to rats, 80% of the radioactivity was recovered in urine and 19% in feces (Braun et al. 1977); administration of 100 mg [^{14}C]-pentachlorophenol/kg resulted in 64% being detected in urine and 34% in feces. The investigators estimated elimination half-lives of 17 and 13 hours for the first phase and 40 and 30 hours for the second phase in low-dose males and females, respectively. Ninety percent of the radioactivity was eliminated in the first phase. High-dose males exhibited elimination half-lives of 13 and 121 hours for the first and second phases, respectively. High-dose females exhibited first-order kinetics, with a half-life of 27 hours. No explanation was offered for the difference in kinetics seen in high-dose females. These data indicate that: (1) the rate of elimination in the slow phase only and the relative distribution of radioactivity in feces varied linearly with increasing dose, (2) females eliminated pentachlorophenol faster than males, and (3) plasma binding and hepatic retention could account for the prolonged second phase of elimination. Different results were reported in rats administered single doses of 37–41 mg [^{14}C]-pentachlorophenol/kg (Larsen et al. 1972). While the half-lives of rapid phases of elimination were comparable, Larsen et al. (1972) reported a half-life of 102 days for the second phase. However, these data are questionable because Larsen et al. (1972) did not obtain 100% recovery in urine and assumed that fecal excretion was constant. Therefore, they only reported a total fecal excretion value after 10 days. Consistent with these findings, Reigner et al. (1991) reported that 60% of the 2.5 mg/kg dose administered to rats was excreted in the urine within the first 72 hours and 8.9% was excreted in feces. In mice, a half-life of 5.8 hours was reported in animals receiving a single dose of 15 mg/kg pentachlorophenol (Reigner et al. 1992b); the urine was collected for 48 hours. The pentachlorophenol was primarily excreted as pentachlorophenol and TCHQ conjugates. Fecal excretion accounted for 6–9% of the dose, primarily as pentachlorophenol conjugates.

Elimination of pentachlorophenol by monkeys was slow and followed first-order kinetics. Braun and Sauerhoff (1976) orally administered single doses of 10 mg [^{14}C]-pentachlorophenol/kg to monkeys and monitored excretion of radioactivity for up to 360 hours after administration. They found that 10–20% of administered radioactivity was steadily excreted in the feces, attesting to a relatively high degree of biliary secretion. Urinary pentachlorophenol accounted for 70–80% of the administered radiolabel. The half-life of elimination was 40.8 hours in males and 92.4 hours in females. The role of enterohepatic circulation and biliary secretion in pentachlorophenol elimination in monkeys was further investigated by

measuring the relative extent of excretion of pentachlorophenol in urine, feces, and bile before and after administration of cholestyramine, a substance that binds phenols (Ballhorn et al. 1981; Rozman et al. 1982). The cholestyramine was administered in the diet 24 hours after pentachlorophenol exposure. At 30 mg/kg/day, control excretion was 92.3% in urine and 7.7% in feces. Following cholestyramine administration, excretion was 12.1% renal and 86.9% fecal. At 50 mg/kg/day, control excretion was 79.9% renal and 20.1% fecal. Following cholestyramine administration, excretion was 15.4% renal and 84.6% fecal. Total excretion was also increased by cholestyramine administration. Total recovery of administered dose over a 6-day period increased from 26 to 45% at the low dose and from 15 to 31% at the high dose (Ballhorn et al. 1981). In a follow-up study, cholestyramine treatment reduced urinary excretion of pentachlorophenol from 35 to 5% of the administered dose and increased fecal excretion from 3 to 54% of the administered dose. The increase in fecal excretion induced by cholestyramine exceeded the decrease in urinary excretion, and total excretion (urinary plus fecal) increased from 38 to 59%. Seventy percent was excreted in bile during the control period, and 52% was excreted in bile after cholestyramine treatment (Rozman et al. 1982). The investigators suggested that the pentachlorophenol in bile binds to the cholestyramine resulting in a decrease in reabsorption and an increase in fecal secretion. They also suggested that the increase in fecal excretion, which exceeded the decrease in urinary excretion, may be indicative of cholestyramine treatment enhanced intestinal elimination.

No studies were located regarding excretion in humans after dermal exposure to pentachlorophenol. Two studies in pigs evaluated excretion following prolonged (264 or 408 hours) dermal exposure to 40 μg/cm^2 [^{14}C-UL]-pentachlorophenol in a soil mixture or an ethanol vehicle (Qiao et al. 1997; Qiao and Riviere 2002). After 264 hours, 3.31 and 5.60% of the absorbed pentachlorophenol in ethanol vehicle was excreted in the urine and feces, respectively (Qiao and Riviere 2002). In the soil mixture studies, 19 and 29% of the radiolabel was excreted in the urine and feces, respectively, after 408 hours under nonocclusive conditions and 21 and 20% under occlusive conditions (Qiao et al. 1997).

The clearance rate of pentachlorophenol from plasma was 0.026±0.003 L/hour/kg in rats receiving a single intravenous injection of 2.5 mg/kg pentachlorophenol (Reigner et al. 1991). Elimination of pentachlorophenol from plasma was biphasic and fit a two-compartment model, with the half-life for the first phase being 0.67±0.46 hours and the half-life for the second phase being 7.11±0.87 hours. Most of the pentachlorophenol was eliminated during the second phase. However, routes of excretion and main metabolites recovered in urine and feces were similar to those seen by these same investigators after oral administration (Reigner et al. 1991). A second study estimated that the mean terminal elimination half-

life of pentachlorophenol was 5.6±0.37 hours in male rats and 9.5±4.2 hours in female rats receiving a single intravenous dose of 5 mg/kg pentachlorophenol (Yuan et al. 1994).

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

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

No PBPK modeling studies were identified for pentachlorophenol.

3.1.6 Animal-to-Human Extrapolations

Reigner et al. (1993) investigated the binding of radiolabeled pentachlorophenol to serum proteins *in vitro*, found that the percentages of unbound pentachlorophenol in serum were 1.37 in mice, 0.85 in rats, 0.67 in monkeys, 0.53 in humans, and 0.43 in cows, and found that these percentages correlated inversely with the total protein levels in the same serum samples. These investigators, assuming that pentachlorophenol itself is responsible for carcinogenicity in mice, developed a new method for interspecies extrapolation in which the interspecies differences in clearance and serum protein binding of pentachlorophenol were taken into account in interspecies scaling. Several pharmacokinetic parameters, including volume of distribution, unbound volume of distribution, clearance, unbound clearance, and unbound clearance time maximum life potential, were scaled to body weight. The method produced estimates of equivalent human doses of pentachlorophenol (derived from experimental doses in mice that caused increased tumor incidences in the NTP [1989] 2-year bioassay) that are up to 4 times smaller than those obtained using body surface area.

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 pentachlorophenol are discussed in Section 5.7, Populations with Potentially High Exposures.

There have been several reports of children accidentally exposed to pentachlorophenol; the children were predominantly exposed via dermal contact and, to a lesser extent, by the inhalation route. The observed health effects include symptoms of hyperthermia (high fever, profuse sweating, increased respiratory rate, labored breathing, tachycardia, hepatomegaly, and irritability) due to the uncoupling of oxidative phosphorylation and death in newborn infants following dermal contact with diapers and bedding washed in an antimildew agent containing pentachlorophenol (Robson et al. 1969; Smith et al. 1996) and in a child exposed to bath water contaminated with pentachlorophenol (Chapman and Robson 1965). The Chapman and Robson (1965) report provides suggestive evidence that young children may be more susceptible to the toxicity of pentachlorophenol than adults. All members of the child's family bathed in the contaminated bath water over a 13-day period; however, the only symptoms reported in the other family members were nasal stuffiness and swollen, painful eyes. A study by McConnachie and Zahalsky (1991) also reported health effects in children. Alterations in immunological parameters were observed in individuals living in log homes treated with a wood preservative containing pentachlorophenol. Fifteen of the 38 subjects were children aged 8–18 years. This study cannot be used to assess whether children would be more susceptible to the toxicity of pentachlorophenol because no comparisons across age groups were made. An animal study that compared LD_{50} values provides evidence that infants may be more susceptible than children. Lower LD_{50} values were found in preweaning animals, as compared to

juvenile rats (25–50 days); however, the LD_{50} value in adult rats was similar to the value for preweaning rats (St. Omer and Gadusek 1987).

There are limited data on potential developmental effects in humans. One study did find an increase in congenital cataracts in children of male sawmill workers exposed to chlorophenate (Dimich-Ward et al. 1996). A number of oral exposure studies in laboratory animals have identified developmental toxicity as a sensitive endpoint. Observed developmental effects include fetal/neonatal mortality (Bernard and Hoberman 2001; Bernard et al. 2002; Exon and Koller 1982; Schwetz et al. 1974, 1978; Welsh et al. 1987), decreased growth (Beard et al. 1999a; Bernard and Hoberman 2001; Bernard et al. 2002; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1974; Welsh et al. 1987), malformation/variations (Schwetz et al. 1974; Welsh et al. 1987), and possibly functional deficits in rats.

Groups possibly at greater-than-average risk of suffering from the toxic effects of pentachlorophenol include persons laboring in hot environments, persons with an inability or decreased ability to disperse body heat, geriatric and pediatric subpopulations, pregnant women, and those that are malnourished or consume an unbalanced diet. People with impaired liver and kidney function are likely to be susceptible to the toxic effects of any chemical/product that is metabolized and/or excreted by these organs, and therefore, may be unusually susceptible to the toxic effects of pentachlorophenol.

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 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to pentachlorophenol are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for pentachlorophenol from this report are discussed in Section 5.6, General Population Exposure.

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

Since pentachlorophenol is excreted in the urine largely unchanged (Ahlborg et al. 1974; Braun et al. 1979; Larsen et al. 1972; Reigner et al. 1991) and can be easily detected and quantified in the urine at concentrations as low as <1 ppb (Chou and Bailey 1986; Drummond et al. 1982; Edgerton et al. 1979; EPA 1980a; Holler et al. 1989; NIOSH 1984; Pekari and Aitio 1982; Rick et al. 1982; Siqueira and Fernicola 1981), pentachlorophenol in the urine is a useful biomarker of exposure. In addition, pentachlorophenol can be easily detected and quantified in blood serum at concentrations as low as <1 ppb (Bevenue et al. 1968; EPA 1980a; Needham et al. 1981; NIOSH 1984) and adipose tissue (Kuehl and Dougherty 1980; Needham et al. 1981; Ohe 1979; Shafik 1973). It has been demonstrated that pentachlorophenol is present in human adipose tissue as an ester of palmitic acid (Ansari et al. 1985). The detection limit for pentachlorophenol in adipose tissue is approximately 5 ppb (Kuehl and Dougherty 1980; Ohe 1979; Shafik 1973). Other potentially useful biomarkers include pentachlorophenol levels in hair (Hardy et al. 2021; Iglesias-Gonzalez et al. 2020) or meconium of neonates (Ostrea et al. 2002). However, measuring pentachlorophenol in body fluids and tissues is not a specific biomarker for pentachlorophenol exposure because other compounds to which exposure may occur (e.g., hexachlorobenzene and lindane) may be metabolized to pentachlorophenol in the body. In addition, the

available data do not permit the establishment of a quantitative relationship between levels of pentachlorophenol in the environment and levels in human fluids or tissues. However, it has been reported that repeated workday exposure to pentachlorophenol at a concentration of 0.5 mg/m^3 has resulted in a maximum steady-state level of pentachlorophenol in plasma of about 0.5 mg/L (Wood et al. 1983). Based on samples taken prior to 1989, background levels of up to 0.1 ppm pentachlorophenol could be found in blood and urine of members of the general population who had no recognized exposure to pentachlorophenol (Cranmer and Freal 1970; EPA 1989; Hill et al. 1989; Kutz et al. 1978).

TCHQ, a major urinary metabolite of pentachlorophenol, has potential use as an indicator of exposure to pentachlorophenol. It has been demonstrated that pentachlorophenol is converted to TCHQ by human microsomal enzymes (Juhl et al. 1985). In human and animal studies, TCHQ has been identified as the major urinary metabolite of pentachlorophenol (Ahlborg et al. 1974; Braun et al. 1977; Reigner et al. 1991; Renner 1989). However, the presence of TCHQ in the urine is not specific to pentachlorophenol and would also be present following exposure to chemicals that are metabolized to pentachlorophenol.

The presence of elevated levels of 8-hydroxydeoxyguanosine in the liver may serve as a nonspecific marker of oxidative DNA damage by pentachlorophenol. Administration of pentachlorophenol (98.6% pure) to mice in the diet for up to 4 weeks produced oxidative damage to hepatic nuclear DNA as evidenced by an increase in the amount of 8-hydroxydeoxyguanosine in DNA (Sai-Kato et al. 1995; Umemura et al. 1996). A single oral dose of pentachlorophenol (98.6% pure) produced an increase in the amount of 8-hydroxydeoxyguanosine in liver DNA but not in kidney or spleen DNA (Sai-Kato et al. 1995).

3.3.2 Biomarkers of Effect

No specific biomarkers of effect were identified for pentachlorophenol.

3.4 INTERACTIONS WITH OTHER CHEMICALS

There is limited information on potential interactions between pentachlorophenol and other chemicals. No interactions between pentachlorophenol and the contaminants of technical-grade pentachlorophenol have been demonstrated in some tests of immunotoxicity (Kerkvliet et al. 1985a). The results of an *in vitro* study in HepG2 cells suggest that exposure to perfluorooctanoic acid (PFOA) or perfluorooctane

sulfonate (PFOS) could enhance the toxicity of pentachlorophenol by increasing cell permeability, which could result in increased intracellular pentachlorophenol levels (Shan et al. 2013).

Since pentachlorophenol is metabolized by hepatic microsomal enzymes, chemicals that alter the activity of these enzymes can modify metabolism, and subsequently, the toxicity of pentachlorophenol (see discussion above). For example, phenobarbital, a microsomal enzyme inducer, increases biotransformation of pentachlorophenol to TCHQ, thereby reducing the level of pentachlorophenol in the body (Ahlborg et al. 1978).

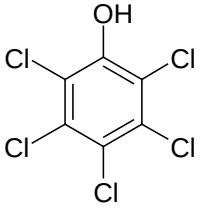
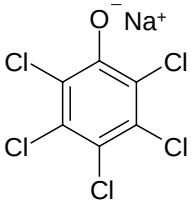
Various agents have been used in experimental animals to try to decrease the toxicity of pentachlorophenol. Cholestyramine has been shown to enhance fecal elimination of chlordecone (Kepone) in rats and humans (Boylan et al. 1977). Ballhorn et al. (1981) and Rozman et al. (1982) found that cholestyramine enhances excretion of pentachlorophenol in Rhesus monkeys and recommends that its use be considered in cases of human pentachlorophenol overexposure.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of pentachlorophenol is located in Table 4-1. A number of contaminants are found in commercial- and technical-grade pentachlorophenol formulations. Commonly found contaminants that were introduced during production include other chlorophenols, CDDs, CDFs, hexachlorobenzene, and chlorophenoxy compounds. Pure pentachlorophenol compounds are typically ≥98% pure with very low levels of CDDs and CDFs. Commercial-grade pentachlorophenol is typically 90% pentachlorophenol, and technical-grade pentachlorophenol formulations typically contains 85–90% pentachlorophenol. A list of contaminants in technical-grade pentachlorophenol and two commercial-grade pentachlorophenol products (Dowicide EC-7 and DP-2) are presented in Table 2-1.

Table 4-1. Chemical Identity of Pentachlorophenol

Characteristic	Pentachlorophenol	Sodium pentachlorophenate
Synonym(s) and registered trade name(s)	PCP; penchlorol; penta; pentachlorophenate; 2,3,4,5,6-pentachlorophenol[b]	Pentachlorophenol sodium; pentachlorophenol sodium salt: pentachlorophenoxy sodium: pentaphenate
For 37% aqueous solution	Chlon; Dowicide 7; Dowicide EC-7; Dura Treet II; EP 30; Fungifen[a]	Dow Dormant Fungicide; Dowicide G; Dowicide
For polymeric form	Grundier Arbezol; Lauxtol; Liroprem; Penta Concentrate; Penta Ready; Penta WR; Permasan; Santophen 20; Woodtreat[b]	G-St; Mystox D; Napclor-G; Santobrite; Sapco25 Weedbeads
Chemical formula	C_6HCl_5O	C_6Cl_5ONa
Chemical structure		
CAS Registry Number	87-86-5	131-52-2

[a]All information obtained from HSDB 2001, except where noted.

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of pentachlorophenol is located in Table 4-2.

Table 4-2. Physical and Chemical Properties of Pentachlorophenol

Property	Pentachlorophenol	Sodium pentachlorophenate
Molecular weight	266.34	288.34
Color	Colorless or white (pure); dark gray to brown (crude product)	White or tan
Physical state	Crystalline solid (pure); pellets or powder (crude product)[b]	Flakes or powder
Melting point	174°C	No data
Boiling point	309–310°C (decomposes)	No data
Density	1.978 g/mL at 22°C/4°C	2.0 mg/L at 22°C/4°C
Odor	Phenolic; very pungent (only when hot)	Phenolic odor
Odor threshold:		
Water	0.857 mg/L at 30°C; 12.0 mg/L at 60°C[b,c]	No data
Air	No data	No data
Solubility:		
Water	14 mg/L at 20°C	330,000 mg/L at 25°C
Organic solvents	Very soluble in alcohol and ether; soluble in benzene; slightly soluble in cold petroleum ether[d]	Soluble in acetone and ethanol
Partition coefficients:		
Log K_{ow}	5.01[b]	No data
Log K_{oc}	4.5[e]	No data
Vapor pressure at 20°C	0.00011 mmHg[f]	Not applicable
Dissociation constant (pKa)	4.70	Not applicable
Henry's law constant at 22°C	2.45×10^{-8} atm-m^3/mol	Not applicable

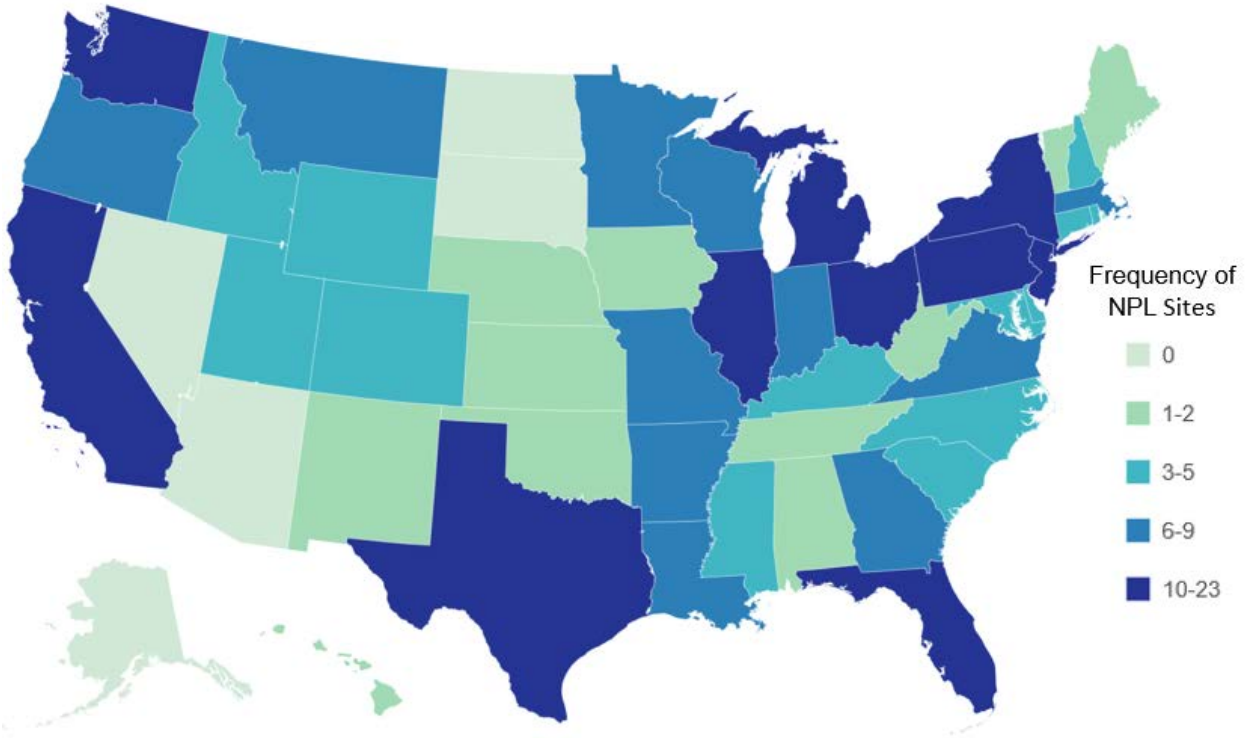
[a]All information obtained from NLM (2021) unless otherwise noted.
[b]Verschueren 1983.
[c]Hoak 1957.
[d]Budavari et al. 1989.
[e]Schellenberg et al. 1984.
[f]EPA 1979.
[g]Lyman et al. 1982.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Pentachlorophenol has been identified in at least 328 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which pentachlorophenol has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 327 are located within the United States, and 1 is located in Puerto Rico (not shown).

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



Source: ATSDR 2019

- Due to its former widespread use, the general population may be exposed to pentachlorophenol via ingestion of drinking water and food, as well as inhalation of air.
- Professional wood treatment applicators applying pentachlorophenol as a wood preservative or employees involved in the manufacture and formulation of pentachlorophenol products are expected to have the greatest exposure, primarily through dermal and inhalation routes.

- Pentachlorophenol production results in the formation of a number of contaminants including CDDs, CDFs, other chlorophenols, hexachlorobenzene, and chlorophenoxy compounds. Technical- and commercial-grade formulations contain varying levels of these contaminants (see Table 2-1 for contaminant levels in several formulations). The formulations used and that people are exposed to are commercial-grade formulations typically consisting of 90% pentachlorophenol.

- The environmental fate of pentachlorophenol is dependent upon the pH of the soil or water. In water and soil, pentachlorophenol is not volatile except under acidic conditions. Pentachlorophenol has greater mobility in soils under neutral or alkaline conditions and has a greater tendency to bioconcentrate under acidic conditions.

- Pentachlorophenol volatilizes from treated wood surfaces.

- Pentachlorophenol is hydrolytically stable and is generally considered moderately persistent under aerobic and anaerobic conditions. It can undergo direct photolysis in sunlit surface waters.

- Pentachlorophenol is a persistent organic pollutant listed in the Stockholm Convention, Annex A.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Pentachlorophenol is produced by the stepwise chlorination of phenols in the presence of catalysts (aluminum trichloride or ferric trichloride) (Pommer and Jaetsch 2012). Outside of the United States, it is also produced by the alkaline hydrolysis of hexachlorobenzene. Typically, commercial-grade pentachlorophenol is 86% pure. Contaminants generally consist of other polychlorinated phenols, CDDs, CDFs, and hexachlorobenzene (HCB), which are formed during the manufacture process (EPA 2008).

Pentachlorophenol is a biocide that was previously broadly used as a fungicide, bactericide, herbicide, molluscicide, algaecide, and insecticide by agriculture and other industries including textiles, paints, oil drilling, and forestry (EPA 2008). It was first registered for use by the U.S. Department of Agriculture (USDA) on December 1, 1950, but is now a restricted use pesticide in the United States, meaning that it can only be applied for certain uses by certified pesticide applicators. According to the National Pesticide Information Retrieval System (NPIRS), only two U.S. corporations (KMG-Bernuth, Inc. and Arbor Preservative Systems, LLC) develop pentachlorophenol-containing products (NPIRS 2021); these products are shown in Table 5-1.

Table 5-1. Manufacturing Information of Pentachlorophenol-Containing Products

Company name	Product	Percent pentachlorophenol	EPA Registration Number
KMG-Bernuth, Inc.	Dura-Treet 40 Wood Preservative	34%	61483-2
KMG-Bernuth, Inc.	KMG-B Penta OL Technical Penta	86%	61483-3
KMG-Bernuth, Inc.	KMG-B Penta OL Penta Blocks	86%	61483-94
Arbor Preservative Systems, LLC	Stella-Jones Penta	86%	97080-10

Source: NPIRS 2021

Pentachlorophenol is usually applied to wood as a mixture of pentachlorophenol and a hydrocarbon solution such as No. 2 fuel oil, kerosene, or mineral spirits (EPA 2008).

According to data from the EPA Chemical Data Reporting (CDR), the production volume of pentachlorophenol by KMG Chemicals was 8,434,248 pounds in 2012, 8,314,302 pounds in 2013, 7,633,241 pounds in 2014, and 13,507,112 pounds in 2015 (EPA 2021). This production volume includes domestically manufactured pentachlorophenol as well as imported pentachlorophenol.

Table 5-2 summarizes information on U.S. companies that reported the manufacture or processing of pentachlorophenol in 2020 to the Toxic Release Inventory (TRI) (TRI20 2021). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list and it contains primarily companies involved in waste disposal or storage of chemicals.

Table 5-2. Facilities that Produce, Process, or Use Pentachlorophenol

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	6	10,000	999,999	8
AR	2	10,000	999,999	1, 5, 8, 9, 12
GA	3	10,000	99,999	8
IN	1	100	999	12
LA	1	100,000	999,999	8
MN	1	100,000	999,999	8
MS	2	10,000	99,999	8
NC	1	100,000	999,999	8
NE	3	1,000	999,999	7, 8, 12
NV	1	1,000,000	9,999,999	8
OH	1	1,000	9,999	12

Table 5-2. Facilities that Produce, Process, or Use Pentachlorophenol

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
OR	5	0	9,999,999	1, 5, 7, 8
TX	3	1,000	999,999	1, 5, 12
UT	1	1,000	9,999	9, 12
WA	4	10,000	999,999	8
WI	1	100,000	999,999	8

[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: TRI20 2021 (Data are from 2020)

5.2.2 Import/Export

In 1982, 121,000 pounds of pentachlorophenol were imported to the United States (328,000 pounds were imported in 1980). According to data from the EPA CDR system, 13,507,112 pounds of pentachlorophenol were imported to the United States and 887,551 pounds of pentachlorophenol were exported by KMG Chemicals, Inc. in 2015. These data have not been made available for years 2016–2020 (EPA 2021).

5.2.3 Use

Pentachlorophenol was one of the most widely used biocides in the United States. It was registered for use by EPA as an insecticide (termiticide), fungicide, herbicide, molluscicide, algicide, and disinfectant, and as an ingredient in antifouling paint (Cirelli 1978), but it has been a restricted-use pesticide since July 1984 (EPA 1984a). Most non-wood preservative uses were cancelled in 1987 (EPA 2008). The only current registered use for pentachlorophenol is as a “heavy-duty” wood preservative (meaning that it is applied via high-pressure cylinders instead of being brushed on); however, its use to treat wood contained in interior settings is prohibited with a few exceptions (e.g., support structures in barns, stables, etc. that

are in direct contact with soil). It is used primarily on treated industrial products such as utility poles, pilings, and railroad ties.

Pentachlorophenol treated wood is not available for sale to the general public. Pentachlorophenol is no longer contained in wood-preserving solutions or insecticides and herbicides available for home and garden use since it is a restricted-use pesticide.

5.2.4 Disposal

As discussed in the EPA Registration Eligibility Decision (RED) for pentachlorophenol, there are two different waste products associated with this substance: wood treated with pentachlorophenol and industrial waste generated by its production and application (EPA 2008). Wood that is to be discarded that was treated with pentachlorophenol is typically land disposed in either construction and demolition landfills, municipal solid waste landfills, or industrial non-hazardous waste landfills. Disposal of wastewaters generated from the production or application of pentachlorophenol are regulated by the Resource Conservation and Recovery Act (RCRA) and are subject to certain restrictions (EPA 1991). For example, many of the reported releases for pentachlorophenol in the TRI are to RCRA Subtitle C landfills which are special landfills under the RCRA that are authorized to accept hazardous waste for disposal and must follow very stringent guidelines for their design and operation (see Section 5.4).

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 2005). 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 is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes

≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

Estimated releases of 102 pounds (~0.0463 metric tons) of pentachlorophenol to the atmosphere from 36 facilities domestic manufacturing and processing facilities in 2020, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI20 2021). These releases are summarized in Table 5-3.

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Pentachlorophenol[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
AL	6	0	488	0	0	0	487	1	488
AR	2	0	59	0	7,872	0	59	7,872	7,931
GA	3	1	78	0	0	0	79	0	79
IN	1	0	0	0	0	0	0	0	0
LA	1	1	7	0	2	0	5	5	10
MN	1	5	6	0	0	0	9	2	11
MS	2	0	215	0	0	0	215	0	215
NE	3	10	2	0	1	0	12	1	13
NV	1	5	0	0	9	0	5	9	14
NC	1	0	7	0	0	0	7	0	7
OH	1	0	0	0	0	0	0	0	0
OR	5	36	1	0	28	0	37	28	65
TX	3	25	0	0	1	0	25	1	26
UT	1	7	0	0	0	0	7	0	7
WA	4	8	0	0	47	0	8	47	55

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Pentachlorophenol[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
WI	1	3	0	0	27	0	3	27	30
Total	36	102	863	0	7,987	0	959	7,993	8,952

[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.

RF = reporting facilities; UI = underground injection

Source: TRI20 2021 (Data are from 2020)

5.3.2 Water

Estimated releases of 863 pounds (~0.39 metric tons) of pentachlorophenol to surface water from 36 domestic manufacturing and processing facilities in 2020, accounted for about 9.6% of the estimated total environmental releases from facilities required to report to the TRI (TRI20 2021). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI20 2021). These releases are summarized in Table 5-3.

5.3.3 Soil

Estimated releases of 7,987 pounds (~3.62 metric tons) of pentachlorophenol to soil from 36 domestic manufacturing and processing facilities in 2020, accounted for about 89% of the estimated total environmental releases from facilities required to report to the TRI (TRI20 2021). These releases are summarized in Table 5-3.

5.4 ENVIRONMENTAL FATE

Pentachlorophenol released into the atmosphere from treated wood can be transported back to surface waters and soils via wet and dry deposition. Atmospheric pentachlorophenol is transformed via photolysis; the compound may slowly undergo free radical oxidation with an estimated half-life of approximately 2 months.

In surface waters, pentachlorophenol undergoes biotransformation and photolysis, and is adsorbed to sediments. Hydrolysis, oxidation, and volatilization do not significantly affect surface water concentrations.

In soils and sediments, pentachlorophenol is metabolized by acclimated microbes, under both aerobic and anaerobic conditions, or is adsorbed. Pentachlorophenol may also be methylated to form pentachloroanisole, a more lipid-soluble compound. Adsorption of pentachlorophenol in soils is pH dependent. The compound has a pKa value of 4.7 and consequently exists in the ionic forms at environmentally relevant pH values. For example, at pH 4.7, pentachlorophenol is 50% ionized, whereas at pH 6.7, the compound is about 99% ionized (Crosby et al. 1981). Adsorption decreases in neutral and basic soils and is strongest in acidic soils. Therefore, the compound is most mobile in neutral-to-basic mineral soils and least mobile in acidic organic soils. Volatilization and photolysis do not appear to be important transport or transformation processes for pentachlorophenol in soils.

5.4.1 Transport and Partitioning

The moderately long persistence and its presence in atmospheric samples at remote locations with no known local sources of pentachlorophenol suggests that this substance is susceptible to long-range atmospheric transport (Cessna et al. 1997; Waite et al. 1998). A reported pKa of 4.7 indicates that pentachlorophenol will exist almost entirely as the conjugate base form at typical pH levels found in the environment, and volatilization is expected to be negligible for ionic substances. Pignatello et al. (1983) reported that volatilization loss of pentachlorophenol as vapor and aerosol from treated river water in outdoor manufactured channels was ≤0.006% of the initial test concentration. The pH of the water was 7.4–7.6, indicating that >99% was present in the form of the anionic species. Volatilization of pentachlorophenol from soil is also not expected to be a major transport pathway. Kilzer et al. (1979) determined the volatilization rates of pentachlorophenol from water and three soil types under laboratory conditions. The volatilization rates (expressed as percentage of applied pentachlorophenol per mL

evaporated water) from water (pH unreported), sand (pH 6.8), loam (pH 6.1), and humus (pH 6.9) were 2.57, 0.13, 0.31, and 0.10%, respectively, in the first hour after application of 50 µg/L pentachlorophenol. During the second hour, the volatilization rates were 2.11, 0.12, 0.15, and 0.12%, respectively.

Although pentachlorophenol does not volatilize significantly from water or soil surfaces except under acidic (≤pH 5) conditions, it is volatilized from treated wood surfaces. Walls in a closed room that were treated with pentachlorophenol released the chemical into the air, with concentrations reaching 1 µg/m^3 on the first day after treatment and 160 µg /m^3 on the fifth day (Gebefugi et al. 1976). Ingram et al. (1986) studied the volatilization of pentachlorophenol under different temperature, air flow rates, and humidity levels from treated wood formulated with three commercially important solvents (methylene chloride, mineral spirits, and P9 Type A oil). The highest levels monitored occurred in the methylene chloride solvent at elevated temperature and high air flow rates. For example, at a flow rate of 1 L/minute and at 35°C, the average air level of pentachlorophenol in the test chamber was 1,050 µg /m^3 using methylene chloride as a solvent, 509 µg /m^3 using mineral spirits, and 74 µg /m^3 using P9 oil (Ingram et al. 1986).

The adsorption or mobility of pentachlorophenol in soils is also pH dependent. Pentachlorophenol is adsorbed to soil or sediment under acidic conditions, but the compound is mobile under neutral or alkaline conditions (Kuwatsuka and Igarashi 1975). Maximum adsorption has been reported at soil pH values of 4.6–5.1, with no adsorption above pH 6.8 (Choi and Aomine 1974). The amount of pentachlorophenol adsorbed at a given pH also increases with increasing organic content of the soil (Chang and Choi 1974).

Schellenberg et al. (1984) investigated the adsorption of chlorinated phenols to natural sediments and aquifer materials. These authors demonstrated that adsorption of pentachlorophenol was highly dependent on the organic content of the adsorbent. An average K_{oc} of 32,900 was measured for pentachlorophenol in lake sediment, river sediment, and aquifer materials.

However, normalized partition coefficients (i.e., K_{oc}) do not accurately predict adsorption for ionizable compounds such as pentachlorophenol since its adsorption does not increase linearly with increasing concentration (Christodoulatos et al. 1994). The use of the equation to normalize partition coefficients is not valid in such cases. Davis et al. (1994) investigated the retardation of pentachlorophenol in groundwater at a former wood treating facility. Data were not well represented by the Freundlich or Langmuir isotherms. The authors observed that retardation of the compound in the aquifer was greater at

lower concentrations (<40 µg/L) than at higher ones (>1,000 or 10,000 µg/L), indicating that pentachlorophenol will move at rates closer to that of the groundwater when present at higher concentrations (>10,000 µg/L). The authors stated that the results indicated that at the lower concentrations found at plume peripheries, pentachlorophenol would be attenuated and then biodegraded, while at higher concentrations such as at the source, the compound would be mobile.

Pentachlorophenol is applied to wood as a liquid formulation composed of pentachlorophenol dissolved in hydrocarbon diluents such as oils, kerosene, or mineral spirits. The presence of cosolvents such as alcohols or petroleum hydrocarbons decreases the adsorption of pentachlorophenol in soils by increasing its solubility in the soil solution (Christodoulatos et al. 1994). This may also be important at spill, storage, and hazardous waste sites where a large amount of cosolvent would be expected. Based on the results of a study of the mobility of pentachlorophenol, pentachlorodibenzodioxins, and pentachlorodibenzofurans in soils contaminated with wood-preserving oil, Jackson and Bisson (1990) indicated that decreased adsorption of the compounds in soil would result from the presence of a subsurface, contaminated oil phase. They predicted that upon contact with groundwater, the compounds would be partitioned into the aqueous phase. In a study of desorption of chlorophenols in contaminated soils, pentachlorophenol was desorbed more readily in the presence of methanol and exhibited a positive correlation with increasing methanol concentration (You and Liu 1996).

Decreased adsorption may also occur without the presence of a cosolvent/contaminant such as methanol or a petroleum hydrocarbon. The release of soil organics and colloids in the presence of dissolved pentachlorophenol was investigated. When pentachlorophenol was added to soil at aqueous concentrations of 1,000–10,000 µg/L, surface organics (tentatively identified as fulvic acids) were solubilized and acted as a cosolvent, decreasing the adsorption of pentachlorophenol (Galil and Novak 1995). Enhanced mobility of pentachlorophenol was also predicted from the observed increased stability of soil colloids that adsorbed 3–13% of the compound but were released from soil particle surfaces into the soil solution.

Pentachlorophenol can be leached from treated wood into surrounding soil. For example, Arsenault (1976) reported that pentachlorophenol migrated from the surface of utility poles to the adjacent soil, which had an average pentachlorophenol concentration of 654 mg/L. However, mobility in soil was limited, as indicated by the average soil concentration of 3.4 mg/L pentachlorophenol at a distance of 12 inches from the poles.

In a review paper, McAllister et al. (1996) reported that available data on the plant uptake and transformation of pentachlorophenol are inconsistent among studies and are inconclusive with regard to the abilities of specific plants to take up the compound. It was observed that the biodegradation of pentachlorophenol by microorganisms and its adsorption to soil limit the availability of the compound for plant uptake. Among the pentachlorophenol metabolites found in plants are tetrachlorophenols and anisoles (McAllister et al. 1996); additionally, oxidation products (tetrachlorobenzenes), conjugated forms of chlorinated phenols, and insoluble metabolites (lignin-incorporated residues) have been observed (Engelhardt and Wallnofer 1986).

Veith et al. (1985) demonstrated that chemicals with a log K_{ow} value >4.0 are likely to bioaccumulate in organisms and food chains. The log K_{ow} presented in Chapter 4 is 5.01 for the un-ionized form, which suggests that pentachlorophenol will bioaccumulate. However, the extent of bioaccumulation will depend on the pH of the medium and physiological pH, since at higher pH levels, pentachlorophenol converts to the more water-soluble pentachlorophenate anion. Bluegill sunfish exposed to 100 µg/L pentachlorophenol accumulated the compound in various tissues (edible, nonedible, or whole fish) to levels of 10–350 times the ambient water concentration in a 16-day static/renewal bioassay. Pentachlorophenol was rapidly eliminated upon transfer of the test organisms to clean water (Pruitt and Grantham1977). Pentachlorophenol was reported to have a bioconcentration factor (BCF) of 81–461 in the soft tissue of a freshwater mussel; however, the compound was rapidly cleared by the test organisms (52% loss within 12 hours) (Makela et al. 1991). Other bioaccumulation tests with aquatic organisms include BCF values of 30–40 in carp muscle tissue and 300–400 in all other tissues (Gluth et al. 1985) and BCF values of 218 (whole fish) to 1,633 (fish lipid basis) for juvenile American flagfish (Smith et al. 1990). In the latter test, which was a flow-through bioassay, the half-life of pentachlorophenol in the tissues was reported to be about 16 hours. Bioaccumulation of pentachlorophenol in algae, aquatic invertebrates, and fish (with BCFs of up to 10,000) has been demonstrated. Representative BCFs are as follows: goldfish, 1,000; polychaeta, 3,830; bluegill sunfish, 13; blue mussel, 324; and eastern oyster, 78 (EPA 1986a). The Japanese Chemicals Inspection Testing Institute (CITI) determined the BCF of pentachlorophenol in carp at two nominal concentrations over the course of an 8-week incubation period (JCHECK 2021).

At an exposure level of 3 µg/L, the BCF was in the range of 39–116 after 8 weeks and at an exposure level of 0.3 µg/L, the BCF was 45–99. The overall weight of evidence would suggest that pentachlorophenol does not bioconcentrate in aquatic organisms as much as other hydrophobic, chlorinated pesticides and that bioconcentration is expected to be pH dependent with greater accumulation under acidic conditions where the free acid is the dominant species instead of the conjugate base.

Biomagnification of pentachlorophenol in terrestrial or aquatic food chains has not been observed. In a 110-day study with rainbow trout, where pentachlorophenol was administered in the diet at a maximum concentration of 3,000 µg/kg, maximum concentrations of the compound in fish tissues were 40 µg/kg after 50 days and 20 µg/kg at the end of the test period. In a 28-day depuration test, tissue half-life of the compound was about 7 days. According to the investigators, these results suggest that pentachlorophenol bioconcentration in fish occurs primarily through direct uptake from water rather than through ingestion of food. The similar pentachlorophenol tissue concentration levels of prey and predator salmonid fish from Lake Ontario were cited as additional evidence of the limited food chain bioaccumulation of the compound (Niimi and Cho 1983).

Pentachlorophenol bioconcentration by earthworms has also been studied by several investigators. In 14-day exposure tests, BCFs of 3.4–13 were reported for uptake of pentachlorophenol adsorbed to soil particulates (Haque and Ebing 1988; van Gestel and Ma 1988). However, when bioconcentration was calculated on the basis of concentration of test compound in soil solution, BCF values of 426–996 were obtained (van Gestel and Ma 1988).

5.4.2 Transformation and Degradation

Air. Atmospheric pentachlorophenol is probably photolyzed in the absence of water, although mechanisms for this reaction are not well known (Crosby and Hamadad 1971; Gab et al. 1975). Photolysis of sorbed or film-state pentachlorophenol in the presence of oxygen has also been observed (Gab et al. 1975). The reaction products were similar to those found in aqueous photolysis. Bunce and Nakai (1989) estimated the rate of photolysis in the atmosphere based on measured quantum yields (254 nm) in the laboratory, molar absorptivity values, and solar intensity values for midday in summer at 40°N; the estimated loss of pentachlorophenol to vapor-phase photolysis was 6.2% per hour. This rate represents the maximum rate at 40°N; the average rate of photolysis for pentachlorophenol will be lower.

No empirical data were found describing the reactivity of pentachlorophenol to free radical oxidation in the atmosphere. Bunce and Nakai (1989) calculated the potential atmospheric degradation of pentachlorophenol due to hydroxyl radical attack. The estimated loss rate was 1.5% per hour (half-life of 66 hours) as calculated from an estimated rate constant of 4.7×10^{-13} cm^3/molecule-second, assuming a peak noon summer hydroxyl radical concentration of 6.2×10^6 radicals/cm^3. Based on the estimated relative rates of photolysis and degradation by hydroxyl radicals, it was concluded that the former process

would likely be the dominant of the two. It is noted that the estimate by Bunce and Nakai (1989) did not take into account the adsorption of the compound to particulates in the atmosphere. Using the method of Meylan and Howard (1993), a half-life of 9.7 days for the vapor-phase reaction of pentachlorophenol with hydroxyl radicals can be obtained from an estimated rate constant of $5.5x10^{-13}$ cm^3/molecule-second and an average hydroxyl radical concentration of $1.5x10^6$ molecule/cm^3. Adsorption of pentachlorophenol to particulate matter, however, will attenuate the rate of this process in the atmosphere.

Water. Photolysis and biodegradation are believed to be the dominant transformation processes for pentachlorophenol in aquatic systems. Hydrolysis and oxidation are not important mechanisms for removal of the compound from surface waters.

The molecular structure of pentachlorophenol is indicative of its stability to hydrolysis or oxidation (EPA 1979). Wong and Crosby (1981) reported that pentachlorophenol did not hydrolyze in aqueous solutions (serving as dark controls in an aqueous photolysis study) at pH 3.3 or 7.3 when held at 26°C for up to 100 hours.

Wong and Crosby (1981) reported that pentachlorophenol in aqueous solutions at 100 mg/L was photolyzed under laboratory ultraviolet (UV)-light irradiation with estimated half-lives of about 100 hours at pH 3.3 and 3.5 hours at pH 7.3. Photolysis of pentachlorophenol in aqueous solution following exposure to sunlight was also rapid; in laboratory experiments, concentrations of pentachlorophenol in water were reduced from 9.3 to 0.4 mg/L in 24 hours and approached zero at the end of 48 hours (Arsenault 1976). Wong and Crosby (1981) also reported rapid photolysis in sunlight (July); pentachlorophenol in pH 7.3 aqueous solution at 100 mg/L photolyzed with a half-life of 48 hours (total elapsed time) and a total disappearance time of 10 days. Degradates formed during photolysis included tetrachlorophenols, three tetrachlorodiols and their respective quinones, chloranilic acid, and eventually 2,3-dichloromaleic acid, which also undergoes photolysis, but at a slightly slower rate than pentachlorophenol. The final products from the complete photolytic degradation of pentachlorophenol were carbon dioxide and chloride ions. In outdoor tests conducted with river water in manufactured channels, Pignatello et al. (1983) demonstrated that photolysis of pentachlorophenol (applied as the sodium salt) was rapid at the water surface (half-life of 0.70 hour at a depth of 0.5 cm). However, photolysis was greatly attenuated with increasing depth of the water column (half-life of 9.63 hours at a depth of 13.8 cm). Photolytic degradation accounted for a 5–28% decrease in the initial test concentration of the compound after 3 weeks. Chi and Huang (2004) found differences in the photodegradation rates of pentachlorophenol between the surface microlayer and subsurface water. The difference in the first-order

rate constants under natural sunlight was correlated with the dissolved organic carbon enrichment in the surface microlayer. The photodegradation rate decreased with increasing salinity and increased with increasing pH.

Pentachlorophenol is biotransformed in aqueous systems by acclimated microorganisms. In a 40-day study of sterile and nonsterile stream water samples that were not amended with acclimated microbial cultures, Baker et al. (1980) reported negligible biodegradation of pentachlorophenol at 0 and 20°C. Pignatello et al. (1983) reported that microbial transformation became the primary removal mechanism of pentachlorophenol (applied as the sodium salt) added to river water in tests conducted in outdoor manufactured channels. After about a 3-week acclimation period, microbial transformation accounted for a 26–46% decline in the initial test concentration of pentachlorophenol. The majority of the microbes responsible for the mineralization of pentachlorophenol were associated with rock and macrophyte surfaces or surface sediments rather than existing in the water phase. In a follow-up study utilizing the same type of outdoor tests, Pignatello et al. (1985) found that biotransformation accounted for a 55–74% decrease in concentration of applied pentachlorophenol after a 3–5-week adaptation period. Biotransformation in the water column above sediments occurred at a greater rate under aerobic than under anaerobic conditions. Ingerslev et al. (1998) reported that in a study utilizing a battery of shake flasks tests, pentachlorophenol at 1 and 100 mg/L biodegraded in 10–30 days under aerobic conditions in surface water from an unpolluted stream after an acclimation period of approximately 55 days. The addition of either sterilized or unsterilized sediment to the samples resulted in reduced acclimation periods but did not affect the postacclimation degradation rates in water.

In a study using radiolabeled pentachlorophenol, Arsenault (1976) demonstrated that the compound was transformed to carbon dioxide, water, and hydrochloric acid in an activated sludge treatment plant. On a pilot-plant scale, the same investigator also showed that a waste stream from a wood-preserving facility containing 23 mg/L of pentachlorophenol could be treated successfully to produce a final effluent concentration of 0.4 mg/L of pentachlorophenol. Screening tests indicate pentachlorophenol is not readily biodegradable. Pentachlorophenol at a concentration of 100 mg/L achieved 0% of its theoretical biochemical oxygen demand using an activated sludge inoculum at 30 mg/L and the Japanese MITI test (Organisation for Economic Cooperation and Development [OECD] 301C guideline), indicating that it is not readily biodegradable (JCHECK 2021). Using a standard OECD 301B guideline, pentachlorophenol was not degraded, nor was it degraded using what Martin et al. (2017) considered a more environmentally relevant biodegradation screening test that used a higher inoculum concentration.

In a microcosm study of unfiltered aquifer samples (geologic material and groundwater) contaminated with polycyclic aromatic hydrocarbons and pentachlorophenol, a loss was observed. Although reductions in the parent compound concentration occurred, only 1% of the applied radiolabeled pentachlorophenol had mineralized by 56 days (Mohammed et al. 1998). Neither nutrient addition nor sample sterilization had a significant effect on mineralization. The observed decreases in the pentachlorophenol concentrations were attributed to adsorption to particulate material and not to biodegradation.

In four simulated lentic environments, Boyle et al. (1980) tested the effects of dissolved oxygen, light, pH, and the presence of a hydrosoil (i.e., pond soil/sediment) on the transformation of pentachlorophenol (applied as the sodium salt). The persistence of pentachlorophenol was associated with three environmental variables: absence of light and hydrosoil; pH near or below pKa; and low oxygen concentration. Major reaction products were pentachloroanisole, 2,3,4,5-tetrachlorophenol, 2,3,4,6-tetrachlorophenol, and 2,3,5,6-tetrachlorophenol; only pentachloroanisole was found in the water phase, and then only in the aerobic systems maintained in light.

Sediment and Soil. Photolysis of pentachlorophenol on soil surfaces is not a major transformation process. Hebert and Miller (1990) reported that UV light was >90% attenuated in the surface 0.2 mm of soil. However, while they will not approach rates of photolysis observed in aqueous solution, photolytic losses on the soil surface may be increased under certain conditions. The effect of upward evaporative flux on the rates of photolytic loss of pentachlorophenol, applied at 1,500 µg/L, was examined in soils maintained at various moisture levels. It was observed that the rates of photolysis on soil increased when near-saturated conditions were utilized, which increased the evaporative flux and translocated the compound to the surface 0.5 mm of the soil where photochemical degradation occurs (Donaldson and Miller 1997). Under near-saturated flow conditions in loamy sand soil, up to 55% more degradation was observed in the irradiated samples than in the dark controls in 14 days.

The rate of pentachlorophenol degradation from adsorption and metabolism in soil is not dependent on soil texture, clay content, free iron oxides, or the degree of base saturation; however, it is partially dependent on the ion exchange capacity of the soil (Engelhardt and Wallnofer 1986). The rate of pentachlorophenol transformation in laboratory tests is more rapid in soils with high organic content than in those with low organic content, and the rate is greater when moisture content is high and soil temperature approaches the optimum for microbial activity (Young and Carroll 1951).

Biodegradation is considered the major transformation mechanism for pentachlorophenol in soil. Half-lives are usually on the order of 2–4 weeks. Pentachlorophenol is metabolized rapidly by most acclimated microorganisms (Kaufman 1978). In a study by Edgehill and Finn (1983) inocula of a strain of pentachlorophenol-acclimated *Arthrobacter* bacteria was added to soils in laboratory and enclosed outdoor tests. The soils were amended with 120–150 mg pentachlorophenol/L and 34 kg pentachlorophenol/hectare, respectively. In the laboratory test conducted in the dark at 30°C, the half-life of pentachlorophenol in inoculated samples was about 1 day, whereas the half-life in uninoculated samples was 12–14 days. Pentachlorophenol loss from uninoculated control plots in outdoor tests was 25% after 12 days at ambient temperatures (8–16°C), while losses from inoculated plots were 50–85%.

Pseudomonas biotransformed [^{14}C]-pentachlorophenol rapidly and released radiolabeled carbon dioxide as well as the intermediate metabolites, tetrachlorophenol and TCHQ. In another study, strains of *Pseudomonas putida* and *Acinetobacter calcoaceticus sp.* were found to be able to use pentachlorophenol as a sole carbon and energy source (Martins et al. 1997).

An investigation was conducted by Frisbie and Nies (1997) to determine whether aged pentachlorophenol residues from contaminated soil at a former wood-treatment site would be biodegraded in the laboratory under aerobic and anaerobic conditions by indigenous microbes from that site. Under aerobic conditions, both existing and newly added pentachlorophenol was biodegraded following a short acclimation period. The degradates 2-monochlorophenol and 4-monochlorophenol were rapidly degraded, but 3-monochlorophenol did not undergo significant degradation. Under anaerobic conditions, pentachlorophenol was degraded to 3-monochlorophenol, which accumulated and was then further degraded; however, approximately 30% of the initial pentachlorophenol was not degraded.

Pentachlorophenol has been observed to degrade more rapidly in anaerobic environments than in aerobic ones. Pentachlorophenol degraded in a paddy soil at 28°C with a half-life of about 3 weeks; reducing conditions increased the rate of reaction slightly (Ide et al. 1972). These observations were confirmed by Kuwatsuka and Igarashi (1975) in 10 different soil types. Pentachlorophenol biotransformation rates were higher under anaerobic (flooded) conditions than under aerobic (upland) conditions. The half-life for pentachlorophenol under flooded conditions ranged from 10 to 70 days, while under upland conditions, the range was 20–120 days, and the rate of reaction increased with the organic matter content. Pentachlorophenol transformation was assumed to proceed by both chemical and microbial means, based on the effects of sterilization, soil temperature, and nature of the reaction products, which included pentachloroanisole; 2,3,4,5-, 2,3,4,6-, and 2,3,5,6-tetrachlorophenol; and 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-,

2,4,6-, and 3,4,5-trichlorophenol. The major products were 2,3,4,5-tetrachlorophenol, and 2,3,6- and 2,4,6-trichlorophenol. Tetrachloro-*p*-benzoquinone and 2,6-dichlorohydroquinone have also been implicated as metabolic intermediates for pentachlorophenol (Reiner et al. 1978).

The degradates, 3,4- and 3,5-dichlorophenol, were also observed in biodegradation studies of pentachlorophenol (Engelhardt and Wallnofer 1986). These authors noted that pentachloroanisole was a major degradate in aerobic soils but was present in minor amounts in anaerobic soils. In anaerobic systems, pentachlorophenol is biodegraded only through reductive dechlorination, and the degradates, 3,5-dichlorophenol and 3-monochlorophenol, may accumulate; complete dechlorination to phenol and its subsequent mineralization to methane and carbon dioxide have been observed (Frisbie and Nies 1997). In a review paper on microbial degradation of pentachlorophenol, McAllister et al. (1996) reported that the various intermediates found in numerous studies indicated that microbial degradation of the compound occurs by different mechanisms that are associated with specific microbial consortia.

Pentachlorophenol is degraded under anaerobic conditions in sewage sludge and sediments. After 6 months of operation, about 60% of the initial concentration of pentachlorophenol added to laboratory-scale, fixed-film reactors containing a digested municipal sewage sludge microbial inoculum was removed. Removal from reactors supplemented with glucose attained 98% of the initial charge over the same time frame. Trichlorophenol and tetrachlorophenol were observed as degradation products (Hendriksen et al. 1991). In other laboratory tests, reductive dechlorination of pentachlorophenol was found to be more rapid in freshwater sediments containing microbial communities adapted to dechlorinate 2,4-dichlorophenol and 3,4-dichlorophenol than in nonadapted sediment microbial communities. Degradation products identified included 2,3,5,6-tetrachlorophenol, 2,3,5-trichlorophenol, 3,5-dichlorophenol, 3-chlorophenol, and phenol (Bryant et al. 1991). Ingerslev et al. (1998) also reported more rapid degradation and shorter or no acclimation periods in freshwater sediments amended with activated sludge that was preexposed to pentachlorophenol at various levels. At concentrations ranging from 10 to 20,000 µg/L, the acclimation periods were reduced from 8.6–21.1 to 0.1–3.2 days when sediments were amended with preexposed activated sludge compared with activated sludge that was not preexposed to pentachlorophenol; only at a toxic concentration of 74,000 µg/L was the acclimation period increased (15.5–59.4 days). At concentrations of 10, 100–2,500, and 20,000 µg/L, preexposure reduced the respective postacclimation half-lives from 32, 3.7–5.6, and 108 days to ≤2.2 days; at 74,000 µg/L, the postacclimation half-life decreased from 80 days to >51.6 days.

Other Media. Laboratory studies were conducted to determine the effect of artificial light and sunlight on concentrations of pentachlorophenol and CDDs in wood treated with pentachlorophenol (Lamparski et al. 1980). Although CDDs are known to be present in pentachlorophenol products as impurities, formation of OCDD, as well as HpCDD and hexachlorodibenzo-*p*-dioxin (HxCDD), was observed even when purified pentachlorophenol was irradiated. Based on the relative levels of the isomers observed, HxCDD and HpCDD were presumed to be degradation products of OCDD not condensation products of tetrachlorophenol and pentachlorophenol. The formation of OCDD was greatly reduced when hydrocarbon oil was utilized as the carrier solvent in place of methylene chloride.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to pentachlorophenol depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of pentachlorophenol 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 pentachlorophenol 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.

Pentachlorophenol historically has been widely detected in environmental media as a result of its widespread past use by industry, the agricultural sector, and the general public, as a cooling-tower algicide and fungicide, herbicide, molluscicide, paint preservative, plywood and fiberboard waterproofing agent, and drilling mud and photographic solution biocide. Pentachlorophenol is now regulated as a restricted-use pesticide. Therefore, it can only be purchased and used by certified applicators, and only for the applications covered by the applicator's certification. Pentachlorophenol is no longer available to the general public. Although the compound has been detected in indoor air, surface waters, groundwater, drinking water, soils, rainwater, and a variety of foods in older monitoring studies, current contamination of these media by the compound is probably more limited given the restricted current usage of pentachlorophenol and its limited environmental persistence.

Table 5-4 shows the lowest limit of detections that are achieved by analytical methods in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-5.

Table 5-4. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air (ng/m^3)[b]	0.06	Cessna et al. 1997
Drinking water (ppb)	0.0002	EPA 1986b
Surface water and groundwater (ppb)	0.076	EPA 1996 (Method 8151)
Soil (ppb)	0.16	EPA 1996 (Method 8151)
Sediment (ppb)	0.16	EPA 1996 (Method 8151)
Whole blood (ppb)	0.25	CDC 2009

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.
[b]Detection limits in air are dependent upon sampling times and volumes.

Table 5-5. Summary of Environmental Levels of Pentachlorophenol

Media	Low	High	For more information
Outdoor air (ng/m^3)	<LOD	136	Section 5.5.1
Indoor air (ng/m^3)	<LOD	104,000	Section 5.5.1
Surface water (µg/L)	<LOD	<LOD	Section 5.5.2
Groundwater (µg/L)	<LOD	2,060	Section 5.5.2
Drinking water (µg/L)	<LOD	2,060	Section 5.5.2
Soil (µg/kg)	<LOD	654,000	Section 5.5.3
Sediment (µg/kg)	<LOD	<1,480	Section 5.5.3
Food (ppb)	<LOD	40	Section 5.5.4

LOD = limit of detection

Detections of pentachlorophenol in air, water, and soil at NPL sites are summarized in Table 5-6.

Table 5-6. Pentachlorophenol Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	410	592	90.2	141	74
Soil (ppb)	150,000	111,000	31.9	173	83
Air (ppbv)	0.0661	0.134	35.7	19	12

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Limited information is available on the levels of pentachlorophenol in ambient air. EPA (1980b) estimated atmospheric concentrations of pentachlorophenol using air models. A cumulative concentration estimate based on all emission sources was 0.15–136 ng/m^3. The lower end of this range coincides with the upper end of the range of computed air concentration estimates based on pentachlorophenol concentrations in rainwater in Hawaii (0.002–0.063 ng/m^3) where pentachlorophenol has been used extensively as an herbicide and wood preservative.

In a study designed to evaluate the potential exposure of pre-school children to environmental pentachlorophenol, Wilson et al. (2007) measured the levels of pentachlorophenol in the 257 children's homes and daycare centers in North Carolina and Ohio (Wilson et al. 2007). For more than a 2-day period, each child's home, daycare center, indoor air, outdoor air, house dust, soils, food, beverages, hand surfaces, and urine were sampled for pentachlorophenol. Inhalation was presumed to be the predominant route of pentachlorophenol exposure. Pentachlorophenol was detected in >50% of indoor air, outdoor air, and dust samples. The 50th percentile indoor air concentrations of pentachlorophenol were 1.50 ng/m^3 in North Carolina homes and 2.14 ng/m^3 in Ohio homes. The 50th percentile indoor air concentrations of pentachlorophenol for daycare centers studied in North Carolina and Ohio were 1.1 and 1.32 ng/m^3, respectively. The 50th percentile pentachlorophenol air concentrations for outdoor air samples obtained from near North Carolina and Ohio homes were 0.91 and 0.43 ng/m^3, respectively. The 50th percentile pentachlorophenol concentrations in outdoor air samples from near the selected North Carolina and Ohio daycare centers were 0.77 and 0.22 ng/m^3, respectively (Wilson et al. 2007). Thus, the children were exposed to higher levels of airborne pentachlorophenol in and around their homes than the levels to which they were exposed in their daycare centers (Wilson et al. 2007).

Pentachlorophenol was detected at a geometric mean concentration of 0.080 ng/L (80 ng/m^3) in 62 of 63 air samples (range 1–904 ng/m^3) taken in 21 log homes treated with the compound (EPA 1986b). The homes, all located in Kentucky, were categorized into six treatment types: (1) "never treated;" (2) external treatment; (3) manufacturer treated; (4) treated and sealed; (5) treated, sealed, and neutralized; and (6) treated and neutralized. Concentrations in "never treated" homes, which were lower than those in treated homes, were believed to be the result of the application of pentachlorophenol to logs during storage to prevent fungal growth. Treated logs were found to be the source of pentachlorophenol in indoor air; air concentrations were highly correlated with pentachlorophenol concentrations in wood cores (geometric mean, 15,900 ng/g wood) and log surface wipes (geometric means, 89.6 and 187 ng/100 cm^2)

(EPA 1986b). Concentrations of pentachlorophenol in older structures built with pressure-treated wood brushed with pentachlorophenol were reported to range from 0.5 to 10 μg/m^3 (500–10,000 ng/m^3) (EPA 1984b). Use of sealers decreased this concentration by 85%. Indoor air interiors of structures built with industrially dipped nonpressure-treated wood were reported to contain levels of pentachlorophenol that ranged from 34 to 104 μg/m^3 (34,000–104,000 ng/m^3) (EPA 1984b). Logs used for home construction are no longer treated with pentachlorophenol.

Air concentrations ranged from 15 to 30 μg/m^3 (15,000–30,000 ng/m^3) at a wood treatment facility in Georgia (ATSDR 2007). The levels in the surrounding residential area ranged from <1.3 to 8.1 μg/m^3 (<1,300–8,100 ng/m^3) (ATSDR 2007).

SPECIATE is EPA's repository of speciation profiles of air pollution sources containing information on the species makeup or chemical composition of organic gases, particulate matter, and other pollutants emitted from these sources. SPECIATE can be used for site assessments and health studies. For additional information, see https://www.epa.gov/air-emissions-modeling/speciate.

5.5.2 Water

Recent water monitoring data can be accessed at EPA's Water Quality Exchange (WQX) through the Water Quality Portal (WQP) (https://www.epa.gov/waterdata/water-quality-data-wqx). These data are provided by submissions from over 400 federal, state, tribal agencies, and other organizations. A search of the national water quality database for STORage and RETrieval (STORET) and National Water Information Systems databases indicated that there were 488 surface water and groundwater samples collected and tested for pentachlorophenol at 244 unique sites in 10 states in 2020–2021. There were no positive detections in groundwater monitoring results, and the only positive detections in surface water monitoring were below the limit of quantification ranging from 0.1 to 0.5 μg/L (WQP 2021). Thirty-eight U.S. streams were monitored from 2012 to 2014 for 719 compounds; pentachlorophenol was found in 10 streams at ~0.1 μg/L (Bradley et al. 2017).

Pentachlorophenol was detected in drinking water samples of log homes that were treated with pentachlorophenol and used cisterns as the sole water source at levels ranging from 0.0002 to 0.001 μg/L (EPA 1986b). In 2001, pentachlorophenol was detected in 33% of sampled stream and raw water that supply a U.S. water treatment facility at concentrations ranging from 0.1 to 0.3 μg/L prior to treatment. After treatment, pentachlorophenol was not detected in finished water (Stackelberg et al. 2004).

Pentachlorophenol is currently a regulated contaminant under the Safe Drinking Water Act (SDWA) and as a consequence, a 6-year review for its occurrence in public water systems is mandated by law. Data from the third 6-year review collected from 2006 to 2011 showed that 40,322 public water systems (PWS) servicing over 234 million people were included for the study of occurrence of pentachlorophenol in PWS (EPA 2016). Pentachlorophenol was detected above its minimum reporting level of 0.04 µg/L in 226 out of the 40,322 PWS tested (0.56%). The range of the 5^{th}–95^{th} percentile concentrations of pentachlorophenol in all the PWS tested was 0.01–0.98 µg/L (EPA 2016). There were also 11 systems out of 40,322 (0.027%) that had at least one measurement in which the concentration of pentachlorophenol exceeded the maximum contaminant level (MCL) of 1 µg/L (EPA 2016). High levels of pentachlorophenol have been observed in private wells that may become contaminated via leaching from utility poles or after an accidental spill. Pentachlorophenol was detected at levels of 2,060 and 1,150 µg/L in private wells in Vermont due to leaching of pentachlorophenol from utility poles that were in contact with the water table providing potable water to homes using these wells (Karlsson et al. 2013).

5.5.3 Sediment and Soil

Arsenault (1976) reported pentachlorophenol concentrations of 3.4–654 ppm (3,400–654,000 µg/kg) in soil within 12 inches of treated utility poles. Pentachlorophenol was detected in the soil samples taken from a depth of 0–3 inches at (320–2,300 µg/kg) and in subsurface soil (820–200,000 µg/kg) at a wood-treatment facility, an NPL site, in Louisiana (ATSDR 1995). It was also found in soil at an inactive landfill in Florida, also an NPL site, at a maximum concentration of 21,000 µg/kg (ATSDR 1993). Pentachlorophenol was found in on-site (up to 13,000 µg/kg) and off-site (up to 1,300 µg/kg) soil samples from the Camilla Wood Preserving Company in Camilla, Georgia (ATSDR 1999). Davis et al. (1994) reported soil levels of pentachlorophenol prior to remediation of >100,000 µg/kg at a former wood treating facility located in Florida. The shuttered Gas Works Park located near Seattle, Washington (closed in 1959) had pentachlorophenol levels measured at 2 of 14 sampling locations at concentrations of 52 and 460 µg/kg (Turney and Goerlitz 1990).

Recent sediment monitoring data can be accessed at the EPA Water Quality Data WQX (https://www.epa.gov/waterdata/water-quality-data-wqx). A search of the STORET and National Water Information Systems databases indicated that there were 25 sediment samples collected and tested for pentachlorophenol at 23 unique sites in the United States in 2020. There were no positive detections at or above the method detection limit of 1,480 ug/kg (WQP 2021). No data were available for 2021.

5.5.4 Other Media

Levels of pentachlorophenol in food are examined as a part of FDA's ongoing food monitoring studies. In 1973–1974, 10 out of 360 composite food samples contained pentachlorophenol at 10–30 ppb: 1 in dairy products, 1 in cereals, 1 in vegetables, and 7 in sugar (Manske and Corneliussen 1976). In the next year, 13 out of 240 composites contained pentachlorophenol (10–40 ppb), again mostly in sugars (Johnson and Manske 1977). FDA Total Diet Study market basket surveys from 1991–1993 through 2003–2004 collected between September 1991 and October 2003 showed that pentachlorophenol was detected in 1 out of 44 samples of cured ham at a concentration of 20 ppb and 1 out of 44 chicken breast samples at a level of 10 ppb (FDA 2006). Pentachlorophenol was detected in all of a series of random samples of Florida food at levels of 1–1,000 ppb, principally in grain products (Dougherty and Piotrowska 1976). Pentachlorophenol was also detected at low levels in peanut butter (1.8–62 µg/kg) and chicken (6–12 µg/kg) (Farrington and Munday 1976). Recent food concentration data in the United States were not located; however, in a survey conducted from 2012 to 2015 in the United Kingdom for 120 retail foods, pentachlorophenol was found at <0.01–1.90 µg/kg whole wet weight basis. Pentachlorophenol was detected infrequently, or not at all, in poultry, fish and shellfish, and milk and dairy products, with the highest concentration found in eggs (Fernandes et al. 2019). Monitoring data from 2015 to 2018 in China of 3,100 animal source foods showed that average pentachlorophenol concentrations declined from 17.42 to 2.39 µg/kg wet weight over the time period (Zhou et al. 2021).

No biological data were located in a search of the STORET and National Water Information Systems databases for 2020–2021. Lake trout collected from Lake Ontario and Lake Superior between May and August of 2000 and 2001 had pentachlorophenol maximum blood plasma residues ranging from 105 to 658 pg/g (0.000105–0.000658 mg/kg) (Campbell et al. 2003). Pentachlorophenol was not detected in fish from Lake Superior or Lake Michigan in a study conducted in 2014–2015 (Baygi et al. 2021).

Pentachlorophenol was detected in the plasma of nestling peregrine falcons from 34 active nests across Ontario and western Quebec collected in 2004 and 2005 (Fernie and Letcher 2010). The geometric mean pentachlorophenol level was 3.16 ng/g (wet weight) with a range of values of 0.46–24.44 ng/g (weight weight).

Levels of pentachlorophenol ranging from 10 to 270 µg/L were reported in 9 out of 65 samples of children's paints in the Netherlands (Van Langeveld 1975). Wang et al. (2021) studied the concentration of wood preservatives in 90 wooden toys manufactured in China; pentachlorophenol was found in 1 of 33 building block toys and 1 of 20 jigsaw toys.

Pentachlorophenol was detected in 6 of 38 dust samples from homes in California tested over a 2-year period at a 95th percentile of 11,511 ng/g of dust (Shin et al. 2020)

5.6 GENERAL POPULATION EXPOSURE

Potential sources of pentachlorophenol exposure for the general population include air, dust, drinking water sources, food, soils, and dermal contact with contaminated products treated with the compound. In eight male anglers (50+ years) from the Lake Superior and Lake Michigan region, pentachlorophenol concentrations in serum were 0.07–0.3 ng/g (Baygi et al. 2021). Using data from spot urine samples collected from 31 participants in the United States, a daily pentachlorophenol intake of 0.34 µg/day was estimated (Honda and Kannan 2018).

Before being regulated as a restricted-use pesticide, pentachlorophenol was used extensively in treating wood. Today, this use is restricted to the treatment of utility poles, railroad ties, and wharf pilings. Dermal exposure to pentachlorophenol by members of the general population may occur upon contact with these wood products. Since pentachlorophenol is readily absorbed through skin (Qiao et al. 1997; Wester et al. 1993), this represents a relevant route of exposure. Pentachlorophenol is known to volatilize from treated wood products (Bunce and Nakai 1989) at a rate that is temperature-dependent (Ingram et al. 1986), and inhalation exposure may also occur with increased levels expected during the summer months. In older residences constructed with treated wood products, inhalation of contaminated indoor air may also be an important source of exposure. A reduction in volatilization of pentachlorophenol by coating the treated wood surfaces with varnishes and epoxy coatings was demonstrated by Ingram et al. (1986).

Inhalation of estimated ambient levels of pentachlorophenol in the atmosphere has an associated exposure level of 6 µg/day for the general population (EPA 1980b); however, it is likely that current exposure estimates are much lower. Based on the pentachlorophenol levels in their 1977 food survey, FDA estimated an average dietary intake of 0.76 mg/day for a typical 15- to 20-year-old male, and EPA (1978) calculated an average dietary intake of 1.5 mg/day and a maximum dietary intake of 18 mg/day. However, the actual intake was lower than estimates because average dietary intakes were based on mean

concentration of positive samples. Daily dietary intake of pentachlorophenol from contaminated food has been estimated by another source to be 0.1–6 µg/day (WHO 1987). Using a six-compartment environmental partitioning model, Hattemer-Frey and Travis (1989) reported that the food chain is the most important source of exposure to pentachlorophenol for the general population. The study authors estimated the average daily dietary intake of the compound to be 16 µg/day from ingestion of contaminated food, primarily root vegetables. Pentachlorophenol was detected in 15% of the foods collected in eight market basket surveys from different regions of the United States during the period of April 1982 to April 1984 (Gunderson 1988). Foods representative of the diets of eight different age/gender population groups were prepared for consumption prior to analysis in a revision to FDA's Total Diet Study methodology. Estimated mean daily intakes (ng/kg/day) of pentachlorophenol for these groups in 1982–1984 were as follows: (1) 6- to 11-month-old infants, 59.0; (2) 2-year-old children, 48.5; (3) 14- to 16-year-old females, 16.2; (4) 1- to 16-year-old males, 20.7; (5) 25- to 30-year-old females, 15.9; (6) 25- to 30-year-old males, 18.2; (7) 60- to 65-year-old females, 13.9; and (8) 60- to 65-year-old males, 15.5. In a later survey of the Total Diet Study, Gunderson (1995) estimated mean daily intakes (ng/kg/day) of pentachlorophenol for these same eight age/gender population groups during a 1986–1991 study as follows: (1) 6- to 11-month-old infants, 0.9; (2) 2-year-old children, 1.4; (3) 14- to 16-year-old females, 0.5; (4) 14- to 16-year-old males, 0.5; (5) 25- to 30-year-old females, 0.8; (6) 25- to 30-year-old males, 0.7; (7) 60–65-year-old females, 0.8; and (8) 60- to 65-year-old males, 0.8. These estimates demonstrate a substantial reduction in the amount of pentachlorophenol in the estimated mean daily intake since the 1982–1984 study. Given the fact that pentachlorophenol was rarely detected in food items from the FDA Total Diet Study collected between September 1991 and October 2003 (FDA 2006), it is therefore likely that current daily intakes are much lower.

Pentachlorophenol has been detected in human adipose tissue, blood, and urine. It is important to know that pentachlorophenol itself is a metabolite of other environmental contaminants (e.g., hexachloro-benzene, pentachlorobenzene, pentachloronitrobenzene), so its detection may also occur as a result of exposure to these substances. As part of the second National Health and Nutrition Examination Survey (NHANES II) and the National Human Adipose Tissue Monitoring Survey (NHATS), urine samples from approximately 6,000 persons between the ages of 12 and 74 years in 64 communities throughout the United States were analyzed for pentachlorophenol during the period of 1976–1980. Pentachlorophenol was detected in over 70% of the urine samples with a geometric mean concentration of 6.3 µg/L, 90^{th} percentile concentration of 15.5 µg/L, and a maximum concentration of 193 µg/L (Kutz et al. 1978; 1992). Geometric mean concentration was higher in males (6.7 µg/L) than females (5.9 µg/L) and the highest geometric means were found among 12- to 19-year-olds, as compared to other age groups (Kutz

et al. 1992). NHANES monitoring data in 1999–2000, 2001–2002, and 2003–2004 demonstrate a decrease in urinary pentachlorophenol levels in the U.S. population. As presented in Table 5-7, the geometric mean levels were not calculated because the proportion of results below the limit of detection was too high to provide a valid result. The creatinine-corrected urinary levels are presented in Table 5-8.

The 90th percentile concentrations in 1999–2000, 2001–2002, and 2003–2004 (0.390, 1.23, and 2.57 µg/L, respectively) were much lower than the level in 1976–1980 (15.5 µg/L). Pentachlorophenol levels were measured in urine samples from pregnant women (n=361), as part of a multi-ethnic study conducted in New York City (Berkowitz et al. 2003). The 10th, 25th, 50th, 75th, and 90th percentile concentrations were 1.1, 2.4, 7.3, 28.4, and 76.0 µg/g creatinine, respectively. An analysis of global trends in pentachlorophenol levels found an exponential decrease in urinary pentachlorophenol levels with U.S. levels decreasing by 90% between the 1967–1978 and 1990–1995 time periods and by 44% between the 1990–2005 and 1996–2003 time periods (Zheng et al. 2011).

Historical data demonstrate the presence of pentachlorophenol in various human tissues. A mean level of 26.3 µg/kg was found in adipose tissue from the general U.S. population (Shafik 1973). In a study of human tissues removed at autopsy, including testes, kidney, prostate glands, livers, and adipose tissue, pentachlorophenol was found in all tissues examined at concentrations ranging from 7 µg/kg in subcutaneous fat to 4,140 µg/kg in testes (Wagner et al. 1991). Geyer et al. (1987) investigated the distribution and bioconcentration of pentachlorophenol in different human tissues by comparing daily intake of pentachlorophenol with tissue concentrations; bioconcentration ratios of 5.7, 3.3, 1.4, 1.4, and 1.0 were obtained in liver, brain, blood, spleen, and adipose tissue, respectively. Pentachlorophenol has also been found in human milk samples from West Germany at 0.03–2.8 µg/kg (Gebefugi and Korte 1983). Hair and air samples from households in France/Luxembourg were compared; 27% of 78 hair samples had pentachlorophenol concentrations of <2.5–30 pg/mg and air concentrations of 1–114 ng/sample. Exposure profiles varied from home to home and between residents in the same household, indicating that the two matrices were not necessarily associated (Raeppel et al. 2016).

Children are likely to be exposed to pentachlorophenol via the same routes that affect adults, such as inhalation of contaminated air, ingestion of contaminated groundwater used as a source of drinking water, ingestion of contaminated food, and dermal contact with contaminated soils or products treated with the compound. In addition, small children are more likely than adults to come into intimate contact with yard dirt, lawns, toys, and house (carpet) dust. Dislodgeable pesticide residues in carpets or on uncovered floors may present a relatively important exposure route for infants and toddlers through dermal contact

Table 5-7. Urinary Pentachlorophenol Levels in the NHANES U.S. Population

	Survey years	Geometric mean (95% CI) (µg/L)	Selected percentiles (95% CI) (µg/L)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	*	0.350 (0.350–0.350)	0.350 (0.350–0.350)	0.390 (0.350–0.960)	1.30 (0.500–2.10)	1,994
	2001–2002	*	<LOD	<LOD	1.23 (0.590–1.76)	1.94 (1.58–2.53)	2,528
	2003-2004	*	<LOD	1.12 (0.570–1.58)	2.57 (2.08–2.99)	3.63 (2.98–4.61)	2,354
Age group							
6–11 years	1999–2000	*	0.350 (0.350–0.350)	0.350 (0.350–0.350)	0.770 (0.350–1.51)	1.65 (0.990–2.00)	482
	2001–2002	*	<LOD	<LOD	1.37 (0.890–1.70)	2.10 (1.58–2.75)	577
	2003–2004	*	<LOD	1.57 (0.970–2.25)	3.23 (2.12–5.67)	5.67 (2.94–6.38)	290
12–19 years	1999–2000	*	0.350 (0.350–0.350)	0.350 (0.350–0.350)	0.660 (0.350–2.60)	2.00 (0.510–5.90)	681
	2001–2002	*	<LOD	<LOD	1.48 (.850–2.30)	2.3 (1.47–5.04)	826
	2003–2004	*	<LOD	1.36 (0.760–1.99)	2.88 (2.08–3.53)	3.80 (3.06–6.38)	674
20–59 years	1999–2000	*	0.350 (0.350–0.350)	0.350 (0.350–0.350)	0.350 (0.350–0.650)	1.10 (0.350–2.00)	831
	2001–2002	*	<LOD	<LOD	1.01 (<LOD–1.76)	1.90 (1.45–2.53)	1,125
	2003–2004	*	<LOD	0.980(<LOD–1.50)	2.40 (1.73–2.79)	3.11 (2.75–3.65)	889
Sex							
Males	1999–2000	*	0.350 (0.350–0.350)	0.350 (0.350–0.350)	0.630 (0.350–1.30)	1.40 (0.480–2.60)	973
	2001–2002	*	<LOD	<LOD	1.32 (0.680–1.80)	1.94 (1.47–3.09)	1,190
	2003–2004	*	<LOD	1.32 (.720–2.05)	2.79 (2.46–3.40)	4.58 (3.50–5.49)	1,147
Females	1999–2000	*	0.350 (0.350–0.350)	0.350 (0.350–0.350)	0.350 (0.350–0.530)	0.890 (0.350–2.00)	1,021
	2001–2002	*	<LOD	<LOD	1.10 (<LOD–1.78)	1.98 (1.54–2.42)	1,338
	2003–2004	*	<LOD	0.880 (<LOD–1.41)	2.12 (1.71–2.74)	3.20 (2.44–3.84)	1,207
Race/ethnicity							
Mexican Americans	1999–2000	*	0.350 (0.350–0.350)	0.350 (0.350–0.350)	0.350 (0.350–0.350)	0.650 (0.350–1.90)	696
	2001–2002	*	<LOD	<LOD	0.990 (<LOD–2.37)	1.62 (0.510–3.64)	680
	2003–2004	*	<LOD	<LOD	1.73 (0.640–3.38)	2.44 (1.73–3.84)	550
Non-Hispanic blacks	1999–2000	*	0.350 (0.350–0.350)	0.350 (0.350–0.350)	0.980 (0.350–2.50)	1.65 (0.860–2.70)	521
	2001–2002	*	<LOD	<LOD	1.73 (1.33–2.33)	2.83 (2.08–3.67)	696
	2003–2004	*	<LOD	<LOD	1.73 (0.640–3.38)	2.44 (1.73–3.84)	610
Non-Hispanic whites	1999–2000	*	0.350 (0.350–0.350)	0.350 (0.350–0.350)	0.390 (0.350–1.10)	1.30 (0.350–2.30)	603
	2001–2002	*	<LOD	<LOD	1.18 (<LOD–1.76)	1.91 (1.48–2.42)	951
	2003–2004	*	<LOD	1.17 (.580–1.74)	2.66 (2.06–3.23)	3.69 (2.99–5.17)	1,039

*= geometric mean not calculated because the proportion of results below the limit of detection (0.25 µg/L in 1999–2000 and 0.5 µg/L in 2001–2002 and 2003–2004) was too high to provide a valid result; CI = confidence interval; LOD = limit of detection; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2009, 2019 (https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Jan2019-508.pdf)

Table 5-8. Urinary Pentachlorophenol Levels in the NHANES U.S. Population (Creatinine Corrected)

	Survey years	Geometric mean (95% CI) (µg/g L)	Selected percentiles (95% CI) (µg/g)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	*	0.300 (0.290–0.320)	0.570 (0.500–0.650)	1.16 (0.950–1.35)	1.67 (1.35–2.11)	1,994
	2001–2002	*	<LOD	<LOD	1.52 (1.25–1.75)	2.26 (1.67–3.09)	2,528
	2003–2004	*	<LOD	1.22 (1.01–1.52)	2.30 (1.84–2.77)	3.44 (2.69–3.96)	2,352
Age group							
6–11 years	1999–2000	*	0.370 (0.340–0.420)	0.650 (0.580–0.780)	0.990 (0.900–1.30)	1.83 (1.10–2.95)	482
	2001–2002	*	<LOD	<LOD	1.84 (1.29–3.18)	3.18 (1.84–4.52)	577
	2003–2004	*	<LOD	1.75 (1.38–2.69)	3.72 (2.50–4.96)	4.96 (3.59–10.6)	290
12–19 years	1999–2000	*	0.250 (0.220–0.290)	0.400 (0.330–0.490)	0.760 (0.500–1.40)	1.57 (0.700–2.51)	681
	2001–2002	*	<LOD	<LOD	1.21 (0.910–1.56)	1.82 (1.25–2.82)	826
	2003–2004	*	<LOD	1.11 (0.800–1.28)	1.67 (1.31–2.65)	2.76 (1.64–3.89)	673
20–59 years	1999–2000	*	0.300 (0.270–0.320)	0.610 (0.510–0.730)	1.25 (1.00–1.40)	1.67 (1.30–2.19)	831
	2001–2002	*	<LOD	<LOD	1.52 (<LOD–1.75)	2.19 (1.67–2.99)	1,125
	2003–2004	*	<LOD	1.10 (<LOD–1.31)	1.99 (1.66–2.59)	2.92 (2.20–3.81)	888
Sex							
Males	1999–2000	*	0.260 (0.240–0.280)	0.470 (0.380–0.560)	0.920 (0.780–1.25)	1.67 (1.16–1.84)	973
	2001–2002	*	<LOD	<LOD	1.13 (0.950–1.40)	1.73 (1.25–2.92)	1,190
	2003–2004	*	<LOD	1.10 (.825-1.38)	1.93 (1.62-2.65)	3.23 (2.06-4.94)	1,146
Females	1999–2000	*	0.360 (0.310–0.430)	0.650 (0.560–0.830)	1.26 (1.09–1.35)	1.67 (1.35–2.19)	1,021
	2001–2002	*	<LOD	<LOD	1.75 (<LOD–2.06)	2.69 (1.94–3.55)	1,338
	2003–2004	*	<LOD	1.37 (<LOD–1.74)	2.50 (2.13–2.98)	3.50 (2.79–4.07)	1,206
Race/ethnicity							
Mexican Americans	1999–2000	*	0.300 (0.270–0.320)	0.500 (0.430–0.560)	1.06 (.710–1.40)	1/57 (1.21–2.00)	696
	2001–2002	*	<LOD	<LOD	1.09 (<LOD–2.36)	1.94 (1.06–3.55)	680
	2003–2004	*	<LOD	<LOD	1.54 (1.01–2.69)	2.33 (1.40–4.62)	549
Non-Hispanic blacks	1999–2000	*	0.250 (0.220–0.310)	0.440 (0.360–0.590	0.850 (0.590–1.30)	1.34 (0.950–1.90)	521
	2001–2002	*	<LOD	<LOD	1.30 (0.800–1.78)	1.94 (1.48–2.79)	696
	2003–2004	*	<LOD	0.919 (0.679–1.25)	1.88 (1.42–2.77)	2.94 (2.21–3.76)	610
Non-Hispanic whites	1999–2000	*	0.320 (0.290–0.350)	0.630 (0.510–0.800)	1.25 (1.00–1.40)	1.67 (1.40–2.19)	603
	2001–2002	*	<LOD	<LOD	1.52 (<LOD–1.78)	2.10 (1.67–3.08)	951
	2003–2004	*	<LOD	1.35 (1.08–1.64)	2.42 (1.94–3.18)	3.54 (2.77–4.78)	1,038

*= geometric mean not calculated because the proportion of results below the limit of detection (0.25 µg/L in 1999–2000 and 0.5 µg/L in 2001–2002 and 2003–2004) was too high to provide a valid result; CI = confidence interval; LOD = limit of detection; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2009, 2019 (https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Jan2019-508.pdf)

and oral ingestion. The tendency of young children to ingest soil, either intentionally through pica behavior or unintentionally through hand-to-mouth activity, is well documented. These behavioral traits can result in ingestion of pentachlorophenol present in soil and dust. Though pentachlorophenol is known to (1) adsorb to soil, especially at lower pH (Chang and Choi 1974; Choi and Aomine 1974; Kuwatsuka and Igarashi 1975); (2) have an insignificant rate of volatilization from soil (Kilzer et al. 1979); and (3) biodegrade at a moderately rapid rate, very little data are available on the actual measurements of pentachlorophenol in soil. No studies are available that describe the dermal absorption of pentachlorophenol in children. Two studies are available, however, that show that absorption of pentachlorophenol occurs in both Rhesus monkeys and swine when dermally exposed to soil amended with pentachlorophenol (see Section 3.1.1). Therefore, it is possible that children may absorb pentachlorophenol dermally when exposed to soil contaminated with pentachlorophenol. Another potential source of exposure for children is pentachlorophenol-treated wood. Wang et al. (2021) studied the concentration of wood preservatives in 90 wooden toys manufactured in China; pentachlorophenol was found in 1 of 33 building block toys and 1 of 20 jigsaw toys, indicating that dermal and oral exposures are possible. Pentachlorophenol was used extensively in treating wood. Today, though no longer used in treatment of wood products in residences and agricultural buildings, pentachlorophenol is still widely used in the treatment of utility poles and railroad ties. Playing near a utility pole such as a telephone or an electrical pole or touching utility poles may pose a risk of dermal exposure. Pentachlorophenol is also known to volatilize from treated wood (Bunce and Nakai 1989), with emissions expected to be highest in the hottest months of the summer (Ingram et al. 1986). Therefore, inhalation exposure may occur for children playing nearby. Old and unpainted playground equipment constructed with pentachlorophenol-treated wood may be another mode of dermal exposure for children.

Foods representative of the diets of eight different age/gender population groups, including children (6–11-month-old infants, 2-year-old children, and 14- to16-year-old males and females), were prepared for consumption prior to analysis in a revision to the FDA's Total Diet Study methodology (Gunderson 1988). Estimated mean daily intakes of pentachlorophenol for children in 1982–1984 were as follows: 59.0 ng/kg/day in 6- to 11-month-old infants; 48.5 ng/kg/day in 2-year-old children; (3) 16.2 ng/kg/day in 14- to 16-year-old females; and 20.7 ng/kg/day in 14- to 16-year-old males. In comparison, the intake for adults ranged from 15.5 to 18.2 ng/kg/day. Much lower intakes were estimated in a later survey of the Total Diet Study during 1986–1991 (Gunderson 1995). Estimated mean daily intakes of pentachlorophenol were 0.9, 1.4, 0.5, and 0.5 ng/kg/day in 6- to 11-month-old infants, 2-year-old children, 14- to 16-year-old females, and 14- to 16-year-old males, respectively; the intake for adults ranged from 0.7 to 0.8 ng/kg/day.

The children of pesticide applicators who use pentachlorophenol may potentially be exposed to elevated levels from contact with their parents' skin, hair, work clothes, and/or other workplace objects. In addition, pentachlorophenol adsorbed onto the parent or the parent's clothing may contaminate household objects when they come in contact with them, potentially indirectly exposing children to pentachlorophenol. Although pentachlorophenol is a restricted-use pesticide and is only supposed to be used by an EPA-certified applicator for specified uses, there have been instances in which children were exposed to pesticides (methyl parathion) from the illegal application of pesticides. No monitoring data are available on this route of exposure to pentachlorophenol.

Potential exposures to pentachlorophenol and other pesticides from multiple environmental and personal media were examined in a study of 257 children selected randomly from households and daycare centers from selected counties in North Carolina and Ohio. The results suggested that the potential for children's exposures to pentachlorophenol is primarily via inhalation, while indirect ingestion may have made a modest contribution. The potential exposure doses of pentachlorophenol from inhalation exposure for these children were estimated to be 12 ng/day for North Carolina and 18 ng/day for Ohio. The potential exposure doses from indirect ingestion for the children were estimated to be 3.4 ng/day for North Carolina and 1.8 ng/day in Ohio. Furthermore, based on an assumption of 50% of chemical absorption in these children, the estimated potential absorbed doses of pentachlorophenol from inhalation were 0.34 ng/kg/day for North Carolina and 0.58 ng/kg/day for Ohio (Wilson et al. 2007). Pentachlorophenol was detected in 89% of the urine samples from the North Carolina children and in 99% of the urine samples from the Ohio children. The overall arithmetic means for urinary pentachlorophenol levels were 0.605 ng/mL for the children who lived in North Carolina and 1.27 ng/mL for the children who lived in Ohio. The level of pentachlorophenol excreted in urine by the children in this study over a 48-hour sampling period significantly exceeded the estimated intake based on environmental sampling, a finding that suggested that the children may have been exposed to other compounds that are biotransformed to pentachlorophenol (Wilson et al. 2007). However, these levels were lower than the 95th percentile values for children reported in the NHANES report (CDC 2009) and the authors noted that they were much lower than established reference levels (Wilson et al. 2007).

Hill et al. (1989) compared the amounts of chlorinated phenols and phenoxy acids found in the urine of children living in the vicinity of a herbicide manufacturing plant to those found in the urine of a control group of children living away from the herbicide plant. There was no significant difference in the amounts of pentachlorophenol or other herbicide residues detected in the two groups with the median

pentachlorophenol concentration of 14 µg/L, suggesting that children living in the vicinity of the herbicide plant were not at a greater risk of exposure. Cline et al. (1989) measured the pentachlorophenol in the serum and urine of adults and children living in pentachlorophenol-treated log houses. The pentachlorophenol serum levels of children were found to average 1.8 times those of their parents. The mean concentrations were: (1) 2- to 5-year-old children, 600 µg/L; (2) 6- to 10-year-olds, 490 µg/L; (3) 11- to 15-year-olds, 370 µg/L; and (4) adults, 310 µg/L. The higher concentration of pentachlorophenol detected in children was attributed to their greater body surface-to-weight ratio and a higher respiratory rate as compared to adults.

Lewis et al. (1994) conducted a nine-home pilot study to monitor the potential exposure of small children to pesticides in the residential environment. Pentachlorophenol was found to be one of the most frequently occurring pesticides and was detected in all of the samples in all nine houses irrespective of the age of the house (year of construction ranged from 1930 to 1989). The mean concentration of pentachlorophenol reported by the authors at various sites around a house is as follows: entryway soil, 0.03 µg/g; walkway soil, 0.02 µg/g; and play area soil, 0.02 µg/g. It was also detected in house dust, 0.83 µg/g; child hand rinse, 0.02 µg; and air, 0.05 $\mu g/m^3$. No attempts were made by the authors to estimate the amounts of carpet dust or soil that the children who participated in the study may have ingested. The authors concluded that dust ingestion could constitute a substantial portion of a child's exposure to pesticides along with dermal absorption from house dust or yard soil.

Maternal transfer during gestation and/or via breast milk is also a potential source of exposure for children. No data were located on the presence of pentachlorophenol in breast milk in the United States. Pentachlorophenol levels have been measured in breast milk of women living in Europe or Asia. Small-scale studies (≤50 women) have reported median breast milk pentachlorophenol levels of 1.43 µg/kg in Upper Bavaria (Gebefugi and Korte 1983), 2.21 µg/kg in Bratislava, Slovakia (Veningerova et al. 1996), 0.020 µg/kg in Sweden (Guvenius et al. 2003), and 3.63 µg/kg in China (Hong et al. 2005).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Several populations with potentially high exposures have been identified; these include occupationally exposed groups, residents near pentachlorophenol manufacturing facilities, and families living in homes historically treated with pentachlorophenol.

Pentachlorophenol exposure in occupational settings can occur through inhalation of contaminated workplace air and dermal contact with the compound or with wood products treated with the compound. Populations with potentially high exposure include individuals involved in the manufacture and use of the compound. EPA (2008) indicated that high levels of exposure are not expected due to mixing/loading operations because treatment plants utilize automated methods for chemical preservative delivery (metered feed/pump) and closed application practices (retorts). There is, however, the potential for workers near the treatment cylinder door to inhale treatment solution mist when treatment has been completed. NCI (1986) suggested that dermal contact is the most important route of occupational exposure to pentachlorophenol because of the manner in which the compound is used (i.e., manual handling of solutions and treated materials) and its low vapor pressure. Workers such as carpenters, lumberyard workers, and loading-dock laborers who handle treated materials could be exposed continually via this route as well as by inhalation.

Pentachlorophenol levels in human tissues are much higher in occupationally exposed groups than in the general public. In an FDA study in Florida, Cranmer and Freal (1970) found an average pentachlorophenol urine level of 4.9 µg/L in the general population, compared with 119.9 µg/L in carpenters, boat builders, and spraymen. A range of 1,100–5,910 µg/L in the urine of Japanese pest control operators exposed to pentachlorophenol, compared with 10–50 µg/L in nonexposed workers was cited by Bevenue and Beckman (1967). A comparison of results from a study in Hawaii on pentachlorophenol in urine of three groups (occupational, nonoccupational, and a mixed population) was done by Bevenue et al. (1967). The pentachlorophenol level of 1,802 µg/L in the occupationally exposed population was almost 50 times higher than the nonoccupational group level of 40 µg/L.

In a study of workers exposed to pentachlorophenol in the wood-preserving industry, Arsenault (1976) reported pentachlorophenol levels of 120–9,680 µg/L in urine, with a mean concentration of 1,683 µg/L. In another study, Ferreira et al. (1997) compared the concentration of pentachlorophenol in the urine and blood of a group of workers occupationally exposed to pentachlorophenol at a wood-transformation unit to those of a control group with no known exposure to pentachlorophenol. The mean levels of pentachlorophenol in the occupationally exposed group were found to be 1,197 and 1,273 µg/L in urine and blood, respectively. The mean concentrations of pentachlorophenol in the control group were considerably lower at 6.4 and 15.3 µg/L in urine and blood, respectively. The urine samples of wood workers from a wood factory in northern Italy were monitored before work at 8 a.m. and after the work shift at 5 p.m. (Colosio et al. 1993a). The results indicated that a greater amount of pentachlorophenol was excreted in the morning (175 µg/L) than in the evening (106 µg/L). A subsequent study by Barbieri

et al. (1995) obtained similar results from which a half-life of about 10 days was estimated for pentachlorophenol excretion in urine. Mean pentachlorophenol blood serum levels in workers using pentachlorophenol or pentachlorophenol-treated materials were found to range from 83 to 57,600 µg/L by Cline et al. (1989). This upper limit is approximately 100 times the value expected from exposure to the threshold limit value (TLV) (Braun et al. 1979). Workers were involved in the construction of log homes, repair of telephone lines, custodial care of log cabin museums, and various operations in wood-preservative and chemical-packaging facilities. One worker from a chemical-packaging facility, with a whole blood pentachlorophenol level of 23,000 µg/L, died of pentachlorophenol poisoning (Cline et al. 1989). Bader et al. (2007) conducted a study in Germany and analyzed pentachlorophenol in post-shift urine samples of 189 painters and 148 bricklayers 1–4 years after the use of pentachlorophenol was banned. The results revealed a median pentachlorophenol urinary level of 2.4 µg/g creatinine in the painters, which was significantly higher than the median pentachlorophenol level of 1.8 µg/g creatinine detected in urine samples from the bricklayers. The range of pentachlorophenol detected in urine samples from the painters was <0.2–52 µg/g creatinine, while the range of pentachlorophenol detected in urinary samples from the bricklayers was <0.2–25 µg/g creatinine (Bader et al. 2007). Continued exposure of painters to residual pentachlorophenol from contaminated wood surfaces may have accounted for the elevated pentachlorophenol levels observed in the painters in comparison to the bricklayers in this study (Bader et al. 2007).

Residents near pentachlorophenol manufacturing plants and wastewater treatment sludge disposal sites may also be exposed to the chemical at higher concentrations than the general public. Residents around NPL sites known to have pentachlorophenol contamination may also be exposed to the chemical at higher levels in contaminated environmental media. An investigation of residents living near a wood treatment facility in Georgia found elevated urinary pentachlorophenol levels in women compared to the U.S. general population; 22% of the women had urinary pentachlorophenol levels that were above the 95th percentile group in the NHANES (Zarus and Rosales-Guevara 2012).

Pentachlorophenol is found as a residue in treated wood that had previously been preserved with this chemical. Examples of consumer items containing pentachlorophenol-treated wood have included boats, furniture, and log homes. In fact, some families living in homes historically treated with pentachlorophenol have been reported to have symptoms of chronic exposure (Jagels 1985). A mean pentachlorophenol blood serum level of 420 µg/L was reported for residents of log homes, whereas a mean level of 40 µg/L was reported for members of the general public with no known exposure to the compound. For residents of the log homes, pentachlorophenol serum levels of children were found to average 1.8 times

those of their parents. Pentachlorophenol urine concentrations for residents of log homes averaged 69 µg/L, whereas urine levels for the general population were found to be 3.4 µg/L. Inhalation was believed to be the most likely route of exposure to pentachlorophenol in log homes (Cline et al. 1989). In a separate study of 66 residents of log homes treated with pentachlorophenol in Kentucky, EPA (1986b) reported a geometric mean pentachlorophenol blood serum level of 47.6 µg/L and a geometric mean urine concentration of 21 µg/g urinary creatinine. Pentachlorophenol was detected in blood and urine of all 66 residents. Since the compound is no longer used in the treatment of wood products for log homes, outdoor furniture, or playground equipment, human exposure from these sources is probably limited to contact with materials treated in the past.

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 pentachlorophenol 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 pentachlorophenol.

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 INFORMATION ON HEALTH EFFECTS

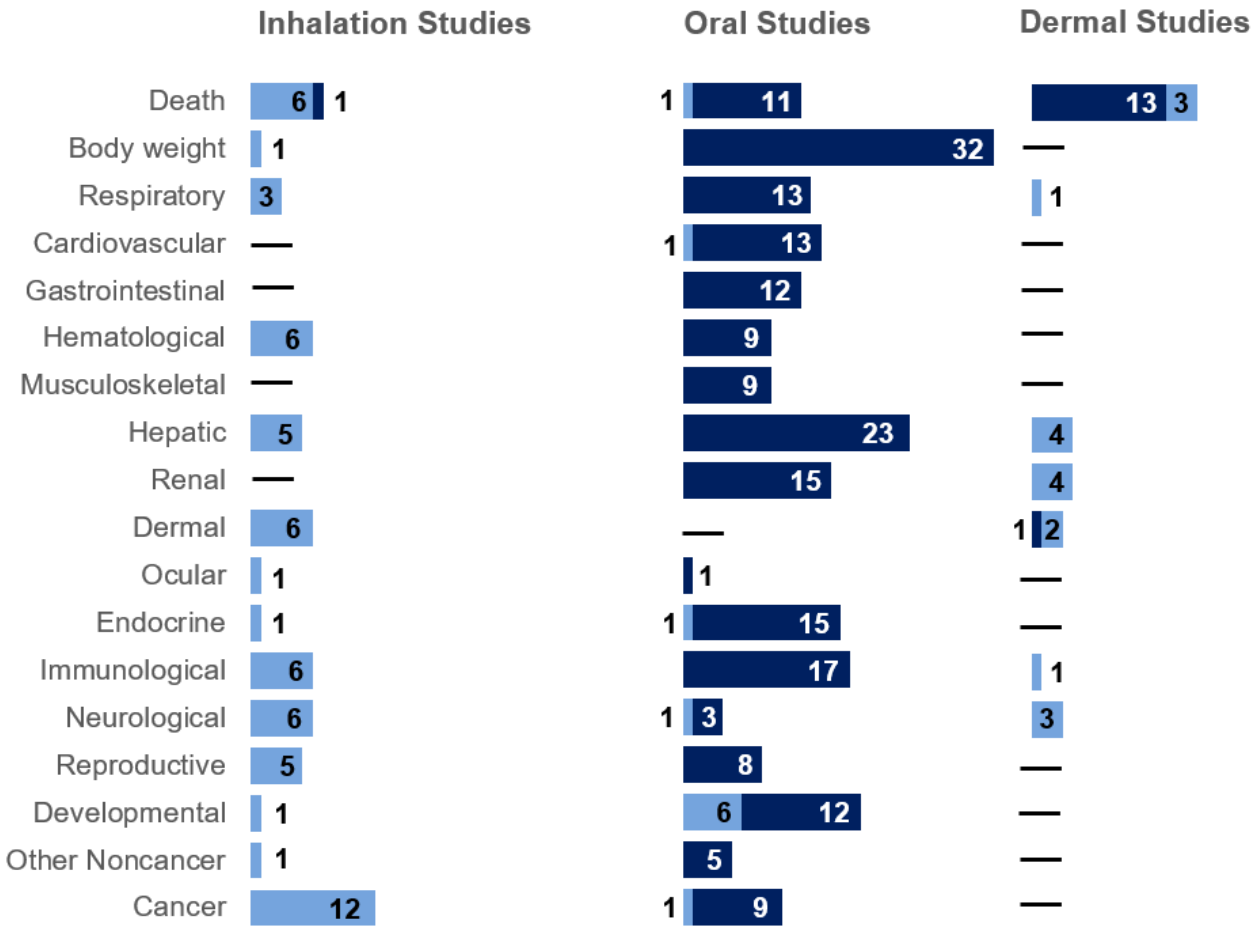
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to pentachlorophenol that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of pentachlorophenol. The number 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 Pentachlorophenol by Route and Endpoint*

Potential body weight, hepatic, and immunological effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



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

Acute-Duration MRLs. Information regarding health effects in humans following acute inhalation exposure are limited to case reports of individuals exposed to pentachlorophenol dust (Gray et al. 1985; Hassan et al. 1985; Rugman and Cosstick 1990). A number of effects have been reported, but the case reports provided limited exposure information. Studies in animals are limited to a lethality study in rats (Hoben et al. 1976b). The acute inhalation database was not considered adequate for MRL derivation. Inhalation studies evaluating a range of potential health effects, including sensitive targets identified in oral exposure studies (liver and developmental endpoints) and neurotoxicity, which was found in human inhalation case reports, would be useful for identifying the critical targets following inhalation exposure and establishing concentration-response relationships. Although a small number of studies have evaluated the acute oral toxicity of pentachlorophenol, the database was considered adequate to derive an acute-duration oral MRL. Additionally, studies evaluating a wide range of endpoints would support the identification of developmental toxicity as the most sensitive endpoint.

Intermediate-Duration MRLs. No intermediate-duration inhalation studies were identified for humans or laboratory animals. Studies evaluating a wide range of potential endpoints, including liver and developmental endpoints, which were sensitive targets following oral exposure, are needed to identify the most sensitive targets of toxicity and establish concentration-response relationships. A number of studies in laboratory animals have evaluated the oral toxicity of pentachlorophenol following intermediate-duration exposure. These studies identified hepatotoxicity and developmental toxicity as the sensitive endpoints. An intermediate-duration oral MRL was not derived because an MRL based on the available data would have been higher than the acute-duration oral MRL.

Chronic-Duration MRLs. A number of epidemiological studies have evaluated the chronic toxicity of inhaled pentachlorophenol. The studies identified a number of targets of toxicity including respiratory, hepatic, hematological, dermal, and developmental effects. These studies could not be used to derive a chronic-duration inhalation MRL because the studies provided limited, if any, exposure information and frequently involved co-exposure to other chemicals. No chronic-duration inhalation laboratory animal studies were identified. Oral exposure studies in laboratory animal studies examining a wide range of endpoints including endpoints identified in epidemiological studies are needed to identify the most sensitive targets of exposure and establish concentration-response relationships. The available studies in rats, mice, and dogs were considered adequate for identifying a sensitive target of toxicity (liver) and for deriving a chronic-duration oral MRL. The intermediate-duration oral studies provide suggestive evidence that contaminants found in technical-grade pentachlorophenol may influence the hepatoxic effects observed at low doses. The chronic MRL is based on a dog study utilizing technical-grade

pentachlorophenol. Additional studies that compare the hepatotoxicity of pure pentachlorophenol to technical-grade pentachlorophenol would add support to the MRL.

Health Effects.

Immunological. Immunological effects have been observed in epidemiological studies (Colosio et al. 1993b; Daniel et al. 1995;Gerhard et al. 1991; McConnachie and Zahalsky 1991) and in laboratory animals exposed to technical-grade pentachlorophenol (Holsapple et al. 1987; Kerkvliet et al. 1982, 1985a, 1985b; NTP 1989; White and Anderson 1985). Most studies of pure pentachlorophenol did not find immunological effects (Kerkvliet et al. 1982, 1985a; NTP 1989), suggesting that the immune effects were due to the contaminants rather than pentachlorophenol. However, two studies of pure pentachlorophenol did find immune alteration (Blakley et al. 1998; Chen et al. 2013a). Additional immune studies comparing the effects observed following exposure to pure pentachlorophenol and technical-grade pentachlorophenol would be valuable in determining whether pentachlorophenol is an immunotoxicant.

Neurological. Overt signs of neurotoxicity have been reported in individuals presumably exposed to high level of pentachlorophenol (Chapman and Robson 1965; Gray et al. 1985; Haley 1977; Smith et al. 1996; Walls et al. 1998). Increases in subjective symptoms of neurotoxicity (Peper et al. 1999; Walls et al. 1998), impaired performance on neurobehavioral tests (Peper et al. 1999), and alterations in nerve conduction velocity (Cheng et al. 1993) have also been reported in epidemiological studies. A 6-month mouse study reported altered performance on neurobehavioral tests (NTP 1989), but these alterations were only observed in animals exposed to technical-grade pentachlorophenol; no effects were observed in mice exposed to commercial-grade pentachlorophenol or pure pentachlorophenol. Further studies are needed to determine whether the observed neurological effects are due to pentachlorophenol or to a contaminant.

Reproductive. Several laboratory animal studies have reported reproductive effects in animals exposed to technical-grade pentachlorophenol (Bernard et al. 2002) or pentachlorophenol of unknown purity (Beard and Rawlings 1998; Beard et al. 1997, 1999a, 1999b; Rawlings et al. 1998). Studies evaluating potential effects on reproductive function in animals exposed to pure pentachlorophenol and technical-grade pentachlorophenol are needed to evaluate whether observed effects are due to pentachlorophenol or contaminants.

Developmental. Developmental effects have been reported in several laboratory animal studies; these effects include increases in mortality, malformations/variations, and decreased growth. One study reported impaired development of the reproductive system (Bernard et al. 2002). Additional studies are needed to further evaluate possible effects on the reproductive system and to evaluate other possible functional impairments, such as impaired development of the nervous system or immune system.

Epidemiology and Human Dosimetry Studies. A number of studies have reported adverse health effects in humans following short- or long-term exposure to pentachlorophenol. The short-term data come from case reports involving home use of pentachlorophenol-containing products such as wood preservative or herbicides in the garden or a series of reports of newborn infants exposed to pentachlorophenol from diapers and linens treated with an antimildew agent. Long-term toxicity information comes from families living in log homes that were treated with pentachlorophenol and occupational exposure in agricultural and wood-treatment industries. Interpretation of these studies is limited by the lack of reliable information on exposure concentrations, exposure route, duration of exposure, possible concomitant exposure to other chemicals, and impurities present in technical-grade pentachlorophenol. Additional epidemiological studies that provide sufficient information for exposure characterization and examine a number of endpoints would be useful for establishing sensitive targets of toxicity in humans and dose-response relationship data.

Biomarkers of Exposure and Effect. Pentachlorophenol is primarily excreted in the urine as pentachlorophenol conjugates. Thus, measurement of pentachlorophenol in the urine is a useful biomarker of exposure. However, data that establish a quantitative relationship between levels in the urine and exposure levels are not available. Pentachlorophenol is also excreted in the urine as TCHQ and TCHQ conjugates. TCHQ level has potential use as an indicator of exposure to pentachlorophenol, although this biomarker is not specific for pentachlorophenol. Additional studies are needed to establish a relationship between exposure level and urinary concentration of TCHQ.

No pentachlorophenol-specific biomarkers of effect have been identified for pentachlorophenol. Development of sensitive biomarkers that are specific for pentachlorophenol effects would be useful in monitoring populations at high risk.

Absorption, Distribution, Metabolism, and Excretion. The absorption, distribution, metabolism, and excretion of pentachlorophenol have been investigated in humans and animals.

Estimates of absorption efficiency are available for short-term inhalation, oral, and dermal exposure. The distribution of pentachlorophenol following inhalation, oral, or dermal exposure has been characterized in acute-duration studies in animals. Long-term studies examining distribution would be useful to determine if there are any duration-related differences in distribution. The available data are adequate for developing metabolic pathways for pentachlorophenol. There are conflicting data on urinary metabolites in humans, with some studies reporting that pentachlorophenol is primarily excreted unchanged and other studies reporting that it is primarily excreted as pentachlorophenol conjugates. It appears that these differences may be due to the treatment of the urine, which could result in the hydrolysis of pentachlorophenol conjugates to pentachlorophenol. Studies are needed to verify the primary urinary metabolites. The elimination half-life has been estimated for several species; however, some studies based the elimination half-life estimates by only monitoring urinary excretion. Since approximately 10% of pentachlorophenol is excreted in the feces, these studies may underestimate the half-life. Two animal studies (Braun and Sauerhoff 1976; Braun et al. 1977) found an apparent difference in elimination kinetics between males and females. Additional studies examining potential sex-related differences would be useful.

Comparative Toxicokinetics. A series of studies conducted by Braun and associates (Braun and Sauerhoff 1976; Braun et al. 1977, 1979) suggest that there are toxicokinetic differences between humans, monkeys, and rats. The results of these studies suggest that the excretion of pentachlorophenol follows a linear, one-compartment model in humans and monkeys. In contrast, excretion in the rats was biphasic (two-compartment model). However, other pharmacological properties, such as maximum plasma concentration, absorption rate constant, volume of distribution, steady-state concentration, and the excretion of glucuronide conjugates, were similar for humans and rats, but not for humans and monkeys. These data suggest that the rat may be a better model for humans than the monkey. Additional studies are needed to further evaluate species differences in the toxicokinetic properties of pentachlorophenol and to identify the most appropriate model for humans.

Children's Susceptibility. Adverse effects on the nervous system, liver, kidneys, and respiratory system, and some deaths were associated with exposure of newborn children to pentachlorophenol in diapers and bedding, and suppression of the immune system was seen in older children exposed to pentachlorophenol. Oral exposure studies in animals provide evidence that pentachlorophenol is a developmental toxicant. Gestational exposure to pentachlorophenol has resulted in decreased fetal and neonatal survival, decreased fetal and neonatal body weight, and skeletal anomalies. The available data provide strong support that these effects are due to pentachlorophenol toxicity rather than due to

contaminant exposure. Laboratory animal studies examining potential differences in the toxicity of pentachlorophenol between juveniles and adult animals were not identified; these types of studies would provide valuable information on potential age-related differences.

Physical and Chemical Properties. The physical/chemical properties of pentachlorophenol are well characterized and allow the prediction of the environmental fate of the compound (see Chapter 4). Estimates of the distribution of pentachlorophenol in the environment based on available constants (e.g., water solubility, log K_{ow}, log K_{oc}, vapor pressure) are generally in good agreement with experimentally determined values. No additional studies are required at this time.

Production, Import/Export, Use, Release, and Disposal. Pentachlorophenol is currently being produced by two manufacturers (NPIRS 2019). Production volume and export data are available for 2011 from the Chemical data Reporting database (EPA 2014, 2017). In the past, pentachlorophenol was one of the most heavily used pesticides in the United States, but it is now regulated as a restricted use pesticide (EPA 1984a). The compound is found in all environmental media (air, soil, and water) as a result of its past widespread use. Disposal of pentachlorophenol is subject to EPA restrictions (EPA 1991, 1992).

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The TRI, which contains this information for 2018, became available in 2019. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Information on environmental fate of pentachlorophenol is sufficient to permit a general idea of transport and transformation of the chemical in the environment. Additional data are needed on the mechanisms of degradation in the atmosphere and water; plant uptake and transformation; and extent of bioaccumulation.

Bioavailability from Environmental Media. Pentachlorophenol is readily and completely absorbed following inhalation (Casarett et al. 1969; Cline et al. 1989; EPA 1986b; Jones et al. 1986), oral (Braun et al. 1979; Uhl et al. 1986), and dermal exposure (EPA 1986b; Qiao et al. 1997; Wester et al. 1993). Using Rhesus monkeys, Wester et al. (1993) demonstrated the dermal absorption from pentachlorophenol-treated soil. It was also shown that when [^{14}C-UL]-pentachlorophenol in a soil-based mixture was applied occlusively or nonocclusively to a clipped 7.5-cm^2 abdominal site of 8- to 10-week-old female pigs, total radiolabel absorption was 29.08% under nonocclusive conditions and 100.72% under occlusive

conditions 408 hours after dosing (Qiao et al. 1997). Additional information on the bioavailability of pentachlorophenol adsorbed to soils would be helpful in assessing the relative importance of ingestion of contaminated soils as a potential route of human exposure. Additional information is also be useful on the desorption of the compound from soils when the soil pH is altered or when pentachlorophenol-contaminated soil comes into contact with cosolvents (such as alcohols or petroleum compounds), which may enhance desorption and/or increase the solubility of pentachlorophenol. Cline et al. (1989) detected elevated levels of pentachlorophenol in the urine of log-home residents. The study authors believed inhalation to be the most likely route of exposure. Additional information would help to correlate the presence of pentachlorophenol in contaminated air and the exposure via inhalation.

Food Chain Bioaccumulation. A data need exists for controlled bioconcentration experiments in fish as a function of pH of the water. The log K_{ow} of pentachlorophenol presented in Chapter 4 is 5.01, suggesting that pentachlorophenol is likely to bioaccumulate. However, the extent of bioaccumulation will depend on the pH of the medium since pentachlorophenol converts at higher pH levels to the more water-soluble pentachlorophenate anion. Pentachlorophenol is bioconcentrated by terrestrial and aquatic organisms (EPA 1986a; Makela et al. 1991; Smith et al. 1990). However, biomagnification of the compound in terrestrial and aquatic food chains has not been demonstrated as a result of the fairly rapid metabolism of the compound by exposed organisms (Niimi and Cho 1983).

Exposure Levels in Environmental Media. Pentachlorophenol has been detected in ambient air, surface water, drinking water, soils, and foods. Estimates of dietary intake of the compound have been made by the World Health Organization (WHO 1987), EPA (1978), and FDA (1989; Gunderson 1988). In a comparison of the 1986–1991 study to the 1982–1984 study, Gunderson (1995) observed a substantial reduction in the amount of pentachlorophenol in the estimated mean daily intake. Lewis et al. (1994) detected low levels of pentachlorophenol in air, dust, and soil in a nine-home (year of construction ranged from 1930 to 1989) pilot study to monitor the potential exposure of small children to pesticides in the residential environment. Further monitoring is would be useful for evaluating the risk of exposure from pentachlorophenol-treated wood in homes. Limited information is available regarding the levels of pentachlorophenol in air in the United States. More ambient monitoring data of air is required to estimate the exposure of the general population via inhalation of pentachlorophenol in the 1990s.

Contemporary monitoring studies demonstrating the presence or absence of pentachlorophenol in various sources of surface and drinking water are also needed.

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

Exposure Levels in Humans. Pentachlorophenol has been measured in blood (NHANES III) (Ferreira et al. 1997), urine (Barbieri et al. 1995; Bevenue et al. 1967; CDC 2009, 2019; Colosio et al. 1993a; Ferreira et al. 1997; Hill et al. 1989, 1995; Thompson and Treble 1994, 1996; Treble and Thompson 1996), cerebrospinal fluid (Jorens et al. 1991), and tissues of humans (Bevenue et al. 1967). Quantitative data that correlate varying levels in the environment with levels in body fluids and health effects are not available. One study exists for residents of log homes treated with pentachlorophenol; levels in blood and urine were highly correlated with levels in indoor air (Lewis et al. 1994). Additional information on exposure levels for populations living near hazardous waste sites would be helpful. Information regarding the exposure levels for populations near pentachlorophenol-treated utility poles would be useful. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. No monitoring studies have been performed to investigate the exposure to and the body burden of pentachlorophenol in children. No studies are available on the dermal absorption of pentachlorophenol in infants and toddlers due to activities such as crawling, which results in contact with the floor (carpet) and soil. Since pentachlorophenol is likely to be adsorbed to these materials, more information would allow the estimation of a child's exposure to pentachlorophenol to be more rigorously determined. A pilot study measured the amounts of pentachlorophenol in dust and soils that are found in areas where children may play, such as carpets and playgrounds (Lewis et al. 1994). As part of the FDA total diet study, mean daily intake of pentachlorophenol by 6- to 11-month-old infants, 2-year-old children, and 14- to 16-year-old males and females were determined (Gunderson 1995). Studies dealing with the weight-adjusted intake of pentachlorophenol by children would help in assessing the effects of pentachlorophenol in children. No studies are available on the amounts of pentachlorophenol present in the breast milk of women in the United States. The estimation of the amounts of pentachlorophenol in soil and house dust that are ingested by children needs to be determined. No information is available on the exposure of children to pentachlorophenol from the parent's body, work clothes, and other objects from work. Studies are required to identify childhood-specific means of decreasing exposure to pentachlorophenol.

6.3 ONGOING STUDIES

An ongoing study that was identified in the National Institutes of Health (NIH) RePORTER (2021) is summarized in Table 6-1.

Table 6-1. Ongoing Studies on Pentachlorophenol

Investigator	Affiliation	Research description	Sponsor
Antioine Snijders	University of California, Lawrence Berkeley Lab	Role of the gut microbiome in pesticide-induced effects on child neurodevelopment	NIEHS

NIEHS = National Institute of Environmental Health Sciences

Source: NIH RePORTER (2021)

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding pentachlorophenol 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 pentachlorophenol.

Table 7-1. Regulations and Guidelines Applicable to Pentachlorophenol

Agency	Description	Information	Reference
		Air	
EPA	Hazardous Air Pollutant	Listed	EPA 2020
EPA	RfC	Not derived	IRIS 2010
WHO	Air quality guidelines	Not listed	WHO 2010
		Water & Food	
EPA	Drinking water standards and health advisories		EPA 2018a
	1-Day health advisory (10-kg child)	1 mg/L	
	10-Day health advisory (10-kg child)	0.3 mg/L	
	DWEL	0.2 mg/L	
	Lifetime health advisory	0.04 mg/L	
	10^{-4} Cancer risk	0.009 mg/L	
	National primary drinking water regulations		EPA 2009
	MCL	0.001 mg/L	
	PHG	0 mg/L	
	RfD	0.005 mg/kg/day	IRIS 2010
WHO	Drinking water quality guidelines		WHO 2017
	Provisional guideline value	0.009 mg/L[a,b]	
FDA	Substances Added to Food	No data[c]	FDA 2021a
	Allowable level in bottled water	0.001 mg/L	FDA 2021b
	Indirect additives used in food contact substances		
	Pentachlorophenol	Permitted under adhesives regulation and wood preservatives regulation with limitation	FDA 2021c
	Sodium pentachlorophenate	Permitted under multiple indirect additives regulations, some with limitation	FDA 2021d

Table 7-1. Regulations and Guidelines Applicable to Pentachlorophenol

Agency	Description	Information	Reference
		Cancer	
HHS	Carcinogenicity classification		NTP 2016
	Pentachlorophenol and byproducts of its synthesis	Reasonably anticipated to be a human carcinogen	
EPA	Carcinogenicity classification	Likely to be carcinogenic to humans	IRIS 2010
	Oral slope factor	4×10^{-1} per mg/kg/day	
IARC	Carcinogenicity classification	Group 1[d]	IARC 2019
		Occupational	
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction	0.5 mg/m^3 [e]	OSHA 2021a, 2021b, 2021c
NIOSH	REL (up to 10-hour TWA)	0.5 mg/m^3 [e]	NIOSH 2019
	IDLH	0.25 mg/m^3	NIOSH 1994
		Emergency Criteria	
EPA	AEGLs-air	No data	EPA 2018b
DOE	PACs-air		DOE 2018a
	Pentachlorophenol		
	PAC-1[f]	1 mg/m^3	
	PAC-2[f]	15 mg/m^3	
	PAC-3[f]	150 mg/m^3	
	Sodium pentachlorophenate		
	PAC-1[f]	0.22 mg/m^3	
	PAC-2[f]	2.4 mg/m^3	
	PAC-3[f]	8.4 mg/m^3	

[a]Concentration in drinking-water associated with an upperbound excess lifetime cancer risk of 10^{-5} (one additional case of cancer per 100,000 of the population ingesting drinking water containing the substance at the guideline value for 70 years).
[b]Value is considered provisional because of variations in metabolism between experimental animals and humans.
[c]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."
[d]Group 1: carcinogenic to humans.
[e]Skin designation.
[f]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

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; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; LOAEL = lowest observed adverse effect level; MCL = maximum contaminant level; 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; PHG = public health goal; 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. Serious health effects (such as irreparable damage to the liver or kidneys, or 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 substance 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.

APPENDIX A

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 S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Pentachlorophenol
CAS Numbers: 87-86-5
Date: April 2022
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: An acute-duration inhalation MRL was not derived for pentachlorophenol because the acute inhalation database is limited to case reports and a lethality study in rats.

Rationale for Not Deriving an MRL: There are several reports of adverse health outcomes in individuals acutely exposed to pentachlorophenol dust (Gray et al. 1985; Hassan et al. 1985; Rugman and Cosstick 1990). Reported health effects included death, signs of central nervous system toxicity and cerebral edema, intravascular hemolysis, and aplastic anemia. The reports do not include exposure information and therefore, were not considered an adequate basis for an MRL. A lethality study in rats (Hoben et al. 1976b) did not evaluate other potential targets of toxicity; the LC_{50} was 14 mg/m^3.

Agency Contacts (Chemical Managers): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Pentachlorophenol
CAS Numbers: 87-86-5
Date: April 2022
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: An intermediate-duration inhalation MRL was not derived for pentachlorophenol because no human or laboratory animal studies were identified.

Rationale for Not Deriving an MRL: No intermediate-duration inhalation studies in humans or laboratory animals were identified.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Pentachlorophenol
CAS Numbers: 87-86-5
Date: April 2022
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: A chronic-duration inhalation MRL was not derived for pentachlorophenol because the chronic inhalation database is limited to epidemiological studies that provided limited, in any, exposure information and involved exposure to several other compounds.

Rationale for Not Deriving an MRL: A number of cohort studies (Baader and Bauer 1951; Cheng et al. 1993; Colosio et al. 1993b; Hryhorczuk et al. 1998; Klemmer et al. 1980; Ramlow et al. 1996; Ruder and Yiin 2011; Sehgal and Ghorpade 1983; Triebig et al. 1987; Walls et al. 1998), case-control studies (Dimich-Ward et al. 1996; Hardell and Eriksson 1999; Hardell et al. 1994, 1995; Kogevinas et al. 1995; Seidler et al. 1996), or cross-sectional studies (Daniel et al. 1995; EPA 1986b; Gerhard et al. 1991; McConnachie and Zahalsky 1991; Peper et al. 1999) and case reports (Gordon 1956; Lambert et al. 1986; Roberts 1963, 1981, 1983, 1990) have evaluated the chronic toxicity of inhaled pentachlorophenol among workers at manufacturing facilities, pesticide applicators, sawmill workers, people living in log homes, and the general population. These studies provided limited, if any, information on exposure levels. Although several adverse health effects have been reported (respiratory, hepatic, hematological, dermal, and developmental effects), it is difficult to determine if these effects are due to exposure to pentachlorophenol, pentachlorophenol contaminants, or other chemicals. None of the studies were considered adequate for MRL derivation. No chronic-duration inhalation studies in laboratory animals were identified.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Pentachlorophenol
CAS Numbers: 87-86-5
Date: April 2022
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.005 mg/kg/day (5 µg/kg/day)
Critical Effect: Increased incidence of delayed skull ossification (Developmental)
Reference: Schwetz et al. 1974
Point of Departure: 5 mg/kg/day
Uncertainty Factor: 1,000
LSE Graph Key: 4
Species: Rat

MRL Summary: An acute-duration oral MRL of 0.005 mg/kg/day (5 µg/kg/day) was derived for pentachlorophenol. The MRL is based on a LOAEL of 5 mg/kg/day for delayed skull ossification in the fetuses of rats administered via gavage pure pentachlorophenol on GDs 6–15 (Schwetz et al. 1974) and an uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: A small number of studies have evaluated the acute oral toxicity of pentachlorophenol; the focus of most of the studies was lethality or developmental toxicity. LD_{50} values of 50–230 mg/kg have been reported in rats and mice (Borzelleca et al. 1985; Deichmann et al. 1942; Renner et al. 1986; St. Omer and Gadusek 1987). At nonlethal doses, decreases in maternal body weight gain, developmental effects (resorptions, decreases in fetal body weight, and soft tissue and skeletal anomalies), and liver effects (increases in liver weight and hepatocellular swelling) have been reported in experimental animals. A summary of the NOAEL and LOAEL values for these effects is presented in Table A-1.

In addition to the body weight, developmental, and liver effects, several studies have reported immunological effects, in particular a decreased response to sheep red blood cells (sRBC) (Holsapple et al. 1987; Kerkvliet et al. 1985a) or inhibition of complement activity (White and Anderson 1985), in mice exposed to technical-grade pentachlorophenol. These effects were not observed in mice similarly exposed to pure pentachlorophenol, suggesting that the effects were likely due to contaminants rather than pentachlorophenol. It is noted that one study did find an immune response (decreases in OVA-specific antibodies) in mice exposed to 6 mg/kg/day pure pentachlorophenol administered 3 times/week for 7 or 14 days (Chen et al. 2013a). Given that the other immunotoxicity studies testing pure pentachlorophenol or commercial-grade pentachlorophenol (Holsapple et al. 1987; Kerkvliet et al. 1985a; NTP 1989) did not find adverse effects at doses as high as 100 mg/kg/day, additional studies are needed to evaluate whether immunotoxicity is a sensitive target of pure pentachlorophenol.

The available data suggest that developmental toxicity is the most sensitive target following acute-duration oral exposure to pentachlorophenol. Skeletal and soft tissue anomalies occurred at doses that did not result in maternal toxicity. More severe developmental effects, including ≥97% fetal resorption, occurred at doses associated with a marked decrease in maternal body weight gain (74% decrease) (Schwetz et al. 1974). The LOAEL values for the maternal and developmental effects in rats exposed to pure pentachlorophenol and technical-grade pentachlorophenol are similar, suggesting that these effects are due to pentachlorophenol exposure rather than a contaminant.

Table A-1. Summary of NOAELs and LOAELs Following Acute-Duration Oral Exposure to Pentachlorophenol

Species, duration, (route)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference	Purity
Rat GDs 6–15 (GO)		5	Delayed ossification of skull at 5 mg/kg/day	Schwetz et al. 1974	Pure (>98%)
			Increased incidence of subcutaneous edema and skeletal anomalies at ≥15 mg/kg/day		
	15	30 (SLOAEL)	Increased incidence of fetal resorptions (97% of fetuses resorbed) and marked decrease in fetal body weights and decreased maternal body weight (74%) on GDs 6–21		
Rat GDs 8–11 (GO)		30 (SLOAEL)	Increased resorptions, increased incidence of skeletal and soft tissue anomalies; 42% decrease in fetal body weight	Schwetz et al. 1974	Pure (>98%)
		30 (SLOAEL)	Decreased maternal body weight (67%) on GDs 6–21		
Rat GDs 12–15 (GO)		30	Increased incidence of soft tissue and skeletal anomalies and decreased fetal body weight and crown-rump length	Schwetz et al. 1974	Pure (>98%)
Mouse 2 weeks (F)		41	Increased liver weight and severe hepatocellular swelling	Umemura et al. 1996	Pure (98.6%)
Rat 2 weeks (GW)		20	Increased serum ALT and AST, hepatocellular necrosis, binucleated and pyknotic hepatocytes, and dilation and congestion of the centrilobular vein and sinusoids	Bekhouche et al. 2019	Methodological grade (purity not specified)
Rat GDs 6–15 (GO)	5	15	Increased resorptions and increased incidence of subcutaneous edema and lumbar spurs	Schwetz et al. 1974	Technical grade (88.4%)
	15	30	Decreased maternal body weight (25%)		
Rat GDs 8–11 (GO)		30 (SLOAEL)	Increased resorptions, increased incidence of skeletal and soft tissue anomalies; 25% decrease in fetal body weight	Schwetz et al. 1974	Technical grade (88.4%)
		30	Decreased maternal body weight (27%)		
Rat GDs 12–15 (GO)		30	Increased incidence of sternebrae variations	Schwetz et al. 1974	Technical grade (88.4%)

Table A-1. Summary of NOAELs and LOAELs Following Acute-Duration Oral Exposure to Pentachlorophenol

Species, duration, (route)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference	Purity
Rat GDs 6–15 (GO)	30	80	Increased resorptions, decreased fetal body weight, increased incidence of soft tissue and skeletal anomalies	Bernard and Hoberman 2001	Technical grade (89%)
	30	80	Decreased maternal body weight (21% lower than controls on GDs 6–16)		
Rabbit GDs 6–18 (GO)	30		No developmental effects	Bernard et al. 2001	Technical grade (88–89%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; (F) = feed; (GO) = gavage in oil; GD = gestation day; (GW) = gavage in water; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; SLOAEL = serious lowest-observed-adverse-effect level

Selection of the Principal Study: A series of developmental toxicity studies conducted by Schwetz et al. (1974) evaluated the developmental toxicity of pure pentachlorophenol and technical-grade pentachlorophenol in rats exposed on GDs 6–15, 8–11, and 12–15. Bernard and Hoberman (2001) and Bernard et al. (2001) also evaluated the developmental toxicity of technical-grade pentachlorophenol in rats and rabbits, respectively. The Schwetz et al. (1974) study of pure pentachlorophenol administered on GDs 6–15 identified the lowest LOAEL of 5 mg/kg/day; see Table A-1 for a list of the LOAELs from the other developmental studies. This study was selected as the principal study.

Summary of the Principal Study:

Schwetz BA, Keeler PA, Gehring PJ. 1974. The effect of purified and commercial-grade pentachlorophenol on rat embryonal and fetal development. Toxicol Appl Pharmacol 28:151-161.

Groups of 15–20 pregnant Sprague Dawley rats were administered 5, 15, 30, or 50 mg/kg/day pure pentachlorophenol (>98 % purity) in corn oil on GDs 6–15; a vehicle-only control group of 33 rats was similarly exposed. A dose-related decrease in maternal body weight gain was observed at 30 and 50 mg/kg/day. Weight gain on GDs 6–21 was 74% less in both affected groups, as compared to controls. No other signs of maternal toxicity were observed. A significant increase ($p<0.05$) in the incidence of fetal resorptions was observed at 30 and 50 mg/kg/day; 97 and 100% of the fetuses were resorbed, respectively. The sex ratio (male:female) of surviving offspring was markedly altered from normal in the 30 mg/kg/day dose groups, with majority of the survivors being male offspring (83:17 versus 50:50 in controls); however, this is based on a very small number of surviving fetuses. Decreases in fetal body weight and crown-rump length were observed at 30 mg/kg/day. A significant increase in delayed ossification of the skull was observed at 5 mg/kg/day. At 15 mg/kg/day, significant increases in the incidences of soft tissue (subcutaneous edema) and skeletal anomalies were observed; the skeletal anomalies occurred in the skull (delayed ossification), ribs (supernumerary, lumbar or fused), lumbar spurs, sternebrae (supernumerary, abnormal shape, delayed ossification, missing or unfused centers of ossification), and vertebrae (supernumerary, delayed or unfused centers of ossification, fused or staggered). At 30 mg/kg/day, anomalies in the ribs, vertebrae, and sternebrae were also observed in the surviving fetuses.

Selection of the Point of Departure for the MRL: The LOAEL of 5 mg/kg/day was selected at the point of departure (POD).

Benchmark dose (BMD) modeling was conducted to identify a potential POD using the incidence data for litters with fetus having delayed ossification of the skull; the incidences (number of affected litter/total litters) were 6/33, 9/15, and 13/18 in the 0, 5, and 15 mg/kg/day groups, respectively; the data for the 30 mg/kg/day group was not modeled (0/12) due to the small number of surviving fetuses (n=6 fetuses). The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 3.1.2) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). None of the models provided adequate fit. Thus, a NOAEL/LOAEL approach was used to identify the POD for the MRL.

Uncertainty Factor:

- 10 for extrapolation from a LOAEL to a NOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = LOAEL ÷ UF
= 5 mg/kg/day ÷ (10 x10 x10) = 0.005 mg/kg/day (5 µg/kg/day)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Skeletal anomalies have also been reported in the offspring of rats exposed to ≥15 mg/kg/day technical-grade pentachlorophenol (Schwetz et al. 1974) and 80 mg/kg/day technical-grade pentachlorophenol (Bernard and Hoberman 2001). Intermediate-duration oral developmental toxicity studies in rats have also reported increased fetal/neonatal mortality, malformations, and/or variations, and decreased growth (Bernard et al. 2002; Exon and Koller 1982; Schwetz et al. 1978; Welsh et al. 1987).

Agency Contacts (Chemical Managers): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Pentachlorophenol
CAS Numbers: 87-86-5
Date: April 2022
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: An intermediate-duration oral MRL was not derived because an MRL based on the available intermediate-duration oral studies would result in an MRL that is higher than the acute-duration oral MRL.

Rationale for Not Deriving an MRL: The available intermediate-duration oral database supports identifying the liver and developing organisms as sensitive targets of toxicity. The NOAEL and LOAEL values for these endpoints are summarized in Table A-2. The liver effects include hepatocellular hypertrophy, hepatocellular degeneration, and necrosis. The developmental effects were primarily decreases in body weight, decreases in litter size, and decreases in neonatal survival. In addition to these effects, some studies have reported reproductive effects (decreases in testicular spermatid counts; Bernard et al. 2002), hematological alterations (decreases in hemoglobin and RBC levels; Knudsen et al. 1974), and alterations in immune function (Blakley et al. 1998; Kerkvliet et al. 1982, 1985a, 1985b; NTP 1989). The reproductive and hematological effects have only been observed in one study, and other studies have reported higher NOAEL values (see Table A-2 for a summary of the NOAEL and LOAEL values). The immunological effects appear to be related exposure to the contaminants in the technical-grade pentachlorophenol and have not been observed in animals exposed to pure pentachlorophenol.

The lowest LOAEL values for liver effects for the three formulation categories are 36 mg/kg/day (hepatocellular hypertrophy) observed in rats exposed to pure pentachlorophenol for 8 months (Kimbrough and Linder 1978), 50 mg/kg/day (hepatocytomegaly) in mice exposed to commercial-grade pentachlorophenol (EC-7 and DP-2) for 6 months (NTP 1989), and 1 mg/kg/day (centrilobular hepatocellular hypertrophy) in rats exposed to technical-grade pentachlorophenol for 8 months (Kimbrough and Linder 1978).

Comparison of the NOAEL and LOAEL values for hepatic effects for the 3 formulation categories identifies differences in relative hepatotoxicity. For pure pentachlorophenol, the lowest LOAEL was 36 mg/kg/day for hepatocellular hypertrophy in rats exposed for 8 months (Kimbrough and Linder 1978); the NOAEL was 6 mg/kg/day. At 67 mg/kg/day, necrosis was observed in female mice exposed for 6 months (NTP 1989). For commercial-grade pentachlorophenol, the lowest dose tested (50 mg/kg/day) resulted in necrosis in male mice exposed to EC-7 or DP-2 for 6 months (NTP 1989). The lowest LOAEL for technical-grade pentachlorophenol was 1 mg/kg/day for centrilobular hepatocellular hypertrophy in rats exposed for 8 months (Kimbrough and Linder 1978). These relative differences are highlighted in the Kimbrough and Linder (1978) study, which tested the same doses of pure and technical-grade pentachlorophenol. In rats exposed to pure pentachlorophenol, no hepatic alterations were observed at 1 or 6 mg/kg/day; at 36 mg/kg/day, centrilobular hepatocellular hypertrophy was observed. In contrast, exposure to technical-grade pentachlorophenol resulted in centrilobular hepatocellular hypertrophy at 1 mg/kg/day and marked vacuolization and periportal fibrosis at 7 and 32 mg/kg/day. Kimbrough and Linder (1978) suggested that the contaminants in the technical-grade pentachlorophenol may have been the causative agent for the low dose effects observed following intermediate-duration exposure.

Table A-2. Summary of NOAELs and LOAELs Following Intermediate-Duration Oral Exposure to Pentachlorophenol

Species, duration, (route)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference	Purity
Hepatic					
Rat 8 months (F)	6	36	Centrilobular hepatocellular hypertrophy	Kimbrough and Linder 1978	Pure (>99%)
Rat 28 days (F)	20	40	Increased liver weight, hepatocellular degeneration	NTP 1999	Pure (99%)
Mouse 4 weeks (F)		41	Increased liver weight and severe hepatocyte swelling	Umemura et al. 1996	Pure (98.6%)
Mouse 6 months (F)		67	Hepatocytomegaly, pigmentation, nuclear alterations, necrosis in males at ≥110 mg/kg/day and females at ≥67 mg/kg/day	NTP 1989	Pure (98.6%)
Mouse 10-12 weeks (F)		90	Necrosis	Kerkvliet et al. 1982	Pure (>99%)
Mouse 6 months (F)		50	Hepatocytomegaly, pigmentation, nuclear alterations, necrosis in males at 50 mg/kg/day and females at 70 mg/kg/day	NTP 1989	EC-7 (90.4%)
Mouse 6 months (F)		50	Hepatocytomegaly, pigmentation, nuclear alterations, necrosis in males at 50 mg/kg/day and females at 70 mg/kg/day	NTP 1989	DP-2 (91.6%)
Rat 8 months (F)		1	Centrilobular hepatocellular hypertrophy	Kimbrough and Linder 1978	Technical grade (85%)
Rat 12 weeks (F)	1.5	3	Centrilobular vacuolization	Knudsen et al. 1974	Technical grade (purity not reported)
Rat 112 days (GO)		10	Increased liver weight and hepatocellular hypertrophy	Bernard et al. 2002	Technical grade (89%)
Mouse 6 months (F)		50	Hepatocytomegaly, pigmentation, nuclear alterations, necrosis in males at 50 mg/kg/day and females at 64 mg/kg/day	NTP 1989	Technical grade (90.4%)
Mouse 10–12 weeks (F)		90	Necrosis	Kerkvliet et al. 1982	Technical grade (86%)

Table A-2. Summary of NOAELs and LOAELs Following Intermediate-Duration Oral Exposure to Pentachlorophenol

Species, duration, (route)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference	Purity
Developmental Effects					
Rat 181 days premating, mating, through GD 20 (F)	4	13	Decreased fetal body weight and crown-rump length, increased skeletal variations, increased resorptions; fetal lethality at 43 mg/kg/day	Welsh et al. 1987	Pure (>99%)
Rat 62 days premating, gestation, lactation (F)	3	30	Decreased litter size and neonatal survival, decreased body weight and growth	Schwetz et al. 1978	EC-7 (90.4%)
Rat 70 days premating, gestation, lactation (GO)		10	Decreased pup body weight on LD 1 and 4 in F1 pups	Bernard et al. 2002	Technical grade (89%)
Rat 70 days premating, gestation, lactation (F)		50	Decreased litter size	Exon and Koller 1982	Technical grade (85%)
Hematological					
Mouse 6 months (F)	380			NTP 1989	Pure (98.6%)
Mouse 6 months (F)	330			NTP 1989	EC-7 (90.4%)
Mouse 6 months (F)	380			NTP 1989	DP-2 (91.6%)
Rat 12 weeks (F)	1.5	3	Decreases in hemoglobin and RBC levels in males	Knudsen et al. 1974	Technical grade (purity not reported)
Rat 70 days premating, gestation, lactation (F)	50			Exon and Koller 1982	Technical grade (85%)
Mouse 6 months (F)	550			NTP 1989	Technical grade (90.4%)
Reproductive Effects					
Rat 8 months (F)	32M			Kimbrough and Linder 1978	Pure (>99%)
Mouse 6 months (F)	380			NTP 1989	Pure (98.6%)

Table A-2. Summary of NOAELs and LOAELs Following Intermediate-Duration Oral Exposure to Pentachlorophenol

Species, duration, (route)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference	Purity
Mouse 6 months (F)	330			NTP 1989	EC-7 (90.4%)
Mouse 6 months (F)	380			NTP 1989	DP-2 (91.6%)
Rat 70 days premating, gestation, lactation (GO)	60F 10M	10 30M	Decreased average testicular spermatid counts in F1 males; decreased fertility at 60 mg/kg/day	Bernard et al. 2002	Technical grade (89%)
Rat 8 months (F)	32M			Kimbrough and Linder 1978	Technical grade (85%)
Rat 12 weeks (F)	12M			Knudsen et al. 1974	Technical grade (purity not reported)
Mouse 6 months (F)	550			NTP 1989	Technical grade (90.4%)

(F) = feed; (GO) = gavage in oil; GD = gestation day; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; RBC = red blood cell

The lowest LOAEL for developmental effects was 13 mg/kg/day for decreases in fetal body weight and crown-rump length, increased skeletal variations, and increased resorptions in the offspring of rats exposed to pure pentachlorophenol (Welsh et al. 1987). No significant alteration in maternal body weight were observed at this dose level. Similar developmental effects and LOAEL values were observed in animals exposed to pure pentachlorophenol, technical-grade pentachlorophenol, and EC-7, suggesting that the pentachlorophenol was the causative agent for the developmental effects.

A comparison of the LOAEL values for hepatic effects (36 mg/kg/day) and developmental effects (13 mg/kg/day) in animals exposed to pure pentachlorophenol suggests that developmental toxicity may be a more sensitive target than hepatic effects and was selected as the critical effect. The Welsh et al. (1987) study of pure pentachlorophenol and the Bernard et al. (2002) study of technical-grade pentachlorophenol identified similar LOAEL values (13 and 10 mg/kg/day, respectively). The Welsh et al. (1987) study was selected as the principal study since it tested pure pentachlorophenol.

To identify potential PODs, BMD modeling was considered for the four developmental effects observed in the Welsh et al. (1987) study. The data for fetal body weight and crown-rump length were not amenable to modeling because the investigators did not include the standard errors of the mean. Thus, the NOAEL of 4 mg/kg/day was identified as the potential point of departure for these effects.

BMD modeling was conducted to identify potential points of departure using the incidence data listed in Table A-3 for litters with two or more resorptions and litters with fetuses having two or more skeletal variations. The data were fit to all available dichotomous models in EPA's BMDS (version 3.1.2) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual 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 (95% lower confidence limit on the BMD) was selected as the point of departure when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. Since the endpoints were developmental toxicity, a BMR of 5% was used.

Table A-3. Incidences of Resorptions and Skeletal Variations in the Fetuses of Rats Exposed to Pentachlorophenol in the Diet

Dose (mg/kg/day)	Litters with two or more resorptions	Litters with two or more skeletal variations
0	13/31	12/28
4	5/11	1/10
13	13/16	12/16
43	17/17	Not evaluated due to small number of surviving fetuses

Source: Welsh et al. 1987

At least one BMD model provided adequate fit for these endpoints. For fetal resorptions, the logistic and probit models provided adequate fit and estimated similar BMD and BMDL values; results are presented in Table A-4. The probit model was selected because it had a slightly higher AIC; the probit modeling results are presented in Figure A-1. The results of the BMD modeling for skeletal variations are presented in Table A-5. The BMDLs for the models providing adequate fit were sufficiently close; the

log-logistic model was selected as it had the highest AIC. This model estimated a BMDL of 0.85 mg/kg/day; the model predictions are presented in Figure A-2.

Table A-4. Model Predictions for Litters with Two or More Resorptions of the Offspring of Rats Exposed to Pure Pentachlorophenol (Welsh et al. 1987)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Scaled residuals[b] Dose above BMD	Scaled residuals[b] Overall largest	AIC	BMD_5 (mg/kg/day)	$BMDL_5$ (mg/kg/day)
Dichotomous Hill	-1			-0.00	-0.00	-0.00	38.60	ND-1	ND-1
Gamma[c]	0	0.00	NA	-0.00	-0.00	-0.00	36.60	ND-2	ND-2
LogLogistic[d]	0	0.00	NA	-0.00	-0.00	-0.00	30.49	ND-2	ND-2
Multistage (1-degree)[e]	1	0.09	0.76	0.06	0.60	0.06	34.75	ND-1	ND-1
Multistage (2-degree)[e]	0	0.00	NA	-0.00	-0.00	-0.00	36.60	ND-2	ND-2
Weibull[c]	0	0.00	NA	-0.00	-0.00	-0.00	36.60	ND-2	ND-2
Logistic	1	0.02	0.90	0.03	0.03	0.03	34.63	0.92	0.58
LogProbit[d]	0	0.00	NA	-0.00	-0.00	-0.00	36.60	ND-2	ND-2
Probit[f]	**1**	**0.00**	**0.99**	**0.00**	**0.00**	**-0.00**	**34.60**	**0.91**	**0.61**

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure dose associated with 10% extra risk); DF = degrees of freedom; ND-1 = not determined; BMDL 10 times lower than lowest non-zero dose; ND-2 = not determined, goodness-of-fit test could not be calculated

Figure A-1. Fit of Probit Model to Data on Litters with Two or More Resorptions In Rats Exposed to Pentachlorophenol

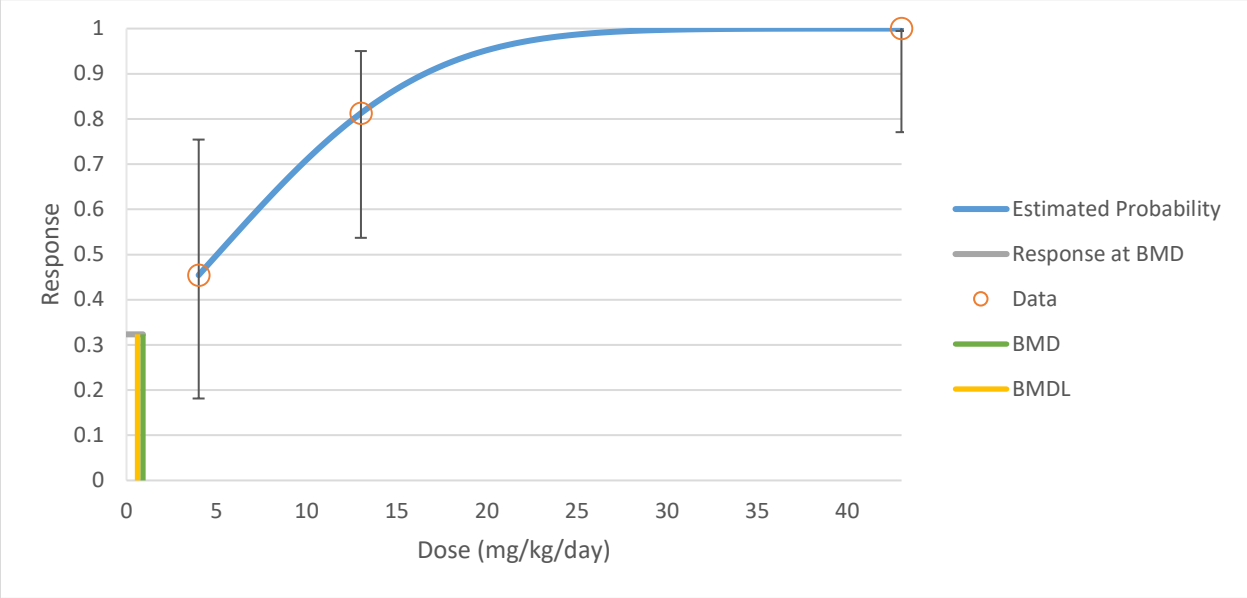


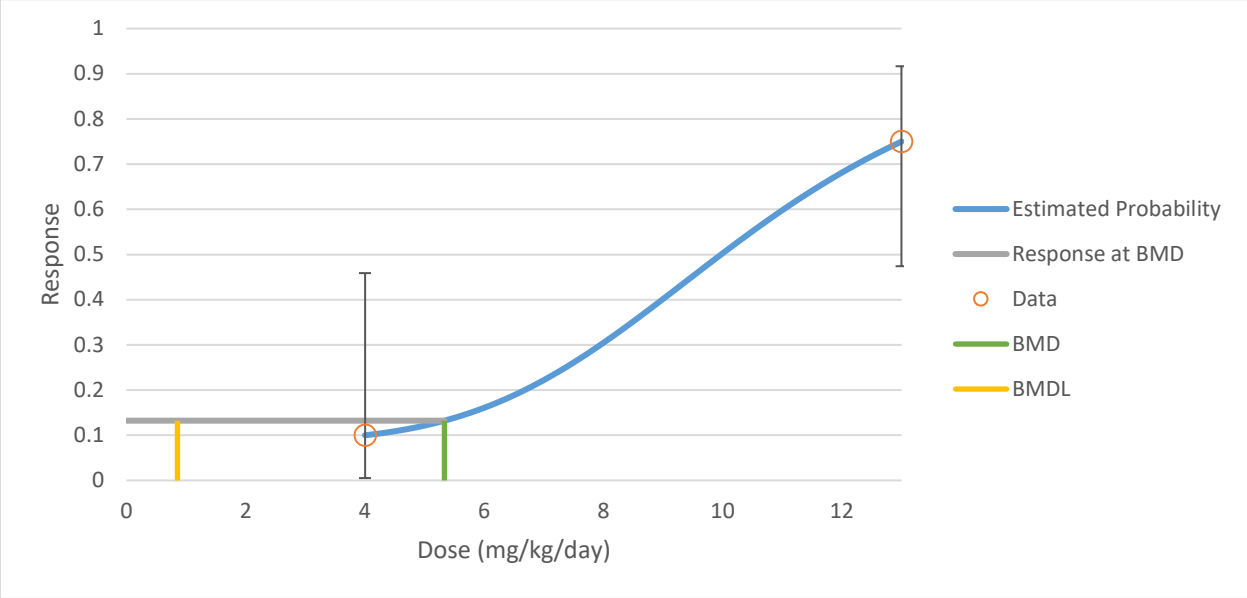
Table A-5. Model Predictions for Litters with Two or More Skeletal Variations in the Offspring of Rats Exposed to Pure Pentachlorophenol (Welsh et al. 1987)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_5 (mg/kg/day)	$BMDL_5$ (mg/kg/day)
Dichotomous Hill	-2	0.00	65535	0.00	0.00	0.00	32.50	3.73	0.85
Gamma[c]	-1	0.00	65535	0.00	0.00	0.00	31.10	3.04	0.55
LogLogistic[d,e]	**-1**	**0.00**	65535	**-0.00**	**-0.00**	**-0.00**	**30.49**	**5.33**	**0.85**
Multistage (1-degree)[f]	0	2.21	NA	-1.31	0.70	-1.31	31.10	ND	ND
Weibull[c]	-1	0.00	65535	-0.00	-0.00	-0.00	30.50	9.25	0.55
Logistic	0	0.00	NA	0.00	0.00	0.00	28.50	ND	ND
LogProbit[d]	-1	0.00	65535	0.00	-0.00	0.00	30.50	9.87	1.05
Probit	0	0.00	NA	0.00	-0.00	-0.00	28.49	ND	ND

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure dose associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit test could not be calculated

Figure A-2. Fit of LogLogistic Model to Data on Litters with 2 or More Skeletal Variations in the Offspring of Rats Exposed to Pentachlorophenol



Comparison of the potential PODs for developmental effects identified the BMDL of 0.61 mg/kg/day for two or more fetal resorptions in a litter as the lowest potential POD. Derivation of an MRL based on the BMDL of 0.61 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) results in an intermediate-duration MRL of 0.006 mg/kg/day. This MRL is slightly higher than the acute-duration oral MRL, which is also based on developmental toxicity.

Agency Contacts (Chemical Managers): Obaid Faroon

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Pentachlorophenol
CAS Numbers: 87-86-5
Date: April 2022
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 0.005 mg/kg/day (5 µg/kg/day)
Critical Effect: Minimal chronic liver inflammation
Reference: EPA 1997
Point of Departure: LOAEL of 1.5 mg/kg/day
Uncertainty Factor: 300
LSE Graph Key: 51
Species: Dog

MRL Summary: A chronic-duration oral MRL of 0.005 mg/kg/day (5 µg/kg/day) was derived for pentachlorophenol. The MRL is based on a LOAEL of 1.5 mg/kg/day for minimal chronic inflammation in the liver of dogs administered via capsule technical-grade pentachlorophenol for 1 year (EPA 1997) and an uncertainty factor of 300 (3 for the use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Six studies have evaluated the chronic toxicity of pentachlorophenol and have reported adverse health effects (summarized in Table A-6). The observed effects include decreases in body weight gain in rats exposed to pure pentachlorophenol (NTP 1999) or EC-7 (Schwetz et al. 1978) and in mice exposed to EC-7 or technical-grade pentachlorophenol (NTP 1989); hematological effects in mice exposed to technical-grade pentachlorophenol (splenic effects) (NTP 1989) and in dogs exposed to technical-grade pentachlorophenol (RBC effects) (EPA 1997); liver effects in rats exposed to pure pentachlorophenol (NTP 1999) or EC-7 (Schwetz et al. 1978), mice exposed to EC-7 or technical-grade pentachlorophenol (NTP 1989), and dogs exposed to technical-grade pentachlorophenol (EPA 1997); and adrenal gland effects in mice exposed to EC-7 (NTP 1989).

The liver alterations were selected as the critical effect based on the consistency of the finding and the lower LOAEL values, as compared to other endpoints. The liver effects consist of hepatocellular hypertrophy, increases in elevated ALT levels, chronic inflammation, and necrosis. Increases in hepatocellular adenomas and carcinomas have also been reported in the mouse studies testing technical-grade pentachlorophenol or EC-7 (NTP 1989). Liver tumors were not observed in rats exposed to pure pentachlorophenol (NTP 1999). The lowest LOAEL for liver effects was 1.5 mg/kg/day for chronic inflammation and increases in liver weight in dogs (EPA 1997). At higher doses (17 mg/kg/day), necrosis was observed in mice (NTP 1989). The available chronic duration data do not allow a comparison between the toxicity of pure pentachlorophenol and technical-grade pentachlorophenol; although a comparison of the LOAEL values suggest some differences, it is difficult to determine if these differences are due to testing different animal species.

Table A-6. Summary of NOAELs and LOAELs For Adverse Effects Following Chronic-Duration Oral Exposure to Pentachlorophenol

Species, duration (route)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference	Purity
Body weight effects					
Rat 2 years (F)	20	30	10 and 14% decrease in body weight gain in males and females, respectively	NTP 1999	Pure (99%)
Rat 1 year with 1 year recovery (F)		60	17 and 22% decrease in body weight gain in males and females, respectively, at end of exposure period	NTP 1999	Pure (99%)
Rat 22–24 months (F)	10	30	12% decrease in body weight gain	Schwetz et al. 1978	EC-7 (90.4%)
Mouse 2 years (F)	17	34	6–12% lower body weights in females	NTP 1989	EC-7 (90.4%)
Mouse 2 years (F)	17	35	5–13% lower body weights in females	NTP 1989	Technical grade (90.4%)
Hematological effects					
Mouse 2 years (F)	114			NTP 1989	EC-7 (90.4%)
Mouse 2 years (F)		18	Diffuse hematopoietic cells in spleen in males at ≥18 mg/kg/day and females at 35 mg/kg/day	NTP 1989	Technical grade (90.4%)
Dog 1 year (C)	1.5	3.5	Decreased RBC count in males at 3.5 mg/kg/day; decreased hemoglobin at 6.5 mg/kg/day; in females, decreased RBC count, hemoglobin, and hematocrit at 6.5 mg/kg/day	EPA 1997	Technical grade (90.9%)
Hepatic effects					
Rat 2 years (F)	10	20	Cystic hepatocyte degeneration	NTP 1999	Pure (99%)
Rat 1 year with 1 year recovery (F)		60	Centrilobular hepatocellular hypertrophy and cystic hepatocyte degeneration	NTP 1999	Pure (99%)
Mouse 2 years (F)		17	Inflammation and necrosis	NTP 1989	EC-7 (90.4%)

Table A-6. Summary of NOAELs and LOAELs For Adverse Effects Following Chronic-Duration Oral Exposure to Pentachlorophenol

Species, duration (route)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference	Purity
Rat 22-24 months (F)	10	30	Elevated ALT	Schwetz et al. 1978	EC-7 (90.4%)
Dog 1 year (C)		1.5	Increased liver weight, minimal-to-mild chronic inflammation; cytoplasmic vacuolation at 6.5 mg/kg/day and minimal necrosis at 6.5 mg/kg/day	EPA 1997	Technical grade (90.9%)
Mouse 2 years (F)		17	Inflammation and necrosis	NTP 1989	Technical grade (90.4%)
Endocrine effects					
Rat 2 years (F)	30		No thyroid or adrenal gland alterations	NTP 1999	Pure (99%)
Rat 1 year with 1 year recovery (F)	60		No thyroid or adrenal gland alterations	NTP 1999	Pure (99%)
Mouse 2 years (F)		18	Adrenal gland hyperplasia in males	NTP 1989	EC-7 (90.4%)
Mouse 2 years (F)		18	Adrenal gland hyperplasia in males	NTP 1989	Technical grade (90.4%)
Dog 1 year (C)		6.5	No thyroid or adrenal gland alterations	EPA 1997	Technical grade (90.9%)

ALT = alanine aminotransferase; (C) = capsule; (F) = feed; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: EPA (1997) was selected as the principal study because it identified the lowest LOAEL for the critical effect.

Summary of the Principal Study:

EPA. 1997. Data evaluation record. Pentachlorophenol. 83-1b: Fifty-two week repeated dose chronic oral study of pentachlorophenol administered via capsule to dogs. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. DP Barcode D225574. MRID 43982701.

Groups of four male and four female beagle dogs were administered, via gelatin capsule, 0, 1.5, 3.5, or 6.5 mg/kg/day technical-grade pentachlorophenol (90.9% pure) for 1 year. The following parameters were used to assess toxicity: daily clinical observations, body weight, feed intake, ophthalmoscopic examination (weeks 13 and 26), hematology and serum clinical chemistry (weeks 13, 26, 39, and 52), urinalysis (weeks 13, 26, and 39), gross necropsy, and comprehensive histopathological examination of tissues and organs.

One male and one female dogs in the 6.5 mg/kg/day group were sacrificed in extremis on study days 247 and 305, respectively. Lethargy, inappetence, emaciation, dehydration, pale mucous membranes, gastrointestinal irritation, and bleeding were observed in the 6.5 mg/kg/day group. Significant decreases in body weight gain were observed in the 6.5 mg/kg/day beginning on exposure day 95; at termination, the females weighed approximately 20% less than controls. Decreases in feed consumption were observed in the females in the 6.5 mg/kg/day group until week 41; at week 41, there was a sudden increase in feed consumption. No significant alterations in body weight were observed in males, although terminal body weight in the 6.5 mg/kg/day was 18% lower than controls. Increased feed consumption (5–20%) was observed in the males. No exposure-related ophthalmoscopic findings were observed. Significant decreases in RBC counts were observed in males at 3.5 and 6.5 mg/kg/day (15 and 22% respectively); hemoglobin was significantly decreased at 6.5 mg/kg/day (17%). In female dogs, RBC counts, hemoglobin, and hematocrit levels were significantly decreased at 6.5 mg/kg/day (10–17% for all parameters). Alterations of serum clinical chemistry parameters consisted of increases in alkaline phosphatase levels at ≥1.5 mg/kg/day, increases in ALT at ≥3.5 mg/kg/day, and increases in AST at 6.5 mg/kg/day; the only statistically significant alterations were the increases in AST (67%) and alkaline phosphatase (580%) in females at 6.5 mg/kg/day. No treatment-related alterations were observed in the urinalysis. Statistically significant increases in relative liver weight were observed in males and females at ≥1.5 mg/kg/day and increases in absolute liver weight were observed in females at ≥1.5 mg/kg/day. Increases in relative and absolute thyroid weight were also observed in females at 6.5 mg/kg/day. Histological alterations in the liver consisted of mild to moderate accumulation of pigment consistent with lipofuscin at >1.5 mg/kg/day, minimal chronic inflammation in males at >1.5 mg/kg/day and in females at >3.5 mg/kg/day, cytoplasmic vacuolation in males at >3.5 mg/kg/day, and minimal necrosis in females at 6.5 mg/kg/day (2/4 compared to 0/4 in controls). Lymphocytic mucosal inflammation was observed at >1.5 mg/kg/day.

Selection of the Point of Departure for the MRL: The LOAEL of 1.5 mg/kg/day was selected as the POD for the MRL. This dose was considered a minimal LOAEL based on the characterization of the chronic inflammation as minimal in severity. The incidences of chronic inflammation were 0/4, 4/4, 4/4, and 3/3 in the 0, 1.5, 3.5, and 6.5 mg/kg/day male dog groups, respectively, and the severity scores (lesions grades were 1=minimal, 2=mild; 3=moderate; and 4=marked) were 0, 1, 1.3, and 1.3, respectively. The incidences of chronic inflammation in the females were 2/4, 2/4, 4/4, and 3/3, respectively, with severity scores of 1, 1.5, 1.8, and 1.7, respectively. The incidence of chronic inflammation in males was not considered suitable for BMD modeling because the incidence in all treated groups was 100%, which would provide limited predictive information at the BMD response rate of 10%.

Uncertainty Factor:

- 3 for the use of a minimal LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = LOAEL ÷ UF
= 1.5 mg/kg/day ÷ (3 x 10 x 10) = 0.005 mg/kg/day (5 µg/kg/day)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Studies in humans primarily exposed to pentachlorophenol via dermal contact have reported hepatic enlargement (Armstrong et al. 1969; Gordon 1956; Robson et al. 1969; Smith et al. 1996), alterations in serum ALT and AST levels (Klemmer et al. 1980), and centrilobular congestion or degeneration (Bergner et al. 1965). A number of acute- and intermediate-duration studies in laboratory animals have identified the liver as a sensitive target.

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APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR PENTACHLOROPHENOL

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 pentachlorophenol.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was 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 pentachlorophenol. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of pentachlorophenol 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 pentachlorophenol are presented in Table B-1.

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

- 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
    - Developmental effects

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

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

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for pentachlorophenol released for public comment in 2021; thus, the literature search was restricted to studies published between January 2018 and November 2021. The following main databases were searched in November 2021:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for pentachlorophenol. 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 pentachlorophenol 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	
11/2021	(("Pentachlorophenol"[mh] OR 87-86-5[rn] OR 131-52-2[rn] OR "pentachlorophenate"[tw] OR "pentachlorophenolate"[tw] OR "(pentachlorophenoxy)-Sodium"[tw] OR "Na-pentachlorophenate"[tw] OR "PCP sodium salt"[tw] OR "PCP-Na"[tw] OR "PCP-Sodium"[tw] OR "Pentachlorophenate sodium"[tw] OR "Pentachlorophenate-Na"[tw] OR "Pentachlorophenol sodium salt"[tw] OR "Pentachlorophenol, sodium salt"[tw] OR "Pentachlorophenoxy sodium"[tw] OR "Pentachlorphenol sodium salt"[tw] OR "Pentaphenate"[tw] OR "Phenol, 2,3,4,5,6-pentachloro-, sodium salt"[tw] OR "Phenol, pentachloro-, sodium deriv."[tw] OR "Phenol, pentachloro-, sodium salt"[tw] OR "PHENOL, PENTACHLORO-SODIUM SALT"[tw] OR "PHENOLATE, PENTACHLORO-, SODIUM"[tw] OR "Sodium PCP"[tw] OR "Sodium pentachloro-"[tw] OR "Sodium pentachlorophenate"[tw] OR "Sodium pentachlorophenate"[tw] OR "Sodium pentachlorophenol"[tw] OR "Sodium pentachlorophenolate"[tw] OR "Sodium pentachlorophenoxide"[tw] OR "Sodium pentachlorophonate"[tw] OR "Sodium pentachlorphenate"[tw] OR "Sodium, (pentachlorophenoxy)-"[tw] OR "Dow dormant fungicide"[tw] OR "Dowicide G"[tw] OR "Dowicide G-ST"[tw] OR "GR 48-11PS"[tw] OR "GR 48-32S"[tw] OR "Mystox D"[tw] OR "Napclor-G"[tw] OR "NAPCP"[tw] OR "Pentanot 25"[tw] OR "Pkhfn"[tw] OR "Preventol PN"[tw] OR "Sapco 25"[tw] OR "Sodium pentach"[tw] OR "Weedbeads"[tw] OR "Witophen N"[tw] OR "1-Hydroxy-2,3,4,5,6-pentachlorobenzene"[tw] OR "1-Hydroxypentachlorobenzene"[tw] OR "2,3,4,5,6-Pentachlorophenate"[tw] OR "2,3,4,5,6-Pentachlorophenol"[tw] OR "Chlorophenasic acid"[tw] OR "CHLOROPHENATE"[tw] OR "PCP (pesticide)"[tw] OR "pentachloro-Phenol"[tw] OR "Pentachlorofenol"[tw] OR "Pentachlorophenate"[tw] OR "Pentachlorophenol"[tw] OR "Pentachlorophenols"[tw] OR "pentaclorofenol"[tw] OR "Pentrachlorophenol"[tw] OR "Perchlorophenol"[tw] OR "Phenol, 2,3,4,5,6-pentachloro-"[tw] OR "Phenol, pentachloro-"[tw] OR "AD 73"[tw] OR "CM 613"[tw] OR "CP 1309"[tw] OR "D037"[tw] OR "EP 30"[tw] OR "MB 333"[tw] OR "Chem-Penta"[tw] OR "Chem-Tol"[tw] OR "Chlon"[tw] OR "Chlorophen"[tw] OR "Dowicide 7"[tw] OR "Dowicide EC 7"[tw] OR "Dowicide EC-7"[tw] OR "Dura Treet II"[tw] OR "Durotox"[tw] OR "Forpen-50 Wood Preservative"[tw] OR "Fungifen"[tw] OR "Glazd penta"[tw] OR "Grundier Arbezol"[tw] OR "Lauxtol"[tw] OR "Liroprem"[tw] OR "Ontrack WE Herbicide"[tw] OR "Ortho Triox Liquid Vegetation Killer"[tw] OR "Osmose Wood Preserving Compound"[tw] OR "Penchlorol"[tw] OR "Penta Concentrate"[tw] OR "Penta ready"[tw] OR "Penta WR"[tw] OR "Penta-kil"[tw] OR "Pentacon"[tw] OR "Penton 70"[tw] OR "Pentor 70"[tw] OR "Penwar"[tw] OR "Peratox"[tw] OR "Permacide"[tw] OR "Permagard"[tw] OR "Permasan"[tw] OR "Permatox DP-2"[tw] OR "Permatox penta"[tw] OR "Permite"[tw] OR "PKhF"[tw] OR "Pol Nu"[tw] OR "Pole topper"[tw] OR "Preventol P"[tw] OR "Santobrite"[tw] OR "Santophen"[tw] OR "Satophen"[tw] OR "Sinituho"[tw] OR "Term-i-trol"[tw] OR "Thompson's wood fix"[tw]

Table B-2. Database Query Strings

Database search date	Query string
	OR "Watershed Wood Preservative"[tw] OR "Weed and Brush Killer"[tw] OR "Weedone"[tw] OR "Witophen P"[tw] OR "Woodtreat A"[tw] OR ("pcp"[tw] AND (chlorophenol* OR phenols OR pesticide* OR insecticide* OR herbicide* OR wood preservative))) AND (2018/01/01:3000[dp] OR 2019/01/01:3000[mhda] OR 2019/01/01:3000[crdat] OR 2019/01/01:3000[edat])) OR ("pentachlorphenol"[tw] AND 1999:3000[dp])
NTRL	
11/2021	Hydroxypentachlorobenzene OR Pentachlorophenate OR Pentachlorophenol OR CHLOROPHENATE OR pentachlorophenolate OR Perchlorophenol OR pentachlorophenoxide OR pentachlorphenol
Toxcenter	
11/2021	FILE 'TOXCENTER' ENTERED AT 18:38:46 ON 03 NOV 2021 CHARGED TO COST=EH038.12.06.LB.04 DIS SAVED L1 15609 SEA 87-86-5 OR 131-52-2 L2 14602 SEA L1 NOT PATENT/DT L3 14536 SEA L2 NOT TSCATS/FS ACT TOXQUERY/Q --------- L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)

Table B-2. Database Query Strings

Database search date	Query string
	L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L22 QUE (ENDOCRIN? AND DISRUPT?)
	L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L29 QUE (NEPHROTOX? OR HEPATOTOX?)
	L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31
	L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L35 QUE L32 OR L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L41 503 SEA L3 AND ED>=20190101
	L42 281 SEA L41 AND L37
	L43 45 SEA L42 AND MEDLINE/FS
	L44 236 SEA L42 NOT MEDLINE/FS
	L45 234 DUP REM L43 L44 (47 DUPLICATES REMOVED) ANSWERS '1-234' FROM FILE TOXCENTER
	L*** DEL 45 S L42 AND MEDLINE/FS
	L*** DEL 45 S L42 AND MEDLINE/FS
	L46 45 SEA L45
	L*** DEL 236 S L42 NOT MEDLINE/FS
	L*** DEL 236 S L42 NOT MEDLINE/FS
	L47 189 SEA L45
	L48 189 SEA (L46 OR L47) NOT MEDLINE/FS
	D SCAN L48

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
11/2021	Compounds searched: 87-86-5; 131-52-2
NTP	
11/2021	87-86-5 131-52-2 "Pentachlorophenol" "Pentachlorophenate"
Regulations.gov	
11/2021	Dockets and Document tabs searched: 87-86-5 131-52-2 Pentachlorophenol Pentachlorophenate
NIH RePORTER	
12/2021	Search Criteria:, Text Search: "pentachlorophenate" OR "pentachlorophenolate" OR "(pentachlorophenoxy)-Sodium" OR "Na-pentachlorophenate" OR "PCP sodium salt" OR "PCP-Na" OR "PCP-Sodium" OR "Pentachlorophenate sodium" OR "Pentachlorophenate-Na" OR "Pentachlorophenol sodium salt" OR "Pentachlorophenol, sodium salt" OR "Pentachlorophenoxy sodium" OR "Pentachlorphenol sodium salt" OR "Pentaphenate" OR "Phenol, 2,3,4,5,6-pentachloro-, sodium salt" OR "Phenol, pentachloro-, sodium deriv." OR "Phenol, pentachloro-, sodium salt" OR "PHENOL, PENTACHLORO-SODIUM SALT" OR "PHENOLATE, PENTACHLORO-, SODIUM" OR "Sodium PCP" OR "Sodium pentachloro-" OR "Sodium pentachloro- phenate" OR "Sodium pentachlorophenate" OR "Sodium pentachlorophenol" OR "Sodium pentachlorophenolate" OR "Sodium pentachlorophenoxide" OR "Sodium pentachlorophonate" OR "Sodium pentachlorphenate" OR "Sodium, (pentachlorophenoxy)-" OR "Dow dormant fungicide" OR "Dowicide G" OR "Dowicide G-ST" OR "GR 48-11PS" OR "GR 48-32S" OR "Mystox D" OR "Napclor-G" OR "NAPCP" OR "Pentanot 25" OR "Pkhfn" OR "Preventol PN" OR "Sapco 25" OR "Sodium pentach" OR "Weedbeads" OR "Witophen N" OR "1-Hydroxy-2,3,4,5,6-pentachlorobenzene" OR "1-Hydroxypentachlorobenzene" OR "2,3,4,5,6-Pentachlorophenate" OR "2,3,4,5,6-Pentachlorophenol" OR "Chlorophenasic acid" OR "CHLOROPHENATE" OR "PCP (pesticide)" OR "pentachloro-Phenol" OR "Pentachlorofenol" OR "Pentachlorophenate" OR "Pentachlorophenol" OR "Pentachlorophenols" OR "pentaclorofenol" OR "Pentrachlorophenol" OR "Perchlorophenol" OR "Phenol, 2,3,4,5,6-pentachloro-" OR "Phenol, pentachloro-" OR "AD 73" OR "CM 613" OR "CP 1309" OR "D037" OR "EP 30" OR "MB 333" OR "Chem-Penta" OR "Chem-Tol" OR "Chlon" OR "Chlorophen" OR "Dowicide 7" OR "Dowicide EC 7" OR "Dowicide EC-7" OR "Dura Treet II" OR "Durotox" OR "Forpen-50 Wood Preservative" OR "Fungifen" OR "Glazd penta" OR "Grundier Arbezol" OR "Lauxtol" OR "Liroprem" OR "Ontrack WE Herbicide" OR "Ortho Triox Liquid Vegetation Killer" OR "Osmose Wood Preserving Compound" OR "Penchlorol" OR "Penta Concentrate" OR "Penta ready" OR "Penta WR" OR "Penta-kil" OR "Pentacon" OR "Penton 70" OR "Pentor 70" OR "Penwar" OR "Peratox" OR "Permacide" OR "Permagard" OR "Permasan" OR "Permatox DP-2" OR "Permatox penta" OR "Permite" OR "PKhF" OR "Pol Nu" OR "Pole topper" OR "Preventol P" OR "Santobrite" OR "Santophen" OR "Satophen" OR "Sinituho" OR "Term-i-trol" OR "Thompson's wood fix" OR "Watershed Wood Preservative" OR "Weedone" OR "Witophen P" OR "pentachlorphenol" (advanced)

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2021 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 458
- Number of records identified from other strategies: 29
- Total number of records to undergo literature screening: 487

B.1.2 Literature Screening

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

- 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.

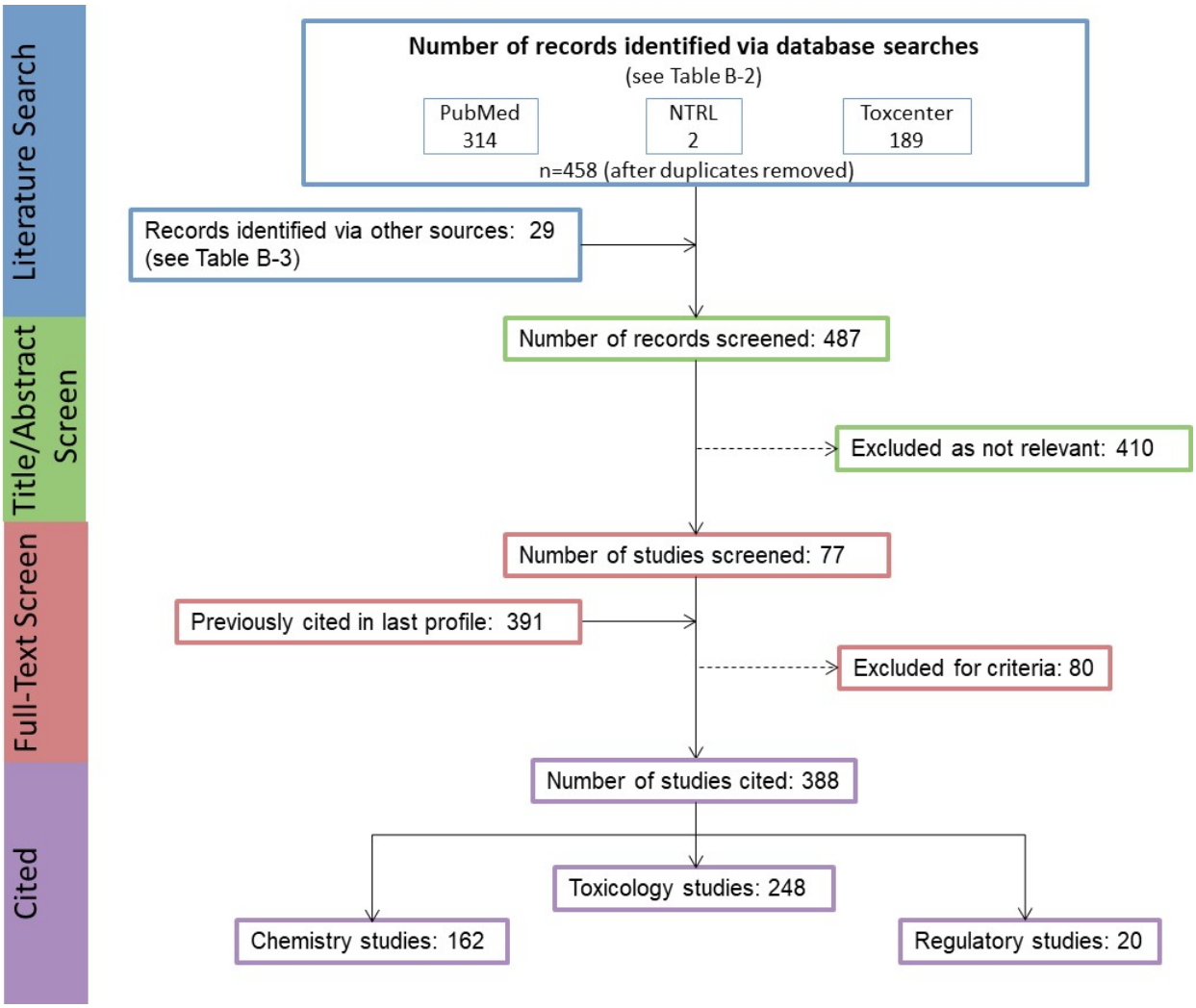
- Number of titles and abstracts screened: 487
- Number of studies considered relevant and moved to the next step: 77

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: 77
- Number of studies cited in the previous draft of the toxicological profile: 391
- Total number of studies cited in the profile: 398

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

Figure B-1. November 2021 Literature Search Results and Screen for Pentachlorophenol



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

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 pentachlorophenol, 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 pentachlorophenol:

- 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 pentachlorophenol. The inclusion criteria used to identify relevant studies examining the health effects of pentachlorophenol 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

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

Cardiovascular effects
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 was conducted to identify studies examining the health effects of pentachlorophenol. 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 draft toxicological profile for pentachlorophenol released for public comment in 2021. See Appendix B for the databases searched and the search strategy.

A total of 3,182 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 pentachlorophenol.

Title and Abstract Screen. In the Title and Abstract Screen step, 487 records were reviewed; 4 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 89 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 89 documents, 117 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 pentachlorophenol and overviews of the results of the oral exposure studies (no inhalation or dermal exposure laboratory animal studies were identified) are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures table in Section 2.1 of the profile (**Error! Reference source not found.**).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for pentachlorophenol identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The available human studies examined a range of effects; these studies and case reports have reported respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, and developmental effects. Animal studies examined a number of endpoints following inhalation, oral, or dermal exposure; the inhalation and dermal studies were limited to an examination of lethality. The oral exposure studies examined most endpoints and reported body weight, gastrointestinal, hematological, hepatic, renal, endocrine, immunological, reproductive, developmental, and other noncancer effects.

Some of these findings were attributed to the contaminants present in technical-grade pentachlorophenol. Of the consistently observed effects attributed to pentachlorophenol, hepatic and developmental effects were considered sensitive outcomes (i.e., effects were observed at low concentrations or doses). Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. There were 117 studies (published in 89 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 Pentachlorophenol 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	1	3	0	0	1	0	4	0	5	1	0	2	3	0	0	1	4
	1	3	0	0	1	0	4	0	5	1	0	2	2	0	0	1	4
Case control	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	8
	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	6
Cross sectional	0	0	0	0	0	0	0	0	1	0	1	2	1	2	0	0	0
	0	0	0	0	0	0	0	0	1	0	1	2	1	1	0	0	0
Case report	0	0	0	0	5	0	1	0	0	0	0	1	1	0	0	0	0
	0	0	0	0	5	0	1	0	0	0	0	1	1	0	0	0	0
Oral studies																	
Cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Case report	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0
	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Dermal studies																	
Cohort	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Case report	0	1	0	0	0	0	4	4	2	0	0	1	3	0	0	0	0
	0	1	0	0	0	0	4	4	2	0	0	1	3	0	0	0	0

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	

Table C-4. Overview of the Health Outcomes for Pentachlorophenol 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																	
Intermediate-duration																	
Chronic-duration																	
Acute-duration	9	0	0	0	0	0	2	0	0	0	0	7	0	0	8	0	0
	6	0	0	0	0	0	2	0	0	0	0	3	0	0	7	0	0
Intermediate-duration	16	8	8	7	6	5	15	9	0	0	9	10	2	6	4	3	4
	8	1	0	0	1	0	15	1	0	0	0	7	0	2	4	3	4
Chronic-duration	7	5	5	5	3	4	6	6	0	1	6	0	1	2	0	2	5
	6	1	0	1	2	0	6	1	0	0	3	0	0	0	0	2	3
Dermal studies																	
Acute-duration																	
Intermediate-duration																	1
																	1
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 pentachlorophenol 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 Pentachlorophenol—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Comparison groups appropriate?	**Study design or analysis account for important confounding and modifying variables?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in the exposure characterization?***	**Confidence in the outcome assessment?***	All measured outcomes reported?	
Outcome: Hepatic Effects							
Cohort							
Cheng et al. 1993	+	–	+	–	–	+	Second
Colosio et al. 1993b	+	–	+	+	+	+	Second
Hryhorczuk et al. 1998	+	–	+	–	–	+	Second
Klemmer et al. 1980	+	–	+	+	+	+	Second
Case Reports							
Armstrong et al. 1969	NA	–	NA	–	+	+	Second
Bergner et al. 1965	NA	–	NA	–	–	–	Third
Gordon 1956	NA	–	NA	–	+	+	Third
Robson et al. 1969	NA	–	NA	–	–	+	Third
Smith et al. 1996	NA	–	NA	–	–	–	Third
Outcome: Developmental Effects							
Cohort							
Berghuis et al. 2018	+	–	+	+	+	+	Second
Meijer et al. 2008	+	–	+	+	+	+	Second
Roze et al. 2009	+	–	+	+	+	+	Second
Ruel et al. 2019	+	–	+	+	+	+	Second

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

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Comparison groups appropriate?	**Study design or analysis account for important confounding and modifying variables?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in the exposure characterization?***	**Confidence in the outcome assessment?***	All measured outcomes reported?	
Case-Control							
Chen et al. 2013b	+	–	+	+	+	+	Second
Dimich-Ward et al. 1996	–	–	+	–	+	+	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 Pentachlorophenol—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Outcome: Hepatic Effects									
Oral acute exposure									
Umemura et al. 1996	–	+	+	+	+	+	+	+	First
Bekhouche et al. 2019	+	+	+	+	+	–	+	+	First
Oral intermediate exposure									
Bernard et al. 2002	++	+	+	+	+	++	+	++	First
Kerkvliet et al. 1982 (technical)	–	+	+	+	+	– –	+	++	First
Kerkvliet et al. 1982 (pure)	–	+	+	+	+	– –	+	++	First
Kimbrough and Linder 1978 (technical)	+	+	+	+	+	+	+	++	First
Kimbrough and Linder 1978 (pure)	+	+	+	+	+	+	+	++	First
Knudsen et al. 1974	–	+	+	+	+	– –	+	++	First
NTP 1989 (technical, 30 days)	–	+	+	+	+	+	+	++	First
NTP 1989 (EC-7, 30 days)	–	+	+	+	+	+	+	++	First
NTP 1989 (pure, 30 days)	–	+	+	+	+	+	+	++	First
NTP 1989 (technical, 6 months)	+	+	+	+	+	+	+	++	First
NTP 1989 (EC-7, 6 months)	+	+	+	+	+	+	+	++	First
NTP 1989 (DP-2, 6 months)	+	+	+	+	+	+	+	++	First
NTP 1989 (pure, 6 months)	+	+	+	+	+	+	+	++	First

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

Reference	Risk of bias criteria and ratings: Selection bias: Administered dose or exposure level adequately randomized?	Selection bias: Allocation to study groups adequately concealed?	Performance bias: Experimental conditions identical across study groups?	Performance bias: Research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Outcome data complete without attrition or exclusion from analysis?	Detection bias: Confidence in the exposure characterization?	Detection bias: **Confidence in the outcome assessment?***	Selective reporting bias: All measured outcomes reported?	Risk of bias tier
NTP 1999	++	+	+	+	+	++	**++**	++	First
Umemura et al. 1996	–	+	+	+	+	+	**+**	+	First
Umemura et al. 2006	–	+	+	+	+	– –	**+**	++	First
Oral chronic exposure									
EPA 1997	+	+	+	+	+	+	**+**	++	First
NTP 1999 (2 years)	++	+	+	+	+	++	**++**	++	First
NTP 1999 (1 year)	++	+	+	+	+	++	**++**	++	First
Schwetz et al. 1978	+	+	+	+	+	++	**+**	+	First
NTP 1989 (technical)	–	+	+	+	+	++	**++**	++	First
NTP 1989 (pure)	–	+	+	+	+	++	**++**	++	First
Outcome: Developmental Effects									
Oral acute studies									
Bernard and Hoberman 2001	++	+	+	+	+	++	**+**	++	First
Schwetz et al. 1974 (pure, GDs 6–15)	–	+	+	+	+	+	**+**	+	First
Schwetz et al. 1974 (pure, GDs 8–11)	–	+	+	+	+	+	**+**	+	First
Schwetz et al. 1974 (technical, GDs 12–15)	–	+	+	+	+	+	**+**	+	First
Schwetz et al. 1974 (technical, GDs 6–15)	–	+	+	+	+	+	**+**	+	First

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

Reference	Risk of bias criteria and ratings: Selection bias: Administered dose or exposure level adequately randomized?	Selection bias: Allocation to study groups adequately concealed?	Performance bias: Experimental conditions identical across study groups?	Performance bias: Research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Outcome data complete without attrition or exclusion from analysis?	Detection bias: Confidence in the exposure characterization?	Detection bias: **Confidence in the outcome assessment?***	Selective reporting bias: All measured outcomes reported?	Risk of bias tier
Schwetz et al. 1974 (technical, GDs 8–11)	–	+	+	+	+	+	+	+	First
Schwetz et al. 1974 (technical, GDs 12–15)	–	+	+	+	+	+	+	+	First
Bernard et al. 2001	++	+	+	+	+	++	+	++	First
Oral intermediate exposure									
Bernard et al. 2002	++	+	+	+	+	++	+	++	First
Exon and Koller 1982	–	+	+	+	+	– –	+	++	First
Schwetz et al. 1978	+	+	+	+	+	++	+	++	First
Welsh et al. 1987	–	+	+	+	+	++	+	++	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 DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to pentachlorophenol 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 pentachlorophenol 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 in Distiller, 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 hepatic effects and developmental 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 Pentachlorophenol—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Hepatic Effects					
Cohort					
Cheng et al. 1993	No	No	Yes	Yes	Low
Colosio et al. 1993b	No	No	Yes	Yes	Low
Hryhorczuk et al. 1998	No	No	Yes	Yes	Low
Klemmer et al. 1980	No	No	Yes	Yes	Low
Case Reports					
Armstrong et al. 1969	No	Yes	No	No	Very low
Bergner et al. 1965	No	No	Yes	No	Very low
Gordon 1956	No	No	Yes	No	Very low
Robson et al. 1969	No	No	Yes	No	Very low
Smith et al. 1996	No	No	No	No	Very low
Outcome: Developmental Effects					
Cohort					
Berghuis et al. 2018	No	Yes	Yes	Yes	Moderate
Meijer et al. 2008	No	Yes	Yes	Yes	Moderate
Roze et al. 2009	No	Yes	Yes	Yes	Moderate
Ruel et al. 2019	No	Yes	Yes	Yes	Moderate
Case-Control					
Chen et al. 2013b	No	No	Yes	Yes	Low
Dimich-Ward et al. 1996	No	No	Yes	Yes	Low

Table C-14. Presence of Key Features of Study Design for Pentachlorophenol—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: Hepatic Effects					
Oral acute exposure					
Umemura et al. 1996	Yes	Yes	Yes	No	Moderate
Bekhouche et al. 2019	Yes	Yes	Yes	No	Moderate
Oral intermediate exposure					
Bernard et al. 2002	Yes	Yes	Yes	Yes	High
Kerkvliet et al. 1982 (technical)	Yes	Yes	Yes	Yes	High
Kerkvliet et al. 1982 (pure)	Yes	Yes	Yes	Yes	High
Kimbrough and Linder 1978 (technical)	Yes	Yes	Yes	Yes	High
Kimbrough and Linder 1978 (pure)	Yes	Yes	Yes	Yes	High
Knudsen et al. 1974	Yes	Yes	Yes	Yes	High
NTP 1989 (technical, 30 days)	Yes	Yes	Yes	No	Moderate
NTP 1989 (EC-7, 30 days)	Yes	Yes	Yes	No	Moderate
NTP 1989 (pure, 30 days)	Yes	Yes	Yes	No	Moderate
NTP 1989 (technical, 6 months)	Yes	Yes	Yes	Yes	High
NTP 1989 (EC-7, 6 months)	Yes	Yes	Yes	Yes	High
NTP 1989 (DP-2, 6 months)	Yes	Yes	Yes	Yes	High
NTP 1989 (pure, 6 months)	Yes	Yes	Yes	Yes	High
NTP 1999	Yes	Yes	Yes	Yes	High
Umemura et al. 1996	Yes	Yes	Yes	No	Moderate
Umemura et al. 2006	Yes	Yes	No	Yes	Moderate
Oral chronic exposure					
EPA 1997	Yes	Yes	Yes	Yes	High
NTP 1999 (2 years)	Yes	Yes	Yes	Yes	High
NTP 1999 (1 year)	Yes	Yes	Yes	Yes	High
Schwetz et al. 1978	Yes	Yes	Yes	Yes	High
NTP 1989 (technical)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for Pentachlorophenol—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 1989 (pure)	Yes	Yes	Yes	Yes	High
Outcome: Developmental Effects					
Oral acute studies					
Bernard and Hoberman 2001	Yes	Yes	Yes	Yes	High
Schwetz et al. 1974 (pure, GDs 6–15)	Yes	Yes	Yes	Yes	High
Schwetz et al. 1974 (pure, GDs 8–11)	Yes	Yes	Yes	Yes	High
Schwetz et al. 1974 (technical, GDs 12–15)	Yes	Yes	Yes	Yes	High
Schwetz et al. 1974 (technical, GDs 6–15)	Yes	Yes	Yes	Yes	High
Schwetz et al. 1974 (technical, GDs 8–11)	Yes	Yes	Yes	Yes	High
Schwetz et al. 1974 (technical, GDs 12–15)	Yes	Yes	Yes	Yes	High
Bernard et al. 2001	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Bernard et al. 2002	Yes	Yes	Yes	Yes	High
Exon and Koller 1982	Yes	Yes	Yes	Yes	High
Schwetz et al. 1978	Yes	Yes	Yes	Yes	High
Welsh et al. 1987	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 Pentachlorophenol Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Hepatic Effects		
Inhalation chronic exposure		
Human studies		
Cheng et al. 1993	Low	Low
Colosio et al. 1993b	Low	
Hryhorczuk et al. 1998	Low	
Klemmer et al. 1980	Low	
Oral acute exposure		
Animal studies		
Umemura et al. 1996	Moderate	Moderate
Bekhouche et al. 2019	Moderate	
Oral intermediate exposure		
Animal studies		
Bernard et al. 2002	High	High
Kerkvliet et al. 1982 (technical)	High	
Kerkvliet et al. 1982 (pure)	High	
Kimbrough and Linder 1978 (technical)	High	
Kimbrough and Linder 1978 (pure)	High	
Knudsen et al. 1974	High	
NTP 1989 (technical, 30 days)	Moderate	
NTP 1989 (EC-7, 30 days)	Moderate	
NTP 1989 (pure, 30 days)	Moderate	
NTP 1989 (technical, 6 months)	High	
NTP 1989 (EC-7, 6 months)	High	
NTP 1989 (DP-2, 6 months)	High	
NTP 1989 (pure, 6 months)	High	
NTP 1999	High	
Umemura et al. 1996	Moderate	
Umemura et al. 2006	Moderate	
Chronic oral exposure		
Animal studies		
EPA 1997	High	High
NTP 1999 (2 years)	High	
NTP 1999 (1 year)	High	
Schwetz et al. 1978	High	
NTP 1989 (technical)	High	
NTP 1989 (pure)	High	
Dermal acute exposure		
Human studies		
Armstrong et al. 1969	Very low	Very low
Gordon 1956	Very low	
Robson et al. 1969	Very low	

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

	Initial study confidence	Initial confidence rating
Smith et al. 1996	Very low	
Dermal chronic exposure		
Human studies		
Bergner et al. 1965	Very low	Very low
Outcome: Developmental effects		
Chronic inhalation exposure		
Human studies		
Dimich-Ward et al. 1996	Low	Low
Acute oral exposure		
Animal studies		
Bernard and Hoberman 2001	High	High
Schwetz et al. 1974 (pure, GDs 6–15)	High	
Schwetz et al. 1974 (pure, GDs 8–11)	High	
Schwetz et al. 1974 (technical, GDs 12–15)	High	
Schwetz et al. 1974 (technical, GDs 6–15)	High	
Schwetz et al. 1974 (technical, GDs 8–11)	High	
Schwetz et al. 1974 (technical, GDs 12–15)	High	
Bernard et al. 2001	High	
Intermediate oral exposure		
Animal studies		
Bernard et al. 2002	High	High
Exon and Koller 1982	High	
Schwetz et al. 1978	High	
Welsh et al. 1987	High	
Chronic oral exposure		
Human studies		
Berghuis et al. 2018	Moderate	Moderate
Chen et al. 2013b	Low	
Meijer et al. 2008	Moderate	
Roze et al. 2009	Moderate	
Ruel et al. 2019	Moderate	

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 hepatic effects and developmental effects 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 pentachlorophenol 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: Hepatic effects			
Human studies	Low	-1 risk of bias	Very Low
Animal studies	High		High
Outcome: Developmental effects			
Human studies	Moderate	-1 risk of bias, -1 inconsistency	Very Low
Animal studies	High	+1 consistency	High

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

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Hepatic effects	Very Low	High
Developmental effects	Very Low	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 pentachlorophenol, 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 pentachlorophenol is presented in Table C-18.

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

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Hepatic effects	Very Low	Health effect	Inadequate evidence
Developmental effects	Very Low	Health effect	Inadequate evidence
Animal studies			
Hepatic effects	High	Health effect	High evidence
Developmental effects	High	Health effect	High evidence

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

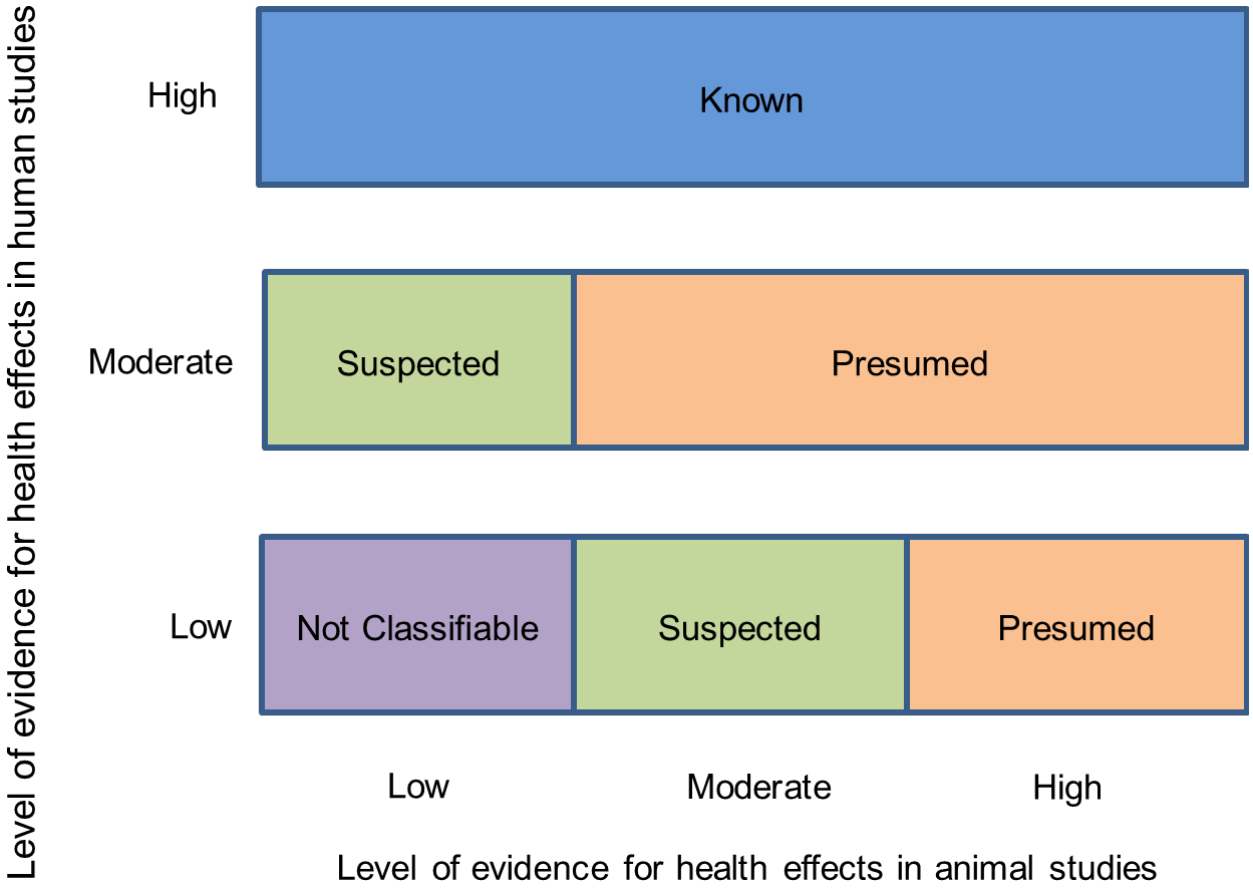
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **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

Figure C-1. Hazard Identification Scheme



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.

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 pentachlorophenol are listed below and summarized in Table C-19.

Presumed Health Effects

- Hepatic effects
  - Inadequate evidence from cohort studies that evaluated porphyrin excretion (Cheng et al. 1993; Hryhorczuk et al. 1998), case reports of hepatic enlargement or centrilobular degeneration (Armstrong et al. 1969; Bergner et al. 1965; Gordon 1956; Robson et al. 1969; Smith et al. 1996), or cohort studies evaluating indirect evidence of liver damage (serum clinical chemistry) (Colosio et al. 1993b; Klemmer et al. 1980).
  - High level of evidence in mice following acute oral exposure (Umemura et al. 1996), rats (Bernard et al. 2002; Kimbrough and Linder 1978; Knudsen et al. 1974; NTP 1999) and mice (Kerkvliet et al. 1982; NTP 1989) following intermediate-duration oral exposure, and in rats (NTP 1999; Schwetz et al. 1978), mice (NTP 1989), and dogs (EPA 1997) following chronic oral exposure.
  - The hepatic effects observed in animals have been reported in animals exposed to pure pentachlorophenol and several types of technical-grade pentachlorophenol.

- Developmental effects
  - Inadequate evidence epidemiological studies. The results of cohort and case-control studies have been inconsistent, with some studies finding associations between maternal or paternal pentachlorophenol levels (Chen et al. 2013b; Dimich-Ward et al. 1996; Meijer et al. 2008; Roze et al. 2009) and others not finding associations (Berghuis et al. 2018; Meijer et al. 2008; Ruel et al. 2019). All of the epidemiological studies involved co-exposure to other developmental toxicants including PCBs, CDDss, and CDFs.
  - High level of evidence of increased resorptions in rats (Bernard and Hoberman 2001; Schwetz et al. 1974), decreases in litter size in rats (Exon and Koller 1982; Schwetz et al. 1978), skeletal anomalies in rats (Schwetz et al. 1974), and decreases in fetal/pup body weight in rats (Bernard and Hoberman 2001; Bernard et al. 2002; Schwetz et al. 1978; Welsh et al. 1987) following oral exposure to pure pentachlorophenol or technical-grade pentachlorophenol.

Table C-19. Hazard Identification Conclusions for Pentachlorophenol

Outcome	Hazard identification
Hepatic effects	Presumed health effect
Developmental 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.

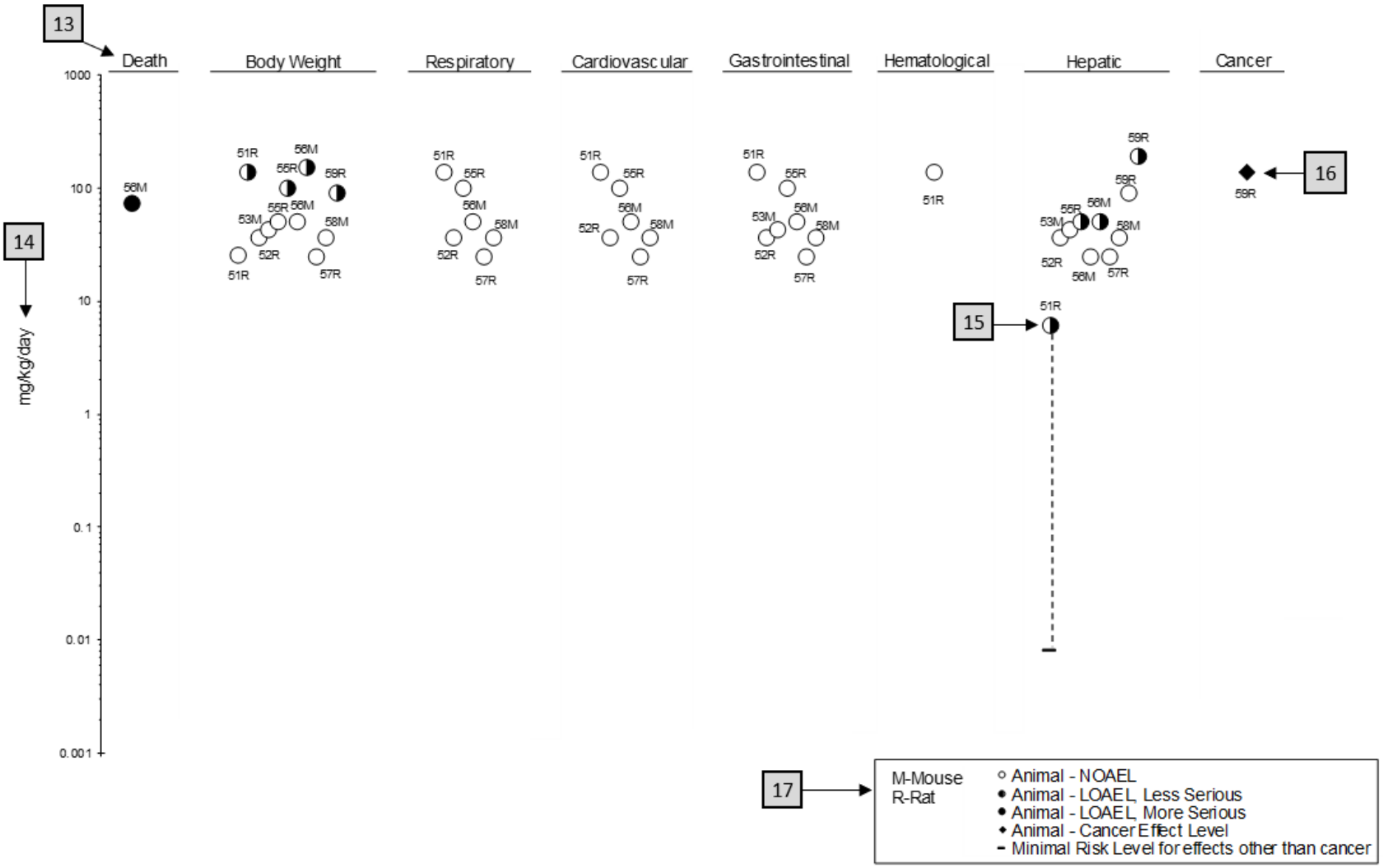
(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
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									
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).
[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).

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:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/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://www.atsdr.cdc.gov/toxfaqs/Index.asp).

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, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • 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 http://pehsu.net/findhelp.html.

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 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 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 dose 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 dose, 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.

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
AP	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 Substance 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	lactic 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 level/limit
REL-C	recommended exposure level-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