Toxicological Profile for Chlorophenols

Draft for Public Comment

July 2021

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FOREWORD

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

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

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

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 and the associated acute, intermediate, and chronic health effects;

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

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

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

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

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S102-1
Atlanta, Georgia 30329-4027

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

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

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

Christopher M. Reh, Ph.D.
Associate Director
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

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Date	Description
July 2021	Draft for public comment toxicological profile released
July 1999	Final toxicological profile released

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Malcolm Williams, D.V.M., Ph.D. (Lead)

ATSDR, Office of Innovation and Analytics, Toxicology Section, Atlanta, GA

Heather Carlson-Lynch, M.S., D.A.B.T.
Claire Heit, Ph.D.
Mario Citra, Ph.D.
SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:

Includes ATSDR; National Center for Environmental Health (NCEH); National Institute for Occupational Safety and Health (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

Additional reviews for science and/or policy:

ATSDR, Office of Community Health and Hazard Assessment; ATSDR, Office of Capacity Development and Applied Prevention Science; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice; EPA, Office of Water.

PEER REVIEWERS

1. Matt Simcik, Ph.D.; Professor, Division of Environmental Health Sciences; School of Public Health; University of Minnesota; Minneapolis, Minnesota

2. Ghulam Ahmad Shakeel Ansari, Ph.D.; Professor, Department of Pathology; The University of Texas Medical Branch; Galveston, Texas

3. Russell C. Cattley; Tyler & Frances Young Professor, V.M.D., Ph.D., DACVP; Head, Department of Pathobiology; College of Veterinary Medicine; Auburn University, Alabama

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.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Chlorophenols are a group of chemicals in which hydrogens are replaced by chlorines (between one and five) on phenol. Phenol is an aromatic compound derived from benzene, the simplest aromatic hydrocarbon, by adding a hydroxy group to a carbon to replace a hydrogen. There are five basic types of chlorophenols: mono[one]chlorophenols, di[two]chlorophenols, tri[three]chlorophenols, tetra[four]chlorophenols, and penta[five]chlorophenol. In all, there are 19 different chlorophenols. Pentachlorophenol is addressed in a separate Toxicological Profile. The 13 chlorophenols listed below are discussed in this document.

Compound	Abbreviation	Chemical Abstracts Service (CAS) Registry Number
2-Chlorophenol	2-CP	95-57-8
4-Chlorophenol	4-CP	106-48-9
2,3-Dichlorophenol	2,3-DCP	576-24-9
2,4-Dichlorophenol	2,4-DCP	120-83-2
2,5-Dichlorophenol	2,5-DCP	583-78-8
3,4-Dichlorophenol	3,4-DCP	95-77-2
3,5-Dichlorophenol	3,5-DCP	591-35-5
2,3,4-Trichlorophenol	2,3,4-TCP	15950-66-0
2,4,5-Trichlorophenol	2,4,5-TCP	95-95-4
2,4,6-Trichlorophenol	2,4,6-TCP	88-06-2
2,3,4,5-Tetrachlorophenol	2,3,4,5-TeCP	4901-51-3
2,3,4,6-Tetrachlorophenol	2,3,4,6-TeCP	58-90-2
2,3,5,6-Tetrachlorophenol	2,3,5,6-TeCP	935-95-5

All of the chlorophenols discussed in this profile are solids at room temperature except 2-CP, which is a liquid at room temperature. Chlorophenols are used in the production of agricultural chemicals, pharmaceuticals, biocides, and dyes. Upon release to the environment, the fate and transport of chlorophenols is dependent upon the pH of the medium in which they are released. Under acidic conditions, these compounds tend to volatilize and adsorb to soil surfaces, while under neutral to alkaline conditions, volatilization from water and moist soils decrease and mobility in soils increase.

Chlorophenols, especially those with more chlorine atoms and certain chlorine positions, are resistant to biodegradation and are thus persistent (some may remain in soil for several years) in the environment.

Chlorophenols have been detected in all environmental media, although detections may vary by compound. Several chlorophenols occur frequently in the urine of humans without known exposures; however, urinary chlorophenols may occur as metabolites of other compounds such as chlorinated benzenes. Occupational exposure to chlorophenols may occur through inhalation or dermal contact in facilities that produce or use these compounds. In the general population, oral exposure to contaminated food and water or inhalation of air are the main routes of exposure to chlorophenols. Water contaminated through chlorination is most likely to contain lower chlorinated phenols, while higher chlorinated phenols are more likely to be found in fish.

1.2 SUMMARY OF HEALTH EFFECTS

The preponderance of studies examining health effects of the chlorophenols discussed herein are oral studies in animals. There are a few case reports of human exposure; available epidemiological studies are limited to populations exposed occupationally, with co-exposures to other compounds, or studies in the general population using urinary chlorophenol concentrations that may reflect exposure to chlorophenols or metabolites of other compounds (e.g., chlorinated benzenes). A total of 67 animal experiments examining health effects of subject chlorophenol compounds in animals exposed orally were identified. There were only 17 dermal and 1 inhalation experiments of animals exposed to chlorophenols discussed in this profile.

Several sensitive health endpoints observed in laboratory animals exposed to chlorophenols after oral exposure were effects on the liver, central nervous system, body weight, immune system, and reproductive function, as shown in Figures 1-1 (2-CP), 1-2 (4-CP), 1-3 (2,4-DCP), 1-4 (2,4,5-TCP), 1-5 (2,4,6-TCP), 1-6 (2,3,4,6-TeCP), and 1-7 (other chlorophenols). Effects on body weight, the liver, and reproductive function were seen after exposure to all of the subject chlorophenols tested for these effects. Central nervous system effects, including lethargy, tremors, convulsions, and/or central nervous system depression, have been observed in humans exposed to 2,4-DCP and in animals exposed orally or dermally to 4-CP, 2,4-DCP, and tetrachlorophenols. Neurological effects reported in animals exposed orally are shown in the figures. Of the three chlorophenols tested for sensitive measures of immunotoxicity (2-CP, 2,4-DCP, and 2,4,6-TCP), only 2,4-DCP showed evidence of adverse effects.

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

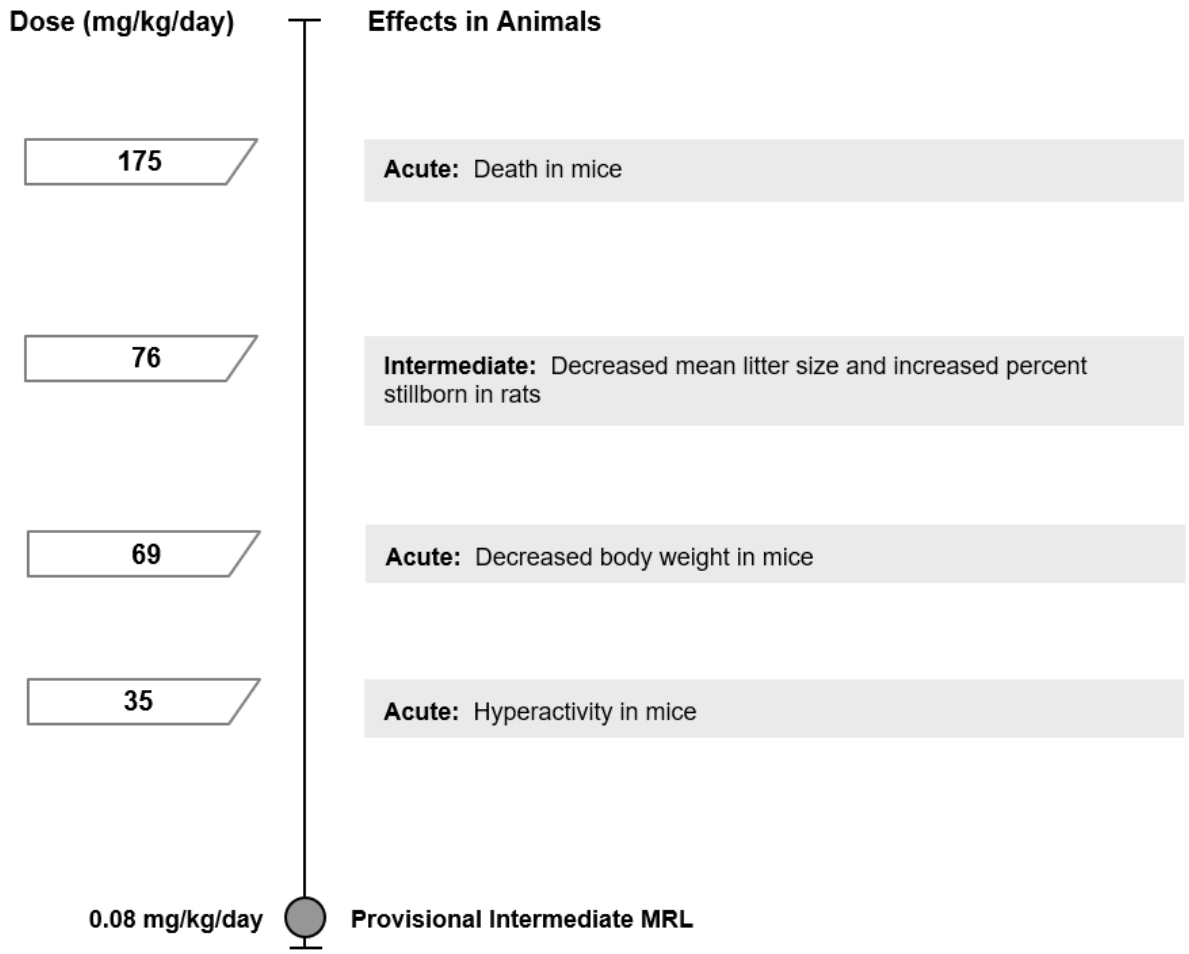


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 4-Chlorophenol

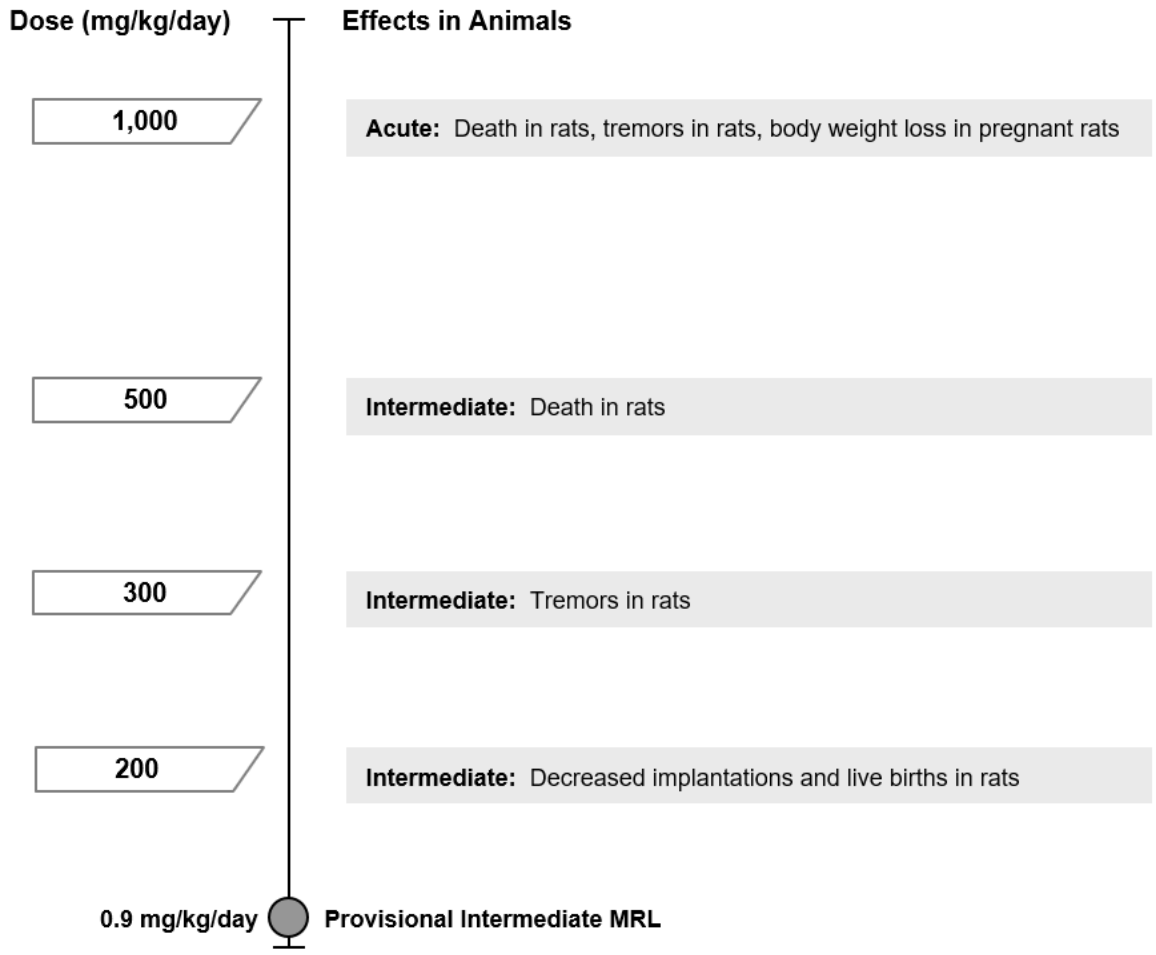


Figure 1-3. Health Effects Found in Animals Following Oral Exposure to 2,4-Dichlorophenol

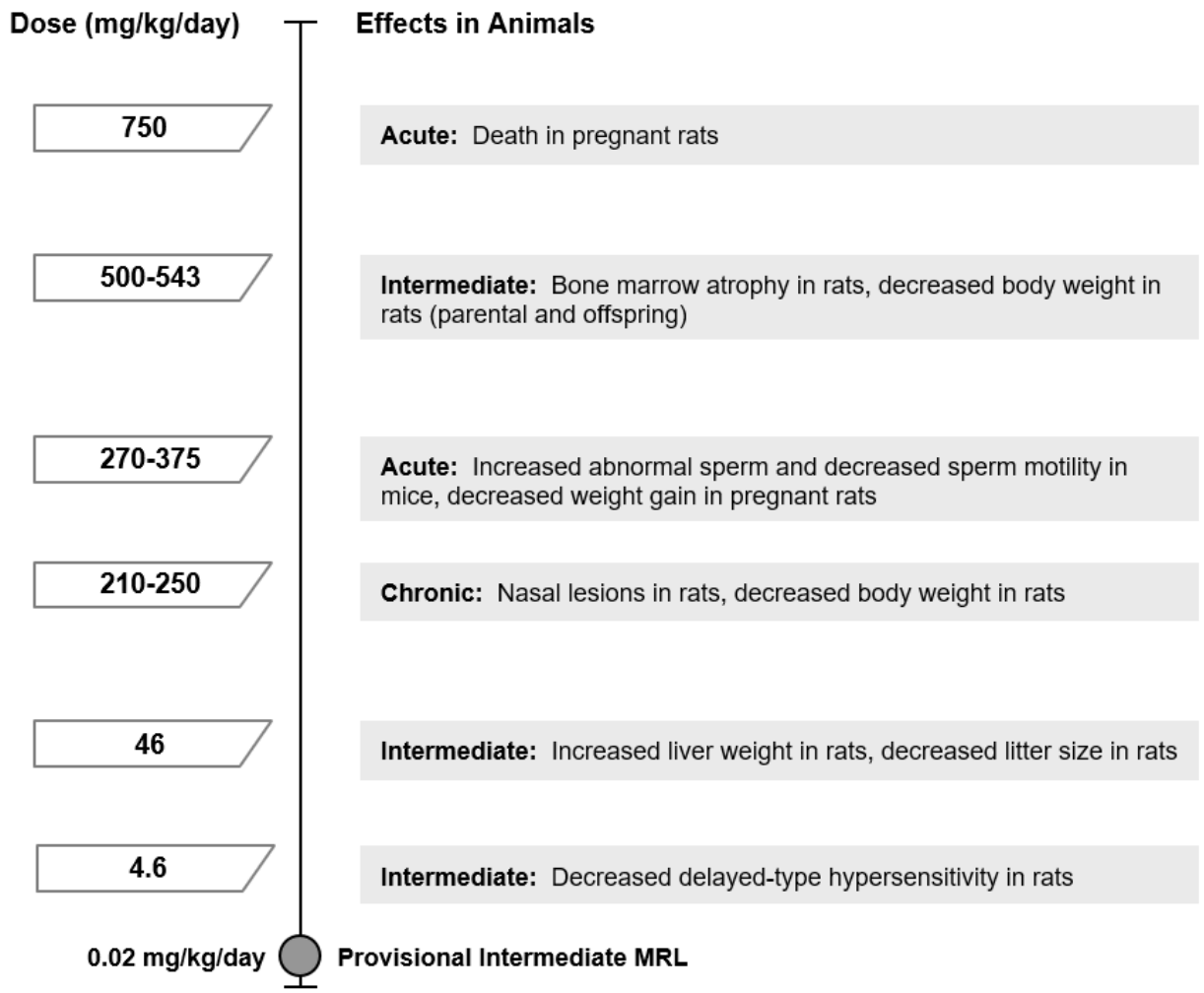


Figure 1-4. Health Effects Found in Animals Following Oral Exposure to 2,4,5-Trichlorophenol

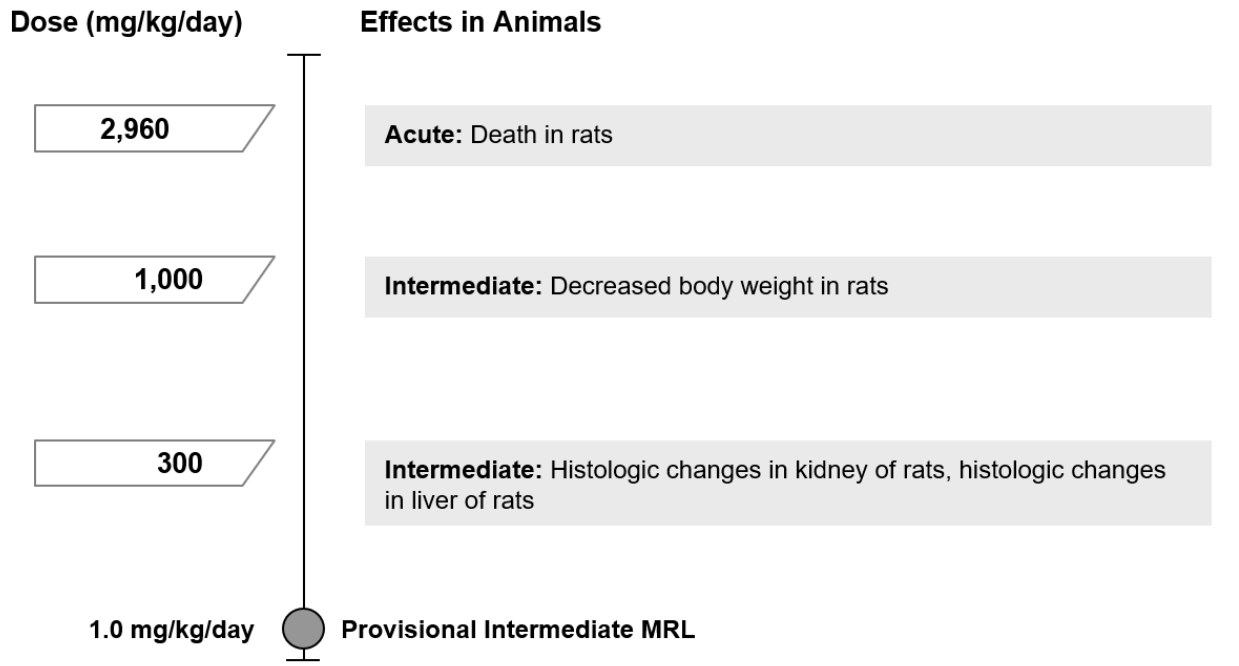


Figure 1-5. Health Effects Found in Animals Following Oral Exposure to 2,4,6-Trichlorophenol

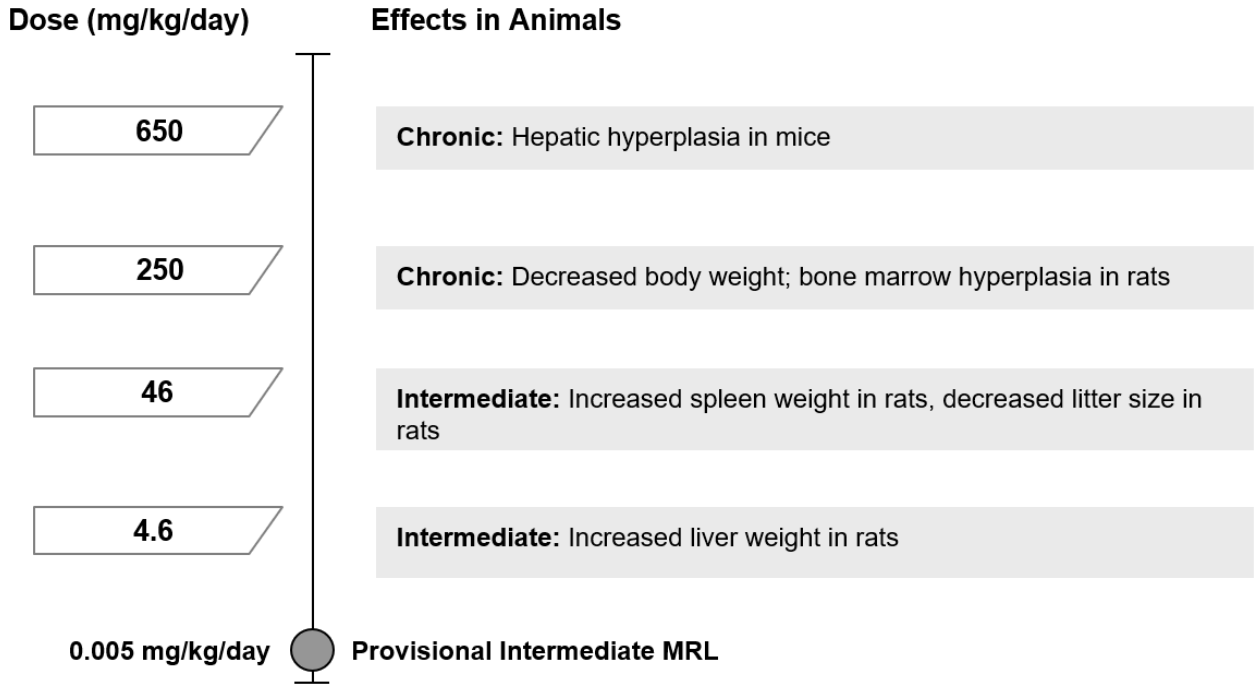


Figure 1-6. Health Effects Found in Animals Following Oral Exposure to 2,3,4,6-Tetrachlorophenol

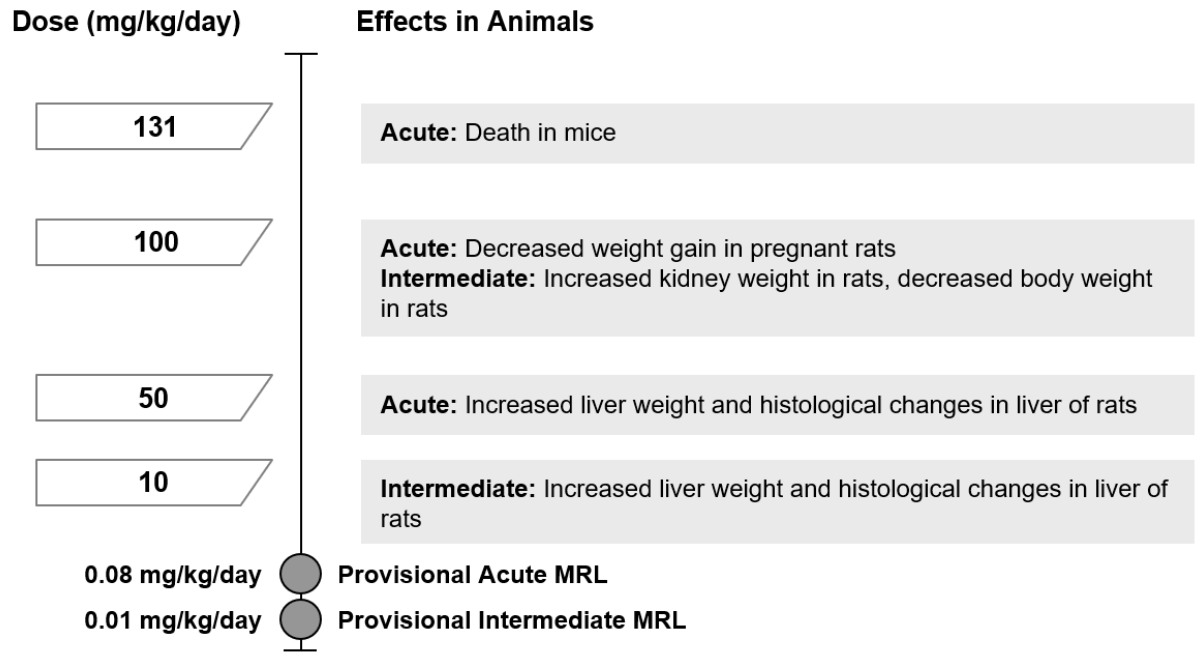
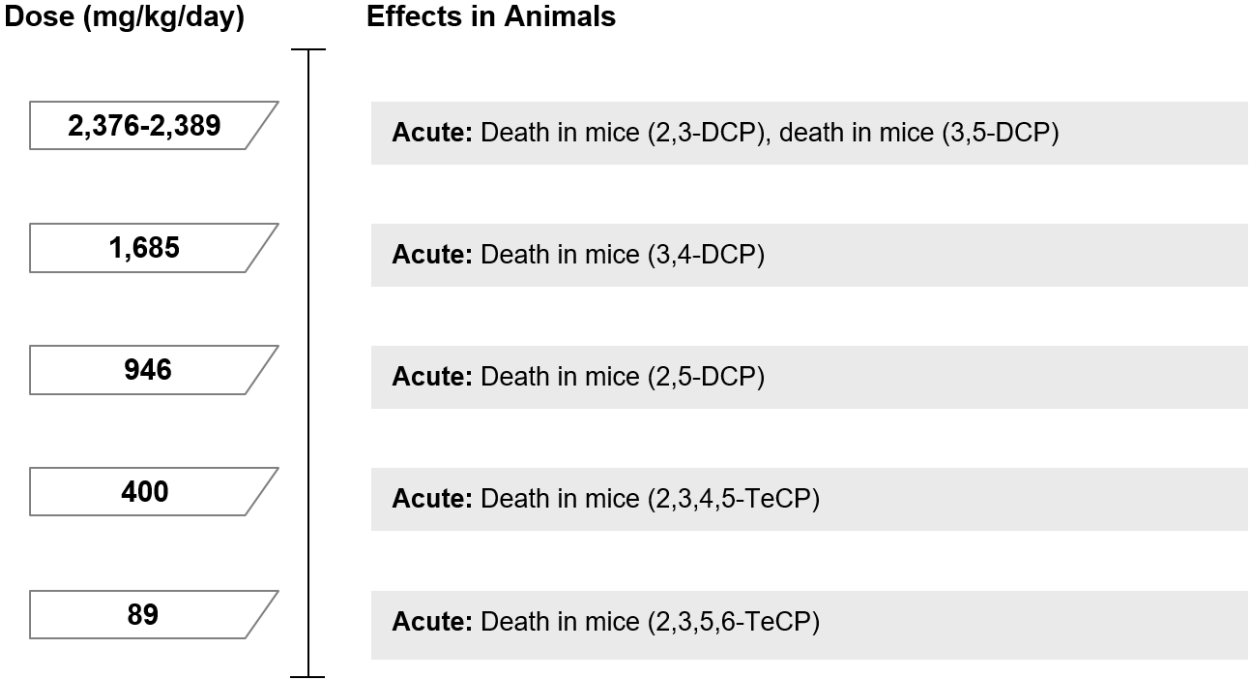


Figure 1-7. Health Effects Found in Animals Following Oral Exposure to Other Chlorophenols



Hepatic Effects. The liver is a well-established target of chlorophenol toxicity in laboratory animals. Hepatic effects including clinical chemistry changes, increased liver weight, hepatocellular hypertrophy, and necrosis have been observed in rats or mice after oral exposure to 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP (Aydin et al. 2009; Bercz et al. 1990; BSRC 2011; Dodd et al. 2012; Exon and Koller 1985; Exon et al. 1984; Hasegawa et al. 2005; Kobayashi et al. 1972; McCollister et al. 1961; NCI 1979; NTP 1989).

Reproductive Effects. Studies of reproductive effects in humans exposed to chlorophenols are limited to assessments using urinary levels of di- or trichlorophenols to assess exposure, and these are not considered to be specific, reliable biomarkers of chlorophenol exposure. In animals exposed to chlorophenols by oral administration, decreases in implantations, litter size, and/or live births per litter have been reported after intermediate-duration exposure to 4-CP (200 mg/kg/day) (BSRC 2011), 2,4-DCP (46 mg/kg/day) (Exon and Koller 1985; Exon et al. 1984), and 2,4,6-TCP (46 mg/kg/day) (Exon and Koller 1985). Acute-duration exposure to 2,4-DCP in mice induced adverse effects on the male reproductive system (including increases in the percentage of abnormal sperm and decreased sperm motility) (Aydin et al. 2009).

Neurological Effects. Neurological effects have been identified in studies of several chlorophenols after oral or dermal exposure. Observed effects include lethargy, tremors, convulsions, and/or central nervous system depression in humans exposed to 2,4-DCP (Kintz et al. 1992) and in animals exposed orally or dermally to 4-CP and 2,4-DCP (Carreon et al. 1980a, 1980b; Hasegawa et al. 2005; Monsanto 1976; NTP 1989; Phornchirasilp et al. 1989b; Rhone-Poulenc 1991; Spencer and Williams 1950) or to 2,3,4,5-, 2,3,4,6-, or 2,3,5,6-TeCP via single dermal application (Shen et al. 1983).

Body Weight Effects. Studies of animals have shown decreases in body weight or body weight gain after acute-, intermediate-, and/or chronic-duration oral exposures to 2-CP (Borzelleca et al. 1985a), 4-CP (Kavlock 1990), 2,4-DCP (Aoyama et al. 2005; NTP 1989; Rodwell et al. 1989), 2,4,5-TCP (McCollister et al. 1961), 2,4,6-TCP (NCI 1979), and 2,3,4,6-TeCP (Dodd et al. 2012; EPA1987). Studies of the remaining chlorophenols discussed in this document are not adequate to evaluate effects on body weight.

Immune System Effects. 2,4-DCP is the only chlorophenol that has shown effects on immune system function; 2-CP and 2,4,6-TCP, both tested for the same endpoints by the same investigators, did not show evidence of immunotoxicity. Rats exposed to a low dose of 2,4-DCP (4.6 mg/kg/day) from conception through weaning (via maternal exposure) and for an additional 12 weeks in drinking water

exhibited a decrease in delayed-type hypersensitivity response; higher doses induced increased serum antibodies to keyhole limpet hemocyanin (Exon and Koller 1985; Exon et al. 1984).

Cancer. Case-control studies and an ecological study have suggested potential associations between chlorophenol exposure and non-Hodgkin's lymphoma (NHL), soft tissue sarcoma, and nasal cancers. However, in the case-control studies (Garabedian et al. 1999; Hoppin et al. 1998; Mirabelli et al. 2000; Richardson et al. 2008), the subjects may have been exposed to pentachlorophenol, and in the ecological study (Lampi et al. 2008), the water supply to which the community was exposed was contaminated with pentachlorophenol in addition to other chlorophenols. Therefore, the observed associations could be attributable to pentachlorophenol exposure in addition to, or instead of, the chlorophenols addressed in this profile. Other epidemiological studies (Eriksson et al. 1981, 1990; Hardell and Eriksson 1988; Hardell et al. 1981, 1995; Hooiveld et al. 1998; Kogevinas et al. 1997; Lynge 1985; Saracci et al. 1991; Zendehel et al. 2014) evaluated links between cancer and occupational exposures during the manufacture or use of phenoxy herbicides. In these settings, workers may have been exposed to pentachlorophenol, phenoxy herbicide compounds, and polychlorinated dioxin and furan contaminants in addition to chlorophenols discussed in this profile. Most of the studies that evaluated subgroups exposed only to chlorophenols other than pentachlorophenol (e.g., Lynge 1985; Saracci et al. 1991) did not show any association.

In well-conducted chronic cancer bioassays of chlorophenol compounds, 2,4-DCP did not induce an increase in cancer incidence in rats and mice treated with 2,4-DCP in the diet at doses up to 440 mg/kg/day (rats) and 1,300 mg/kg/day (mice) (NTP 1989), while rats and mice exposed to 2,4,6-TCP in the diet exhibited increased incidences of leukemia and liver cancer (respectively) at doses of 250 mg/kg/day (rats) and 650 mg/kg/day (mice) (NCI 1979). Other chlorophenols discussed in this profile have not been adequately tested for potential carcinogenicity.

The U.S. Environmental Protection Agency (EPA) (IRIS 1990) has classified 2,4,6-TCP in Group B2 (probably carcinogenic to humans based on sufficient evidence in animal bioassays). Similarly, the International Agency for Research on Cancer (IARC 2019) has assigned 2,4,6-TCP to Group 2B (possibly carcinogenic to humans) based on sufficient evidence for its carcinogenicity in experimental animals. Finally, the National Toxicology Program (NTP 2016) Report on Carcinogens has concluded that 2,4,6-TCP is "reasonably anticipated to be a human carcinogen," also based on sufficient evidence in animals.

1.3 MINIMAL RISK LEVELS (MRLs)

No MRLs for inhalation exposure to any of the subject chlorophenols were derived because the data were not adequate.

The toxicity data assessing oral exposure were considered adequate to derive provisional acute-duration oral MRLs for 2,3,4,6-TeCP and provisional intermediate-duration oral MRLs for 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP. There were not adequate data to derive provisional chronic oral MRLs for any of the subject chlorophenols. For the remaining chlorophenols (2,3-, 2,5-, 3,4-, and 3,5-DCP; 2,3,4-TCP; and 2,3,4,5- and 2,3,5,6-TeCP), the data were insufficient to support derivation of oral MRLs for any exposure duration.

As Figures 1-8 (2-CP), 1-9 (4-CP), 1-10 (2,4-DCP), 1-11 (2,4,5-TCP), 1-12 (2,4,6-TCP), and 1-13 (2,3,4,6-TeCP) show, the available oral data for chlorophenols suggest that the liver, central nervous system, reproductive system, body weight, and immune system effects are the most sensitive targets of toxicity in laboratory animals. Because the available data for each of the individual chlorophenols are quite limited, the lowest LOAEL for a given health endpoint and duration may vary (i.e., there may be a lower neurological LOAEL for acute-duration exposure than for intermediate-duration exposure) depending on the species tested, exposure regimen, and endpoints evaluated in each study.

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

Figure 1-8. Summary of Sensitive Targets of 2-Chlorophenol – Oral

The central nervous system, reproductive system, and body weight are the most sensitive targets of 2-chlorophenol oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

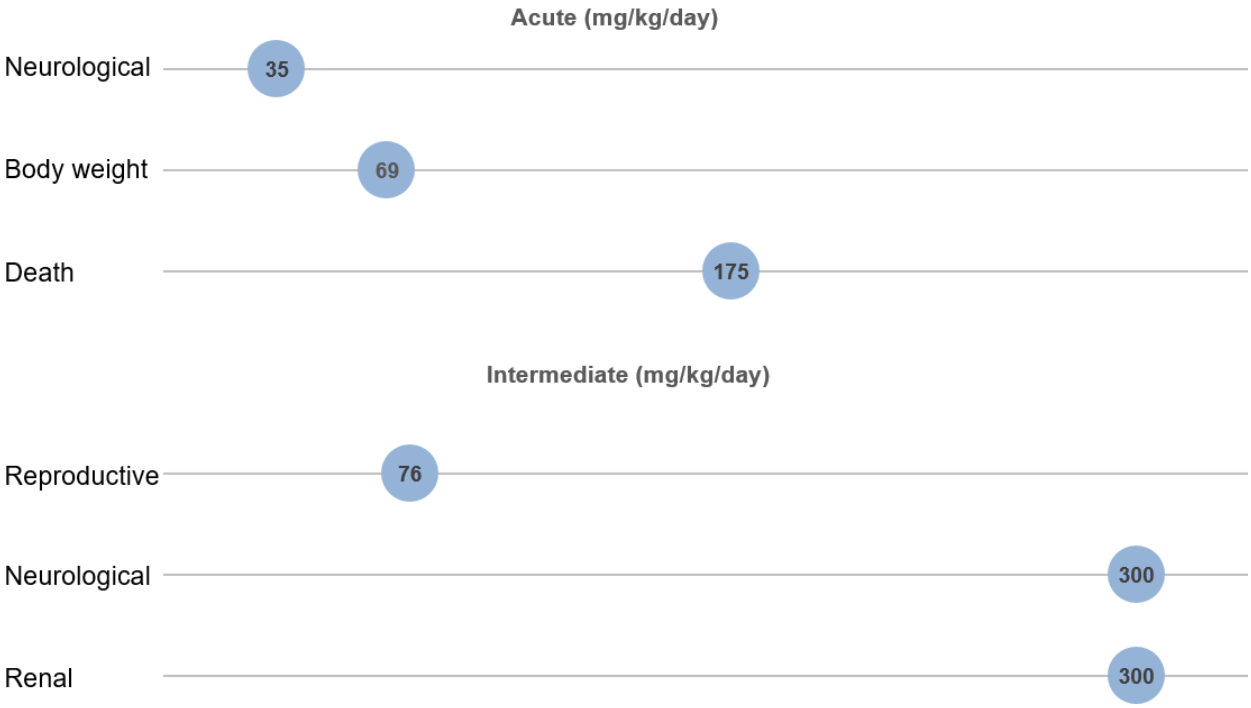


Figure 1-9. Summary of Sensitive Targets of 4-Chlorophenol – Oral

The reproductive and central nervous systems are the most sensitive targets of 4-chlorophenol oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

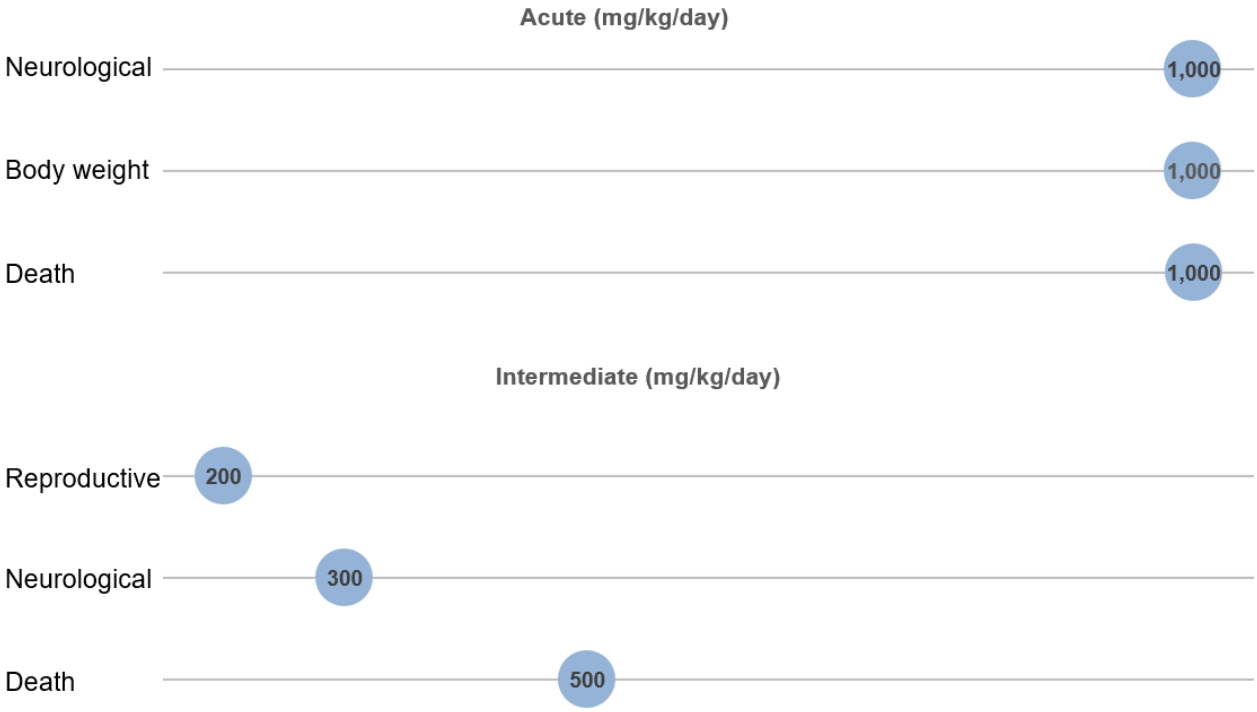


Figure 1-10. Summary of Sensitive Targets of 2,4-Dichlorophenol – Oral

The immune and reproductive systems and liver are the most sensitive targets of 2,4-dichlorophenol oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

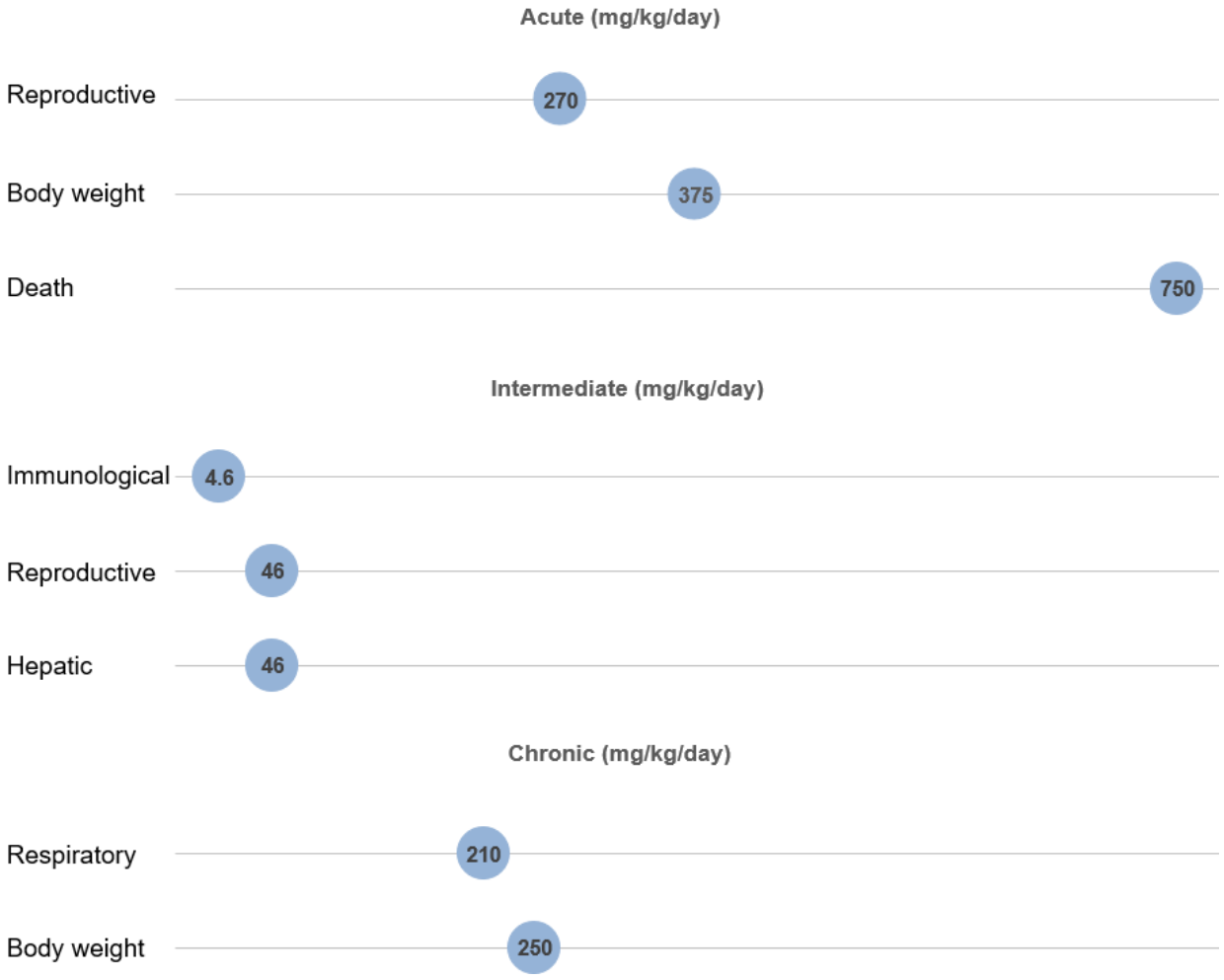


Figure 1-11. Summary of Sensitive Targets of 2,4,5-Trichlorophenol – Oral

The liver and kidney are the most sensitive targets of 2,4,5-trichlorophenol oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

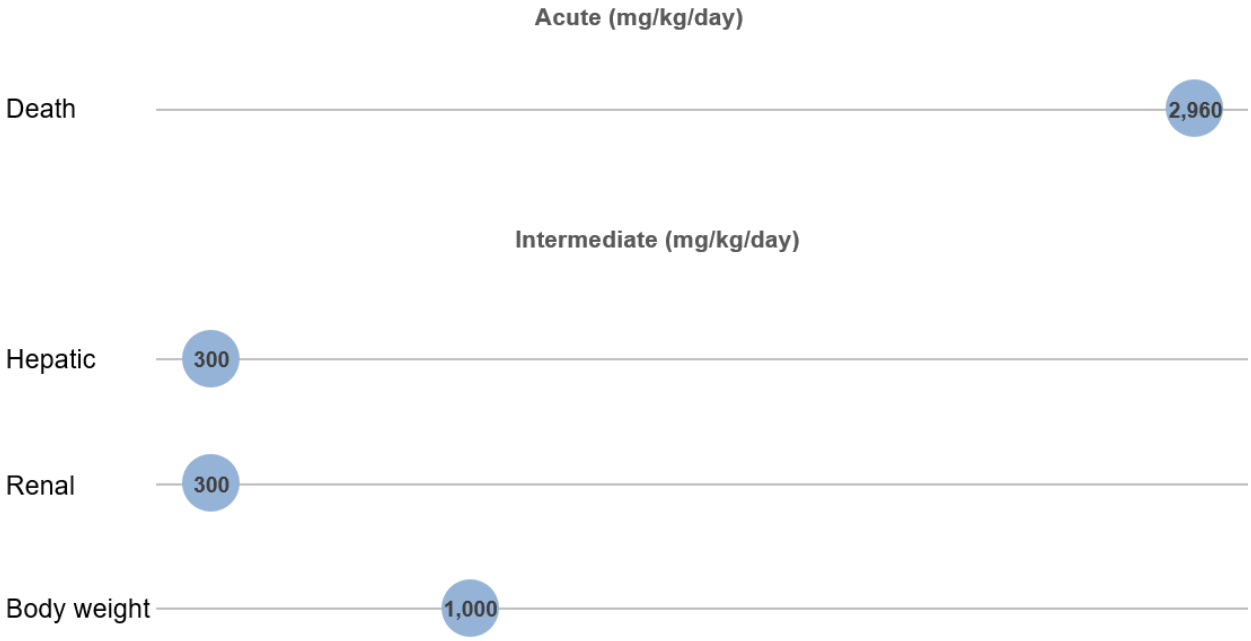


Figure 1-12. Summary of Sensitive Targets of 2,4,6-Trichlorophenol – Oral

The liver, reproductive system, and immune system are the most sensitive targets of 2,4,6-trichlorophenol oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

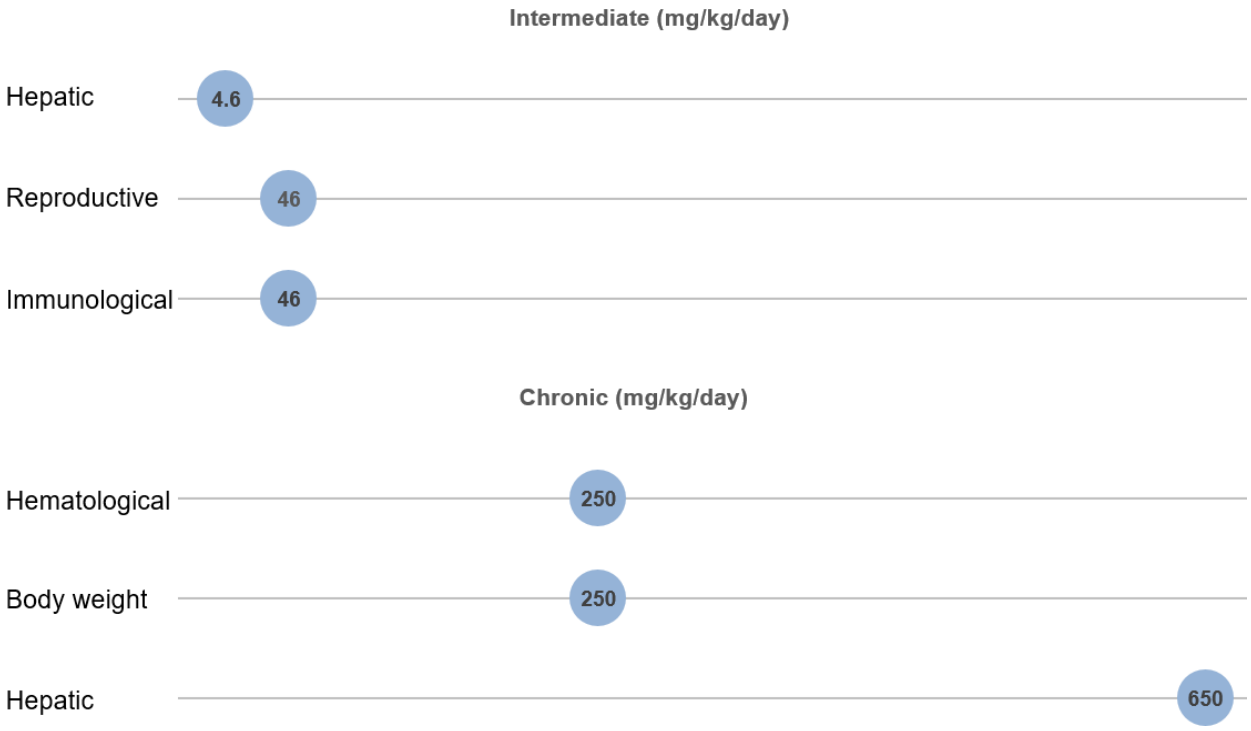


Figure 1-13. Summary of Sensitive Targets of 2,3,4,6-Tetrachlorophenol – Oral

The liver, kidneys, and body weight are the most sensitive targets of 2,3,4,6-tetrachlorophenol oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

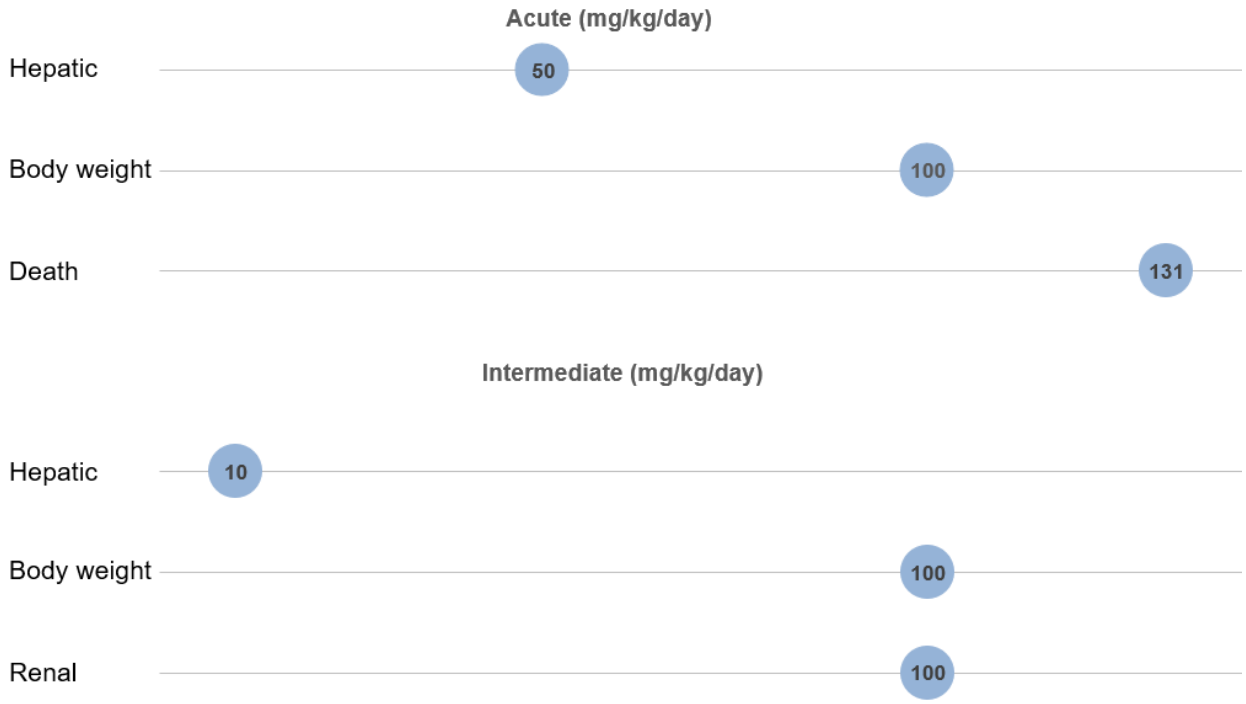


Table 1-1. Provisional Minimal Risk Levels (MRLs) for Chlorophenols[a]

Exposure duration	Provisional MRL	Critical effect	POD/HEC	Uncertainty and modifying factors	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)					
2-Chlorophenol					
Acute	Insufficient data for MRL derivation				
Intermediate	0.08	Decreased litter size; increased percentage of stillborn pups	NOAEL: 7.6	UF: 100	Exon and Koller 1982, 1983a, 1983b, 1985
Chronic	Insufficient data for MRL derivation				
4-Chlorophenol					
Acute	Insufficient data for MRL derivation				
Intermediate	0.9	Decreased number live pups/litter	$BMDL_{1SD}$: 85.77	UF: 100	BSRC 2011
Chronic	Insufficient data for MRL derivation				
2,4-Dichlorophenol					
Acute	Insufficient data for MRL derivation				
Intermediate	0.02	Decreased delayed-type hypersensitivity	$BMDL_{1SD}$: 2.07	UF: 100	Exon and Koller 1985; Exon et al. 1984
Chronic	Insufficient data for MRL derivation				
2,4,5-Trichlorophenol					
Acute	Insufficient data for MRL derivation				
Intermediate	1.0	Degenerative changes in liver and kidney	NOAEL: 100	UF: 100	McCollister et al. 1961
Chronic	Insufficient data for MRL derivation				
2,4,6-Trichlorophenol					
Acute	Insufficient data for MRL derivation				
Intermediate	0.005	Increased liver weight	$BMDL_{1SD}$: 0.46	UF: 100	Exon and Koller 1985
Chronic	Insufficient data for MRL derivation				

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

2,3,4,6-Tetrachlorophenol					
Acute	0.08	Increased liver weight; centrilobular hypertrophy and minimal necrosis	$BMDL_{1SD}$: 8.45	UF: 100	Dodd et al. 2012
Intermediate	0.01	Increased liver weight; centrilobular vacuolation and hypertrophy	$BMDL_{10}$: 1.02	UF: 100	Dodd et al. 2012
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information. Insufficient data were available to derive oral MRLs for 2,3-dichlorophenol, 2,5-dichlorophenol, 3,4-dichlorophenol, 3,5-dichlorophenol, 2,3,4-trichlorophenol, 2,3,4,5-tetrachlorophenol, or 2,3,5,6-tetrachlorophenol.

BMDL = benchmark dose, lower confidence limit; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; SD = standard deviation; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of chlorophenols. 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.

This Toxicological Profile addresses the health effects of the 13 chlorophenols listed below.

Compound	Abbreviation	CAS Registry Number
2-Chlorophenol	2-CP	95-57-8
4-Chlorophenol	4-CP	106-48-9
2,3-Dichlorophenol	2,3-DCP	576-24-9
2,4-Dichlorophenol	2,4-DCP	120-83-2
2,5-Dichlorophenol	2,5-DCP	583-78-8
3,4-Dichlorophenol	3,4-DCP	95-77-2
3,5-Dichlorophenol	3,5-DCP	591-35-5
2,3,4-Trichlorophenol	2,3,4-TCP	15950-66-0
2,4,5-Trichlorophenol	2,4,5-TCP	95-95-4
2,4,6-Trichlorophenol	2,4,6-TCP	88-06-2
2,3,4,5-Tetrachlorophenol	2,3,4,5-TeCP	4901-51-3
2,3,4,6-Tetrachlorophenol	2,3,4,6-TeCP	58-90-2
2,3,5,6-Tetrachlorophenol	2,3,5,6-TeCP	935-95-5

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. Figures 2-1 (2-CP), 2-2 (4-CP), 2-3 (2,4-DCP), 2-4, (2,4,5-TCP), 2-5 (2,4,6-CP), 2-6 (2,3,4,6-TeCP), and 2-7 (other chlorophenols) 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 chlorophenols, but may not be inclusive of the entire body of literature.

Animal inhalation studies are presented in Table 2-1 and Figure 2-8. Animal oral studies are presented in Table 2-2 and Figure 2-9 (2-CP), Table 2-3 and Figure 2-10 (4-CP), Table 2-4 and Figure 2-11 (2,4-DCP), Table 2-5 and Figure 2-12 (2,4,5-TCP), Table 2-6 and Figure 2-13 (2,4,6-TCP), Table 2-7 and Figure 2-14 (2,3,4,6-TeCP), and Table 2-8 and Figure 2-15 (other chlorophenols). Animal dermal studies are presented in Table 2-9.

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 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 2,4,6-TCP are indicated in Table 2-6 and Figure 2-13.

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

The discussion of the available data for health effects in this chapter begins with an overview of the health effects and comparisons across the different chlorophenols (except pentachlorophenol, which is addressed in a separate toxicological profile). Human studies, which are generally not specific to an individual chlorophenol, are discussed next. Finally, compound-specific subsections describe the animal data; these subsections are provided in order from monochlorophenols through di-, tri-, and tetrachlorophenols (in the order shown in the list above). If there are no data for a given chlorophenol, there is no subsection for that compound. Apart from acute lethality data in animals, no information was located on the health effects of the following chlorophenols in humans or animals exposed by any route: 2,3-DCP, 3,4-DCP, and 2,3,4-TCP. Toxicity data on 2,3,4,5- and 2,4,5,6-TeCP were limited to acute oral lethality and acute dermal toxicity studies.

A total of 44 human studies of chlorophenols were identified in the literature searches. Only two of these, case reports of dermal exposure to 2,4-DCP, are included in the study counts in the figures. The remaining studies of humans exposed to chlorophenols largely fell into two categories: (1) studies of workers exposed to mixtures of chlorophenols, chlorophenoxy compounds and other herbicides, and, often, tetrachlorodibenzo-*p*-dioxin (TCDD); or (2) studies that use urinary chlorophenol concentrations in the general population, often from the National Health and Nutrition Examination Survey (NHANES), as a measure of exposure. Because of the co-exposures in studies of occupationally-exposed persons, it is typically not possible to attribute any observed effects to chlorophenols either as a group or individually. While studies using urinary concentrations to assess exposure often provide data on individual chlorophenols, the presence of these compounds in urine does not conclusively indicate exposure to chlorophenols, as they may occur in urine as metabolites of other compounds, including chlorobenzenes (Billi et al. 1985; Yoshida et al. 2002), hexachlorocyclohexanes (Engst et al. 1976; Koransky et al. 1975), lindane (Karapally et al. 1973), VC-13 (Shafik et al. 1973), 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (Hill et al. 1989), or higher chlorophenols (Renner and Mucke 1986). Further discussion of this issue is provided in Section 3.3.1 (Biomarkers of Exposure). Although the human studies of occupational exposure and studies that use urinary chlorophenol levels to assess exposure are not included in the study counts, these studies are discussed in this chapter as they provide some (albeit limited) information that is useful for hazard identification.

The results of human and animal studies suggest that the chlorophenols discussed in this profile induce effects on the liver, central nervous system, body weight, and reproductive function. In addition, kidney effects have been observed after exposure to 2,4,5-TCP and 2,3,4,6-TeCP, while 2,4-DCP has shown immune system effects.

- **Hepatic effects:** No human data are available. In animals exposed orally, hepatic effects including clinical chemistry changes, increased liver weight, hepatocellular hypertrophy, and necrosis have been observed in rats and mice exposed to 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP.

- **Reproductive effects:** No reliable human data are available. Animal studies of oral exposure have shown decreases in implantations, litter size, and/or live births per litter after exposure to 4-CP, 2,4-DCP, and 2,4,6-TCP. Adverse effects on the male reproductive system (increases in abnormal sperm and decreases in sperm motility) were seen in mice after oral exposure to 2,4-DCP.

- **Neurological effects:** A case report of human fatality after 2,4-DCP exposure reported that the victim had seizures prior to death. In animals exposed orally to 2- and 4-CP and 2,4-DCP or via dermal exposure to tetrachlorophenols, clinical signs of neurotoxicity including lethargy, tremors, convulsions, and/or central nervous system depression were observed. There were no human or animal studies examining sensitive measures of neurotoxicity.

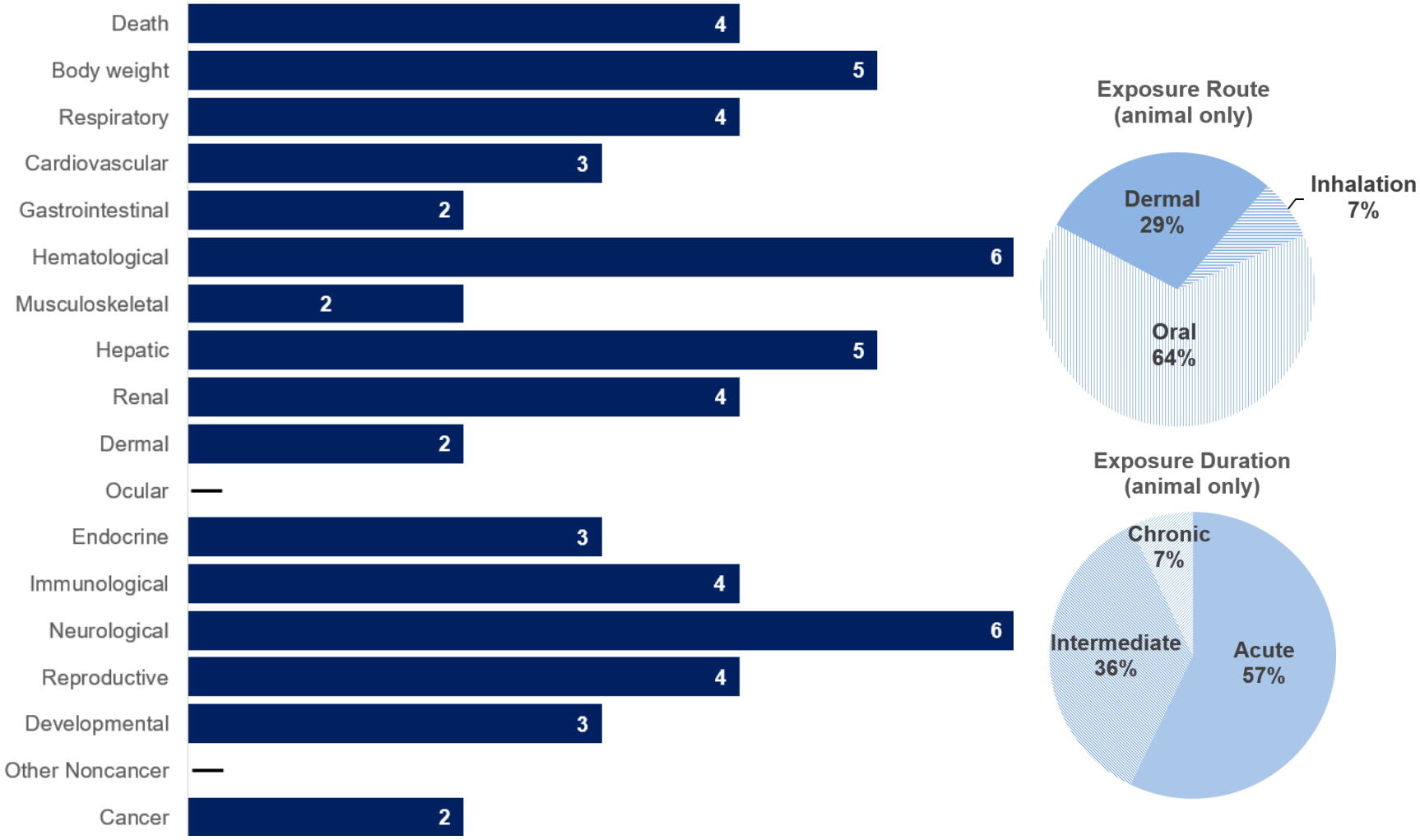
- **Body weight effects:** No human data are available. Body weight decreases or reductions in body weight gain were noted after acute-, intermediate-, and/or chronic-duration oral exposures to 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP.

- **Immunological effects:** No human data are available. The limited data from studies examining sensitive measures of immune system function show that 2,4-DCP decreases delayed-type hypersensitivity and increases antibody production, but 2-CP and 2,4,6-TCP did not induce similar effects.

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

Most studies examined the potential hematological, neurological, body weight, and hepatic effects of 2-chlorophenol

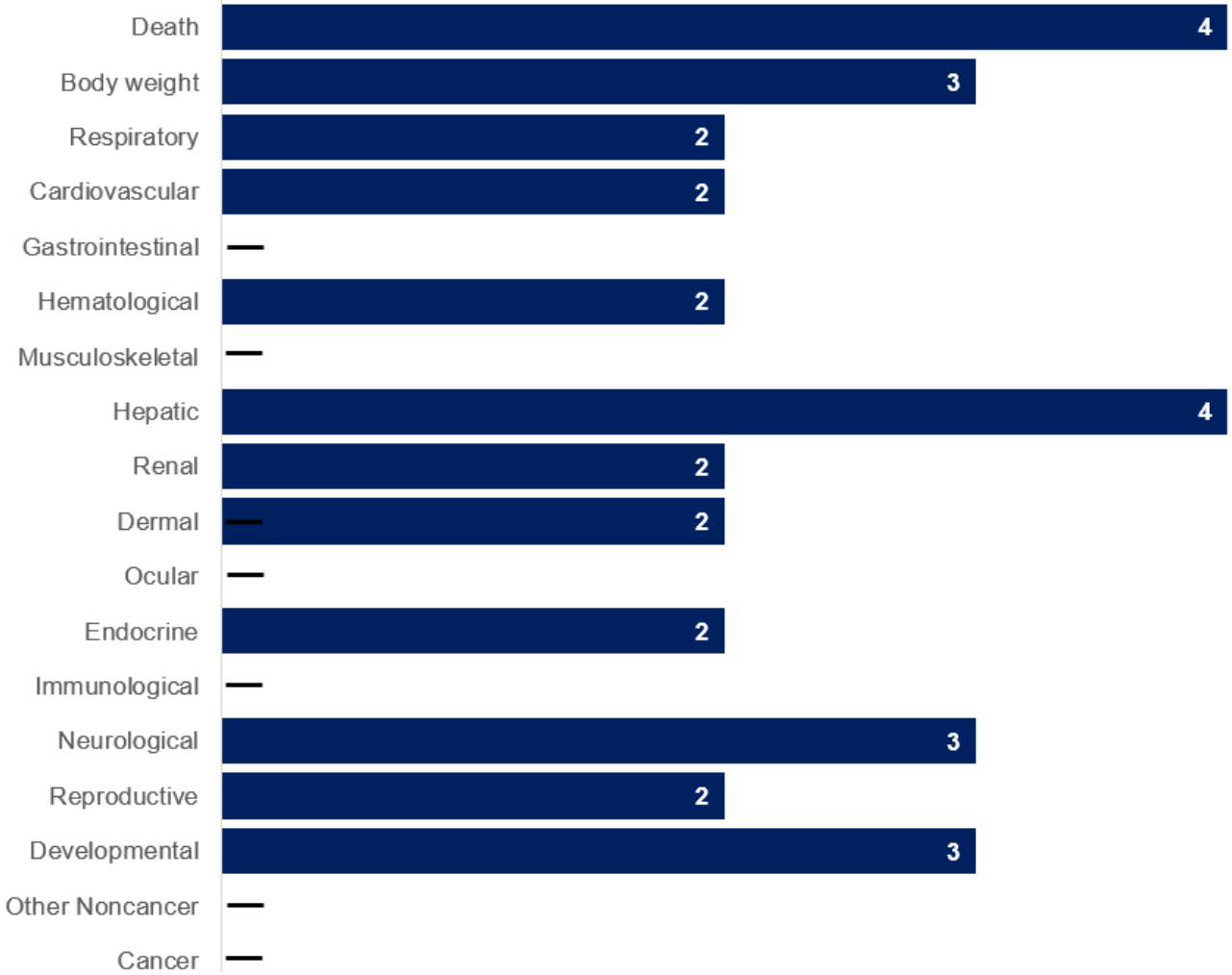
All studies pertaining specifically to 2-chlorophenol are in **animals** (counts represent studies examining endpoint)

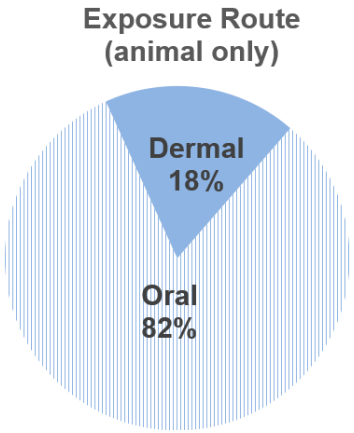


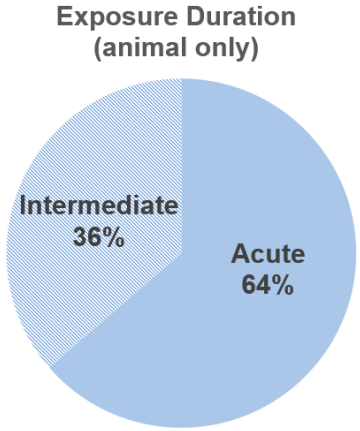
*Includes studies discussed in Chapter 2. A total of 14 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-2. Overview of the Number of Studies Examining 4-Chlorophenol Health Effects

Most studies examined the potential mortality and hepatic effects of 4-chlorophenol
All studies pertaining specifically to 4-chlorophenol are in animals (counts represent studies examining endpoint)





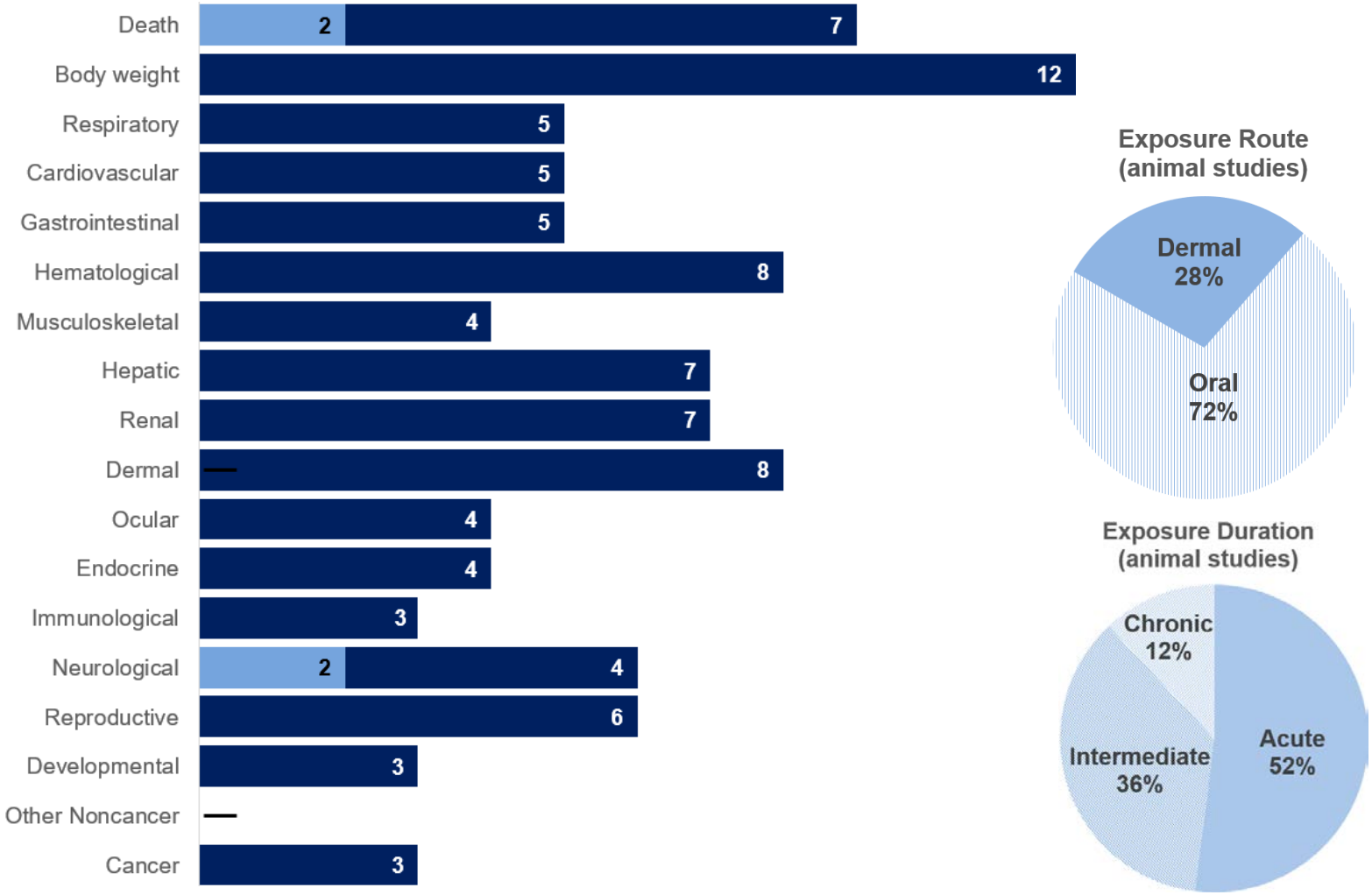


*Includes studies discussed in Chapter 2. A total of 11 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-3. Overview of the Number of Studies Examining 2,4-Dichlorophenol Health Effects

Most studies examined the potential mortality, body weight, hematological, and dermal effects of 2,4-dichlorophenol

Only 2 **human** studies examined 2,4-dichlorophenol health effects; the rest are in **animals** (counts represent studies examining endpoint)

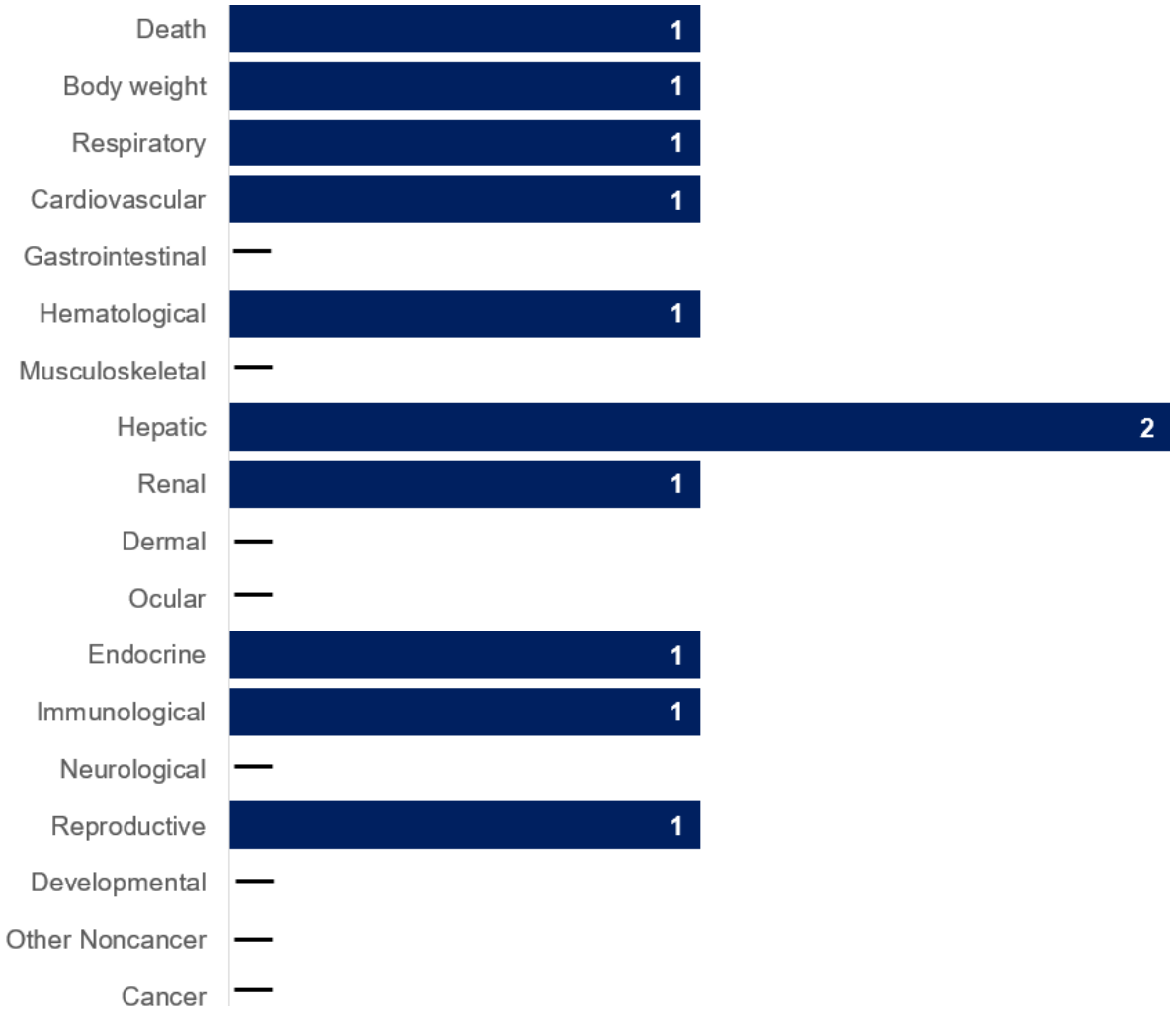


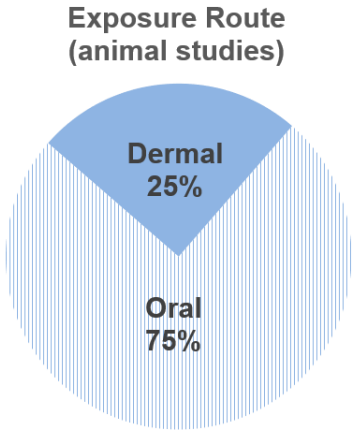
*Includes studies discussed in Chapter 2. A total of 23 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

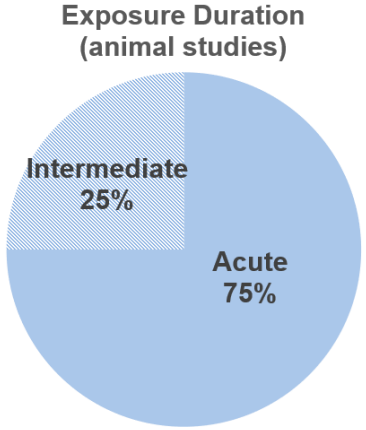
Figure 2-4. Overview of the Number of Studies Examining 2,4,5-Trichlorophenol Health Effects

Most studies examined the potential hepatic effects of 2,4,5-trichlorophenol

All studies pertaining specifically to 2,4,5-trichlorophenol are in **animals** (counts represent studies examining endpoint)



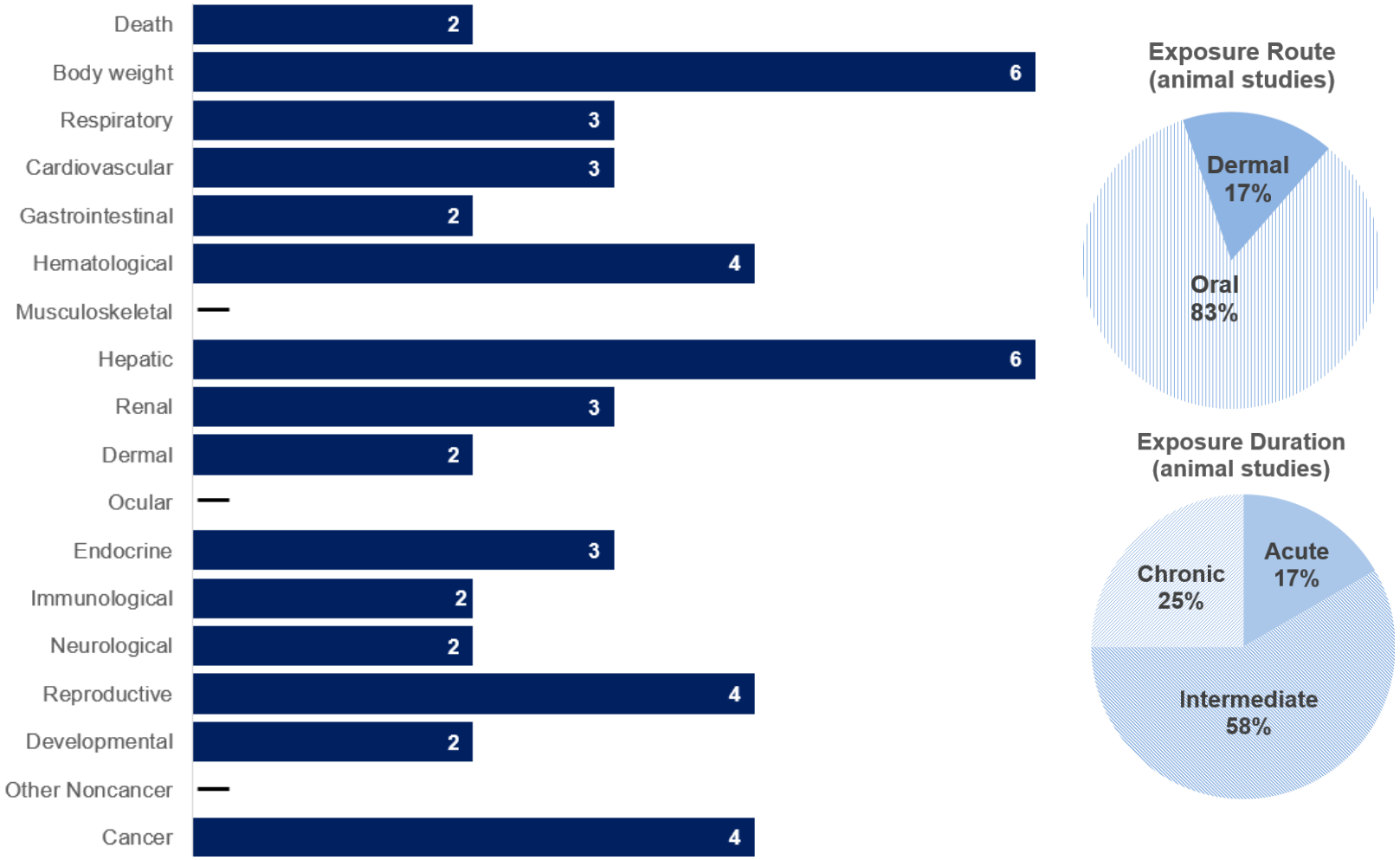




*Includes studies discussed in Chapter 2. A total of 4 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-5. Overview of the Number of Studies Examining 2,4,6-Trichlorophenol Health Effects

Most studies examined the potential body weight and hepatic effects of 2,4,6-trichlorophenol
All studies pertaining specifically to 2,4,6-trichlorophenol are in **animals** (counts represent studies examining endpoint)

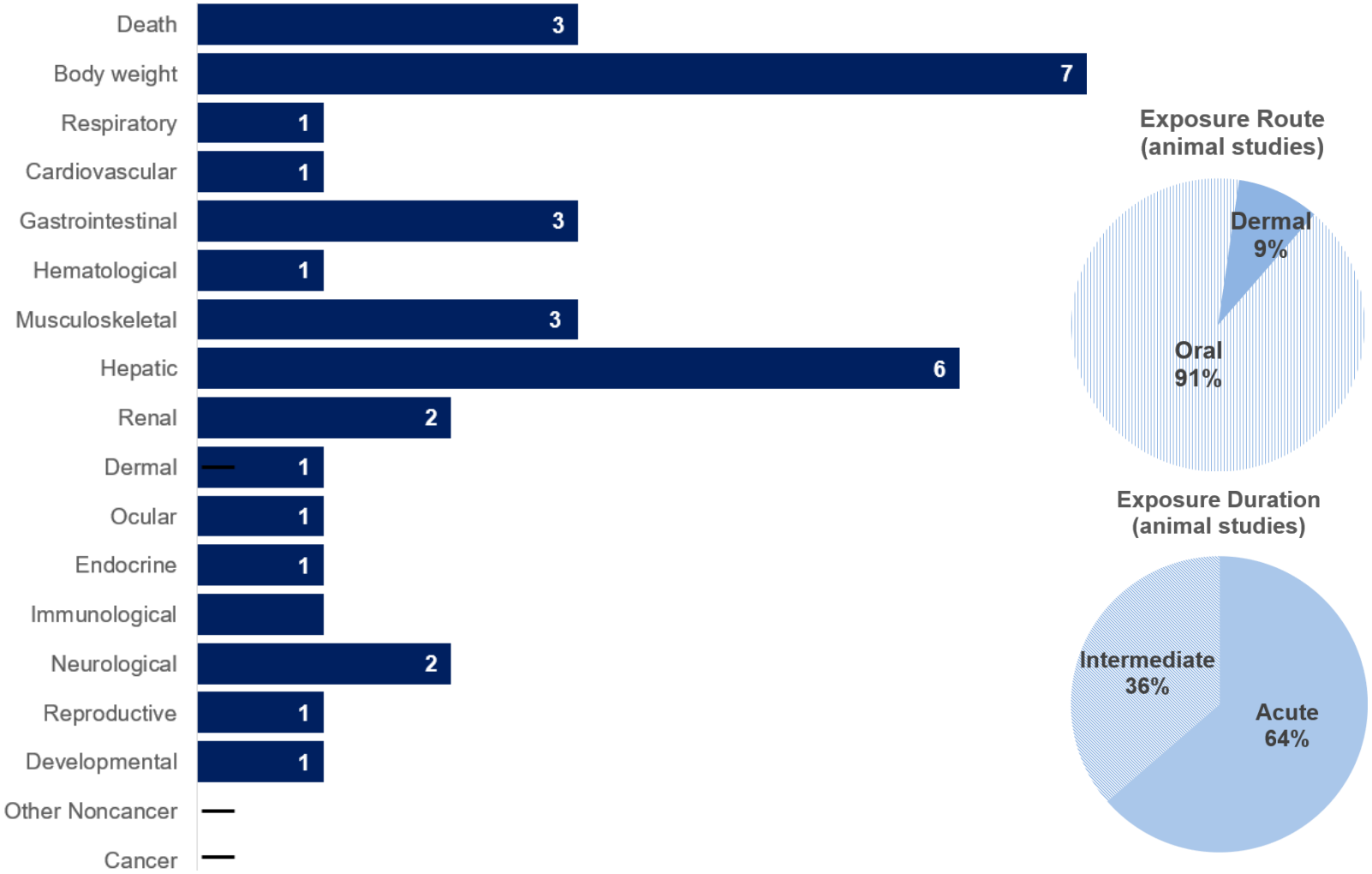


*Includes studies discussed in Chapter 2. A total of 12 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-6. Overview of the Number of Studies Examining 2,3,4,6-Tetrachlorophenol Health Effects

Most studies examined the potential body weight and hepatic effects of 2,3,4,6-tetrachlorophenols

All studies pertaining specifically to 2,3,4,6-tetrachlorophenol are in animals (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 11 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-7. Overview of the Number of Studies Examining Other Chlorophenol Health Effects

All studies examined the potential mortality, neurological, and dermal effects of other chlorophenols

All studies pertaining specifically to other chlorophenols are in **animals** (counts represent studies examining endpoint)

*Includes studies discussed in Chapter 2. A total of 10 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Chlorophenols – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
1	Rat (Wistar) 5 M, 5 F	4 hours	17, 104, 908	BW, GN, CS, LE	Bd wt	908			
					Resp	104	908 M		Tachypnea in 1/5 rats
					Neuro	104	908		Restlessness, hunched posture
2-Chlorophenol Rhone-Poulenc 1991									

[a]The number corresponds to entries in Figure 2-8; differences in levels of health effects and cancer effects between male and females are not indicated in the figure. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

Bd wt or BW = body weight; CS = clinical signs; F = female(s); GN = gross necropsy; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurotoxicity; NOAEL = no-observed-adverse-effect level; Resp = respiratory

Figure 2-8. Levels of Significant Exposure to Chlorophenols – Inhalation

Acute (≤14 days)

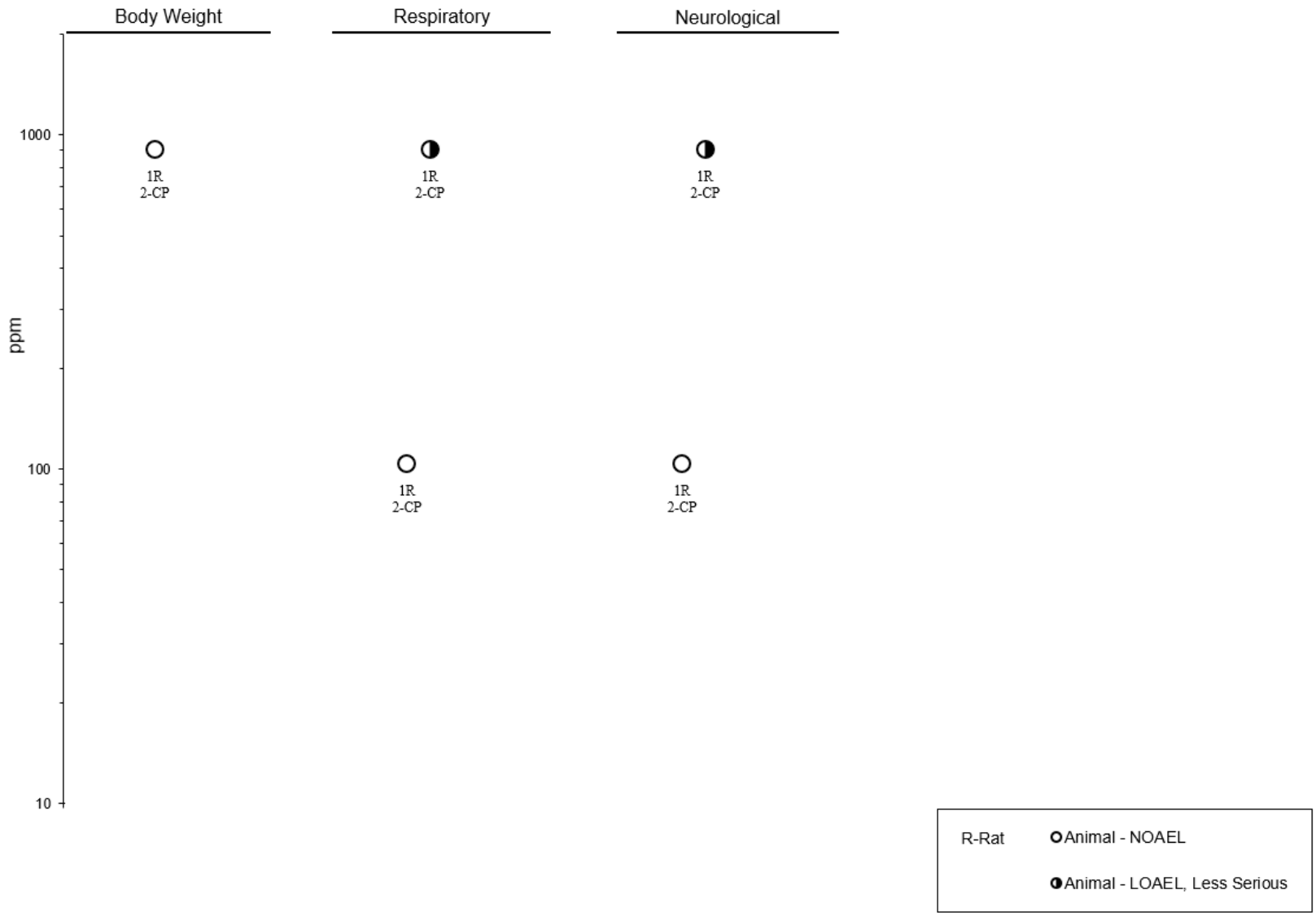


Table 2-2. Levels of Significant Exposure to 2-Chlorophenol – Oral

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)	Effects
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 10	10 days (GO)	0, 13, 64, 129, 257	CS, BW, FI, WI, BC, HE, OW, GN, HP	Bd wt	257			
					Resp	257			
					Cardio	257			
					Gastro	257			
					Hemato	257			
					Musc/skel	257			
					Hepatic	257			
					Renal	257			
					Endocr	257			
					Immuno	257			
					Neuro	257			No effect on brain weight or brain or sciatic nerve histology
					Repro	257			No effect on gonad weights or reproductive organ histology
Daniel et al. 1993									
2	Rat (Sprague-Dawley) 12	9 days; PNDs 4–12 (GO)	0, 20, 100, 500	LE	Death			500	All rats died by 9th day of dosing in dose range-finding study
Hasegawa et al. 2005									
3	Mouse (CD-1 ICR) 12 M, 12 F	14 days (GO)	0, 35, 69, 175	BW, OW, GN, BC, CS, BI, LE, OF, HE	Death			175	24/24 died
					Bd wt	35	69		Decreased body weight
					Hemato	69			
					Hepatic	69			
					Renal	69			
					Immuno	69			
					Neuro		35		Hyperactivity
Borzelleca et al. 1985a									

Table 2-2. Levels of Significant Exposure to 2-Chlorophenol – 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)	Effects
4	Mouse (CD-1 ICR) 10 M, 10 F	Once (GW)	NS	CS, LE	Death			345 F	LD_{50}
Borzelleca et al. 1985a, 1985b									
INTERMEDIATE EXPOSURE									
5	Rat (Sprague-Dawley)	Dams: from weaning through mating at PND 90, gestation, and lactation Offspring: from conception through weaning (PND 21) and for additional 12 weeks (W)	0, 0.76, 7.6, 76	BW, DX, RX, OF, OW, HP	Bd wt	76			
					Hemato	76			
					Hepatic	76			
					Immuno	76			
					Repro	7.6[b]	76		Decreased mean litter size and increased percent stillborn
					Develop	76			No effect on weaning weight or survival to weaning
Exon and Koller 1982, 1983b, 1985									
6	Rat (Sprague-Dawley) 10	90 days (GO)	0, 17, 50, 150	CS, BW, FI, WI, BC, HE, OW, GN, HP	Bd wt	150			
					Resp	150			
					Cardio	150			
					Gastro	150			
					Hemato	150			
					Musc/skel	150			
					Hepatic	150			
					Renal	150			
					Endocr	150			
					Immuno	150			
					Neuro	150			No effect on brain weight or brain or sciatic nerve histology

Table 2-2. Levels of Significant Exposure to 2-Chlorophenol – 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)	Effects
					Repro	150			No effect on gonad weights or reproductive organ histology
Daniel et al. 1993									
7	Rat (Sprague-Dawley) 12/sex	28 days (GO)	0, 8, 40, 200, 1,000	BW, CS, HE, BI, GN, OW, HP, DX	Bd wt	1,000			
					Resp	1,000			
					Cardio	1,000			
					Hemato	1,000			
					Hepatic	200	1,000		Increased incidence slight centrilobular hepatocellular hypertrophy
					Renal	1,000			
					Endocr	1,000			
					Neuro	500		1,000	Increased incidence of tremors (9/24), hypoactivity (13/24), and abnormal gait (11/24)
					Repro	1,000			No effect on histopathology of testes, epididymides, ovaries, or uteri
					Develop	1,000			
Hasegawa et al. 2005									
8	Rat (Sprague-Dawley) 12/sex	PNDs 4–21 (GO)	0, 8, 50, 300	BW, CS, HE, BI, GN, OW, HP, DX	Neuro	50		300	Increased incidence of tremors (23/24 combined, compared with 0/24 control)
					Develop	50	300		Increased incidences basophilic renal tubules
Hasegawa et al. 2005									

Table 2-2. Levels of Significant Exposure to 2-Chlorophenol – 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)	Effects
CHRONIC EXPOSURE									
9	Rat (Sprague-Dawley) 24–32 M, F	From conception through weaning (PND 21) and until death or 24 months (W)	0, 0.62, 6.2, 62	HE, HP	Hemato	62			
Exon and Koller 1985									

[a]The number corresponds to entries in Figure 2-9; differences in levels of health effects and cancer effects between male and females are not indicated in the figure. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive a provisional intermediate-duration MRL of 0.08 mg/kg/day. The NOAEL of 7.6 mg/kg/day was divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). See Appendix A for details.

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental effects; Endocr = endocrine; F = female(s); FI = food intake; FX = fetal toxicity; (GO) = gavage in oil; (GW) = gavage in water; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; 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; NS = not specified; OF = organ function; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; RX = reproductive effects; (W) = water; WI = water intake

Figure 2-9. Levels of Significant Exposure to 2-Chlorophenol – Oral
Acute (≤14 days)

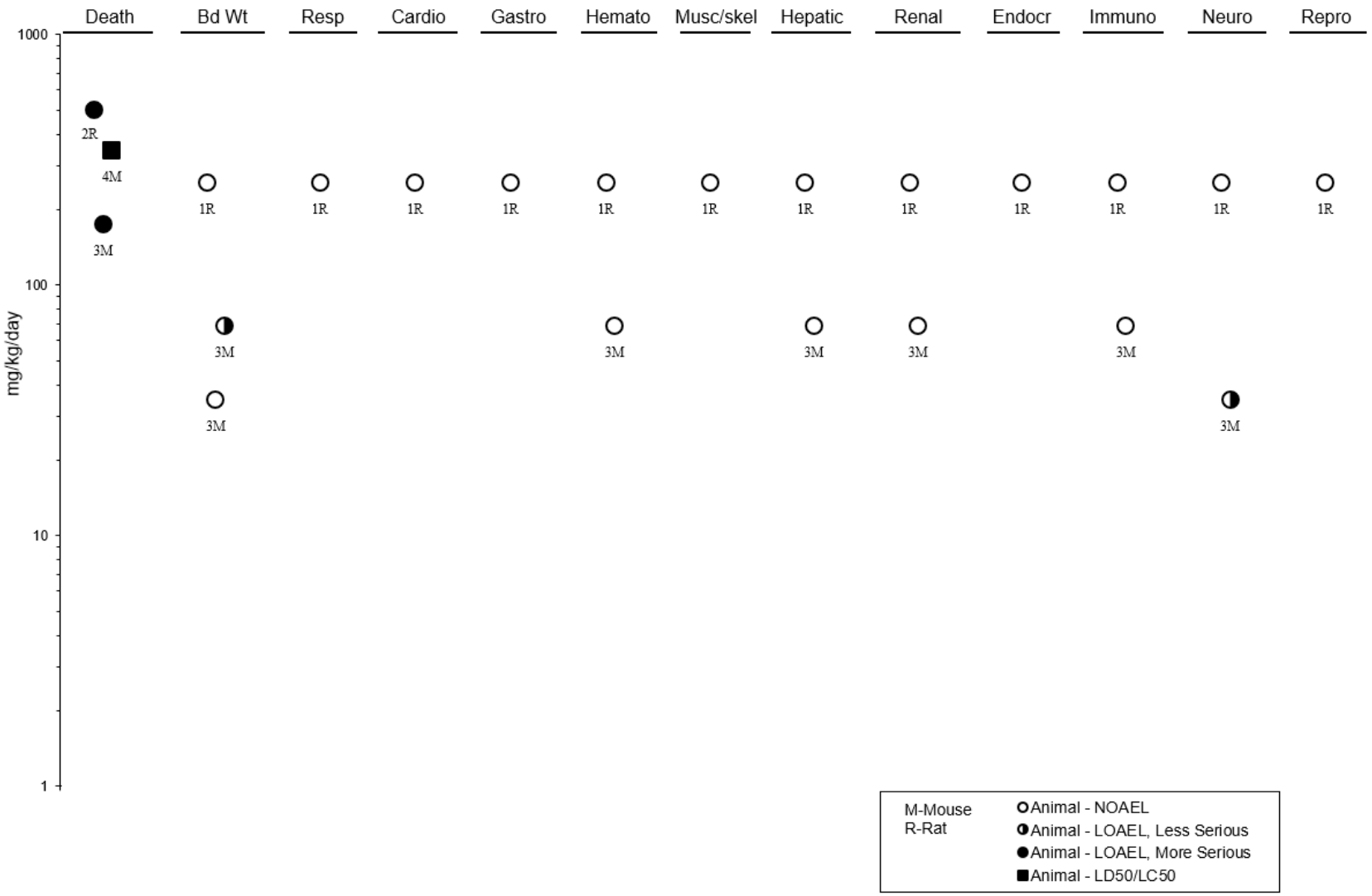


Figure 2-9. Levels of Significant Exposure to 2-Chlorophenol – Oral
Intermediate (15-364 days)

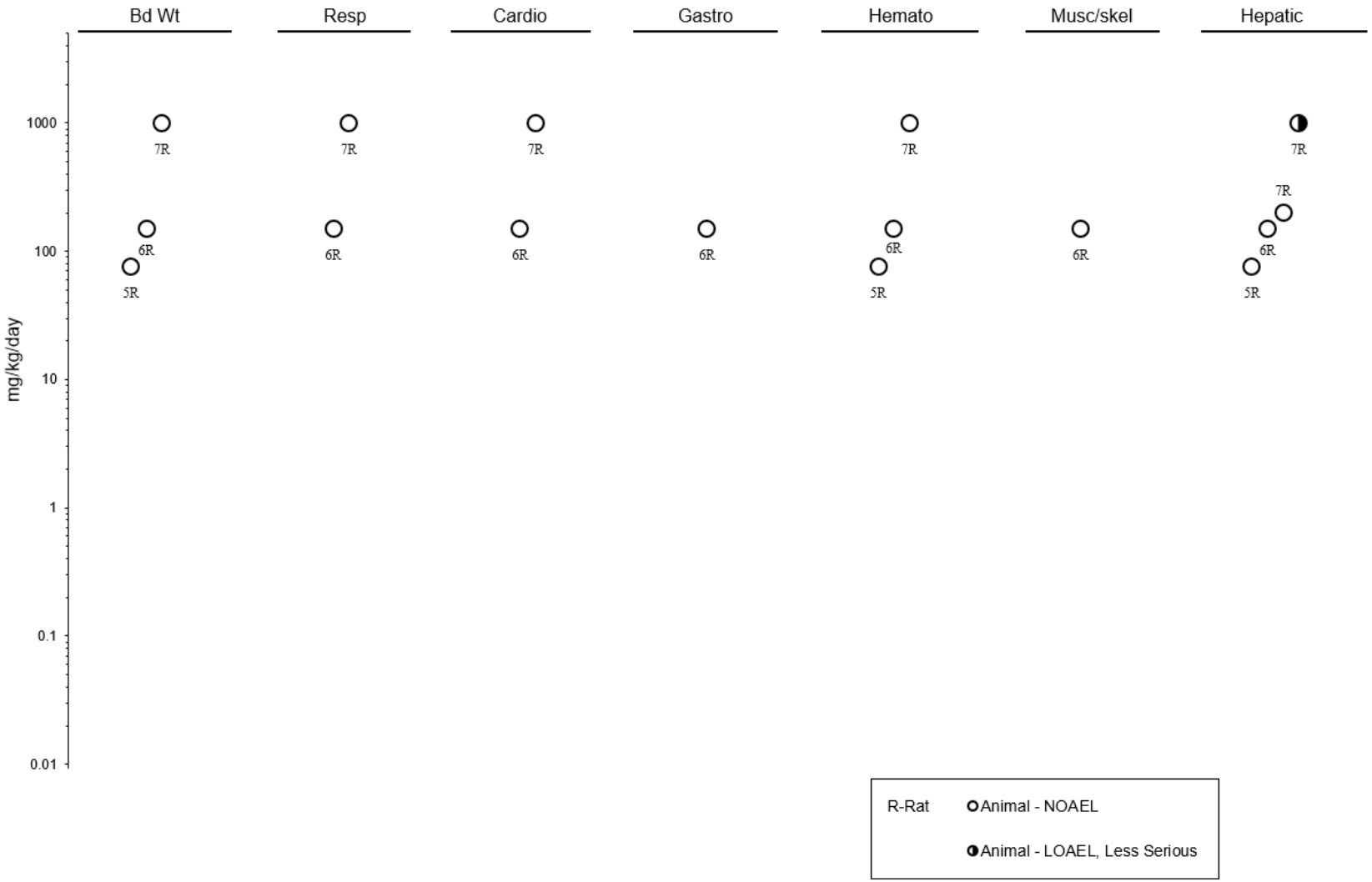


Figure 2-9. Levels of Significant Exposure to 2-Chlorophenol – Oral

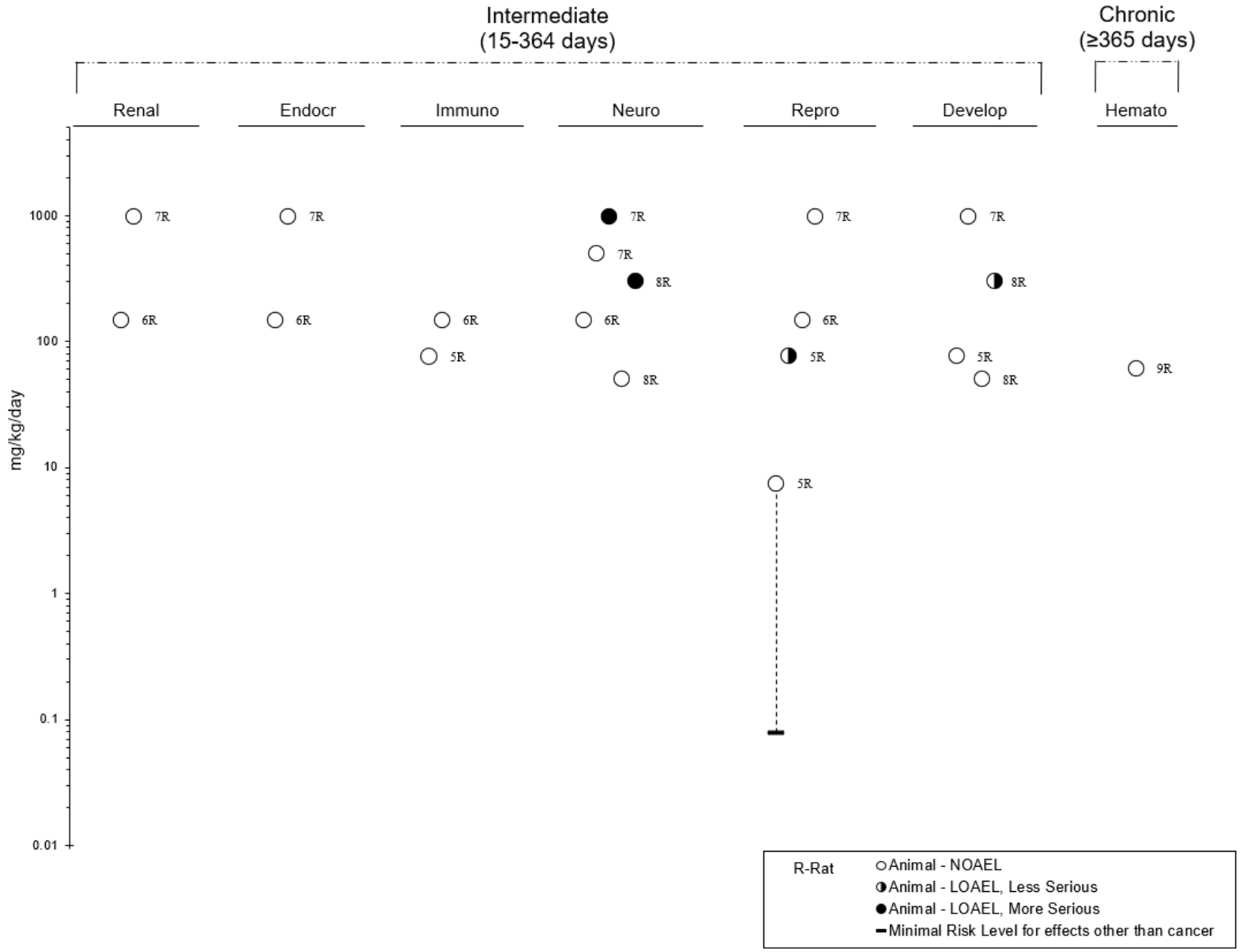


Table 2-3. Levels of Significant Exposure to 4-Chlorophenol – Oral

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)	Effects
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 6–13 F	Once on GD 11 (G)	0, 100, 333, 667, 1,000	BW, MX, DX	Bd wt	667 F	1,000 F		Maternal body weight loss of 10 g in 24 hours
					Develop	1,000			
Kavlock 1990									
2	Rat (Sprague-Dawley) 4–9 M	2 weeks 7 days/week (GO)	0, 0.32, 0.64, 1.28, 2.58, 5.2, 10.2, 20.6	OW, BC, BI	Hepatic	2.58 M			Foamy cytoplasm and clustering of mitochondria and endoplasmic reticulum in hepatocytes was not considered adverse
Phornchirasilp et al. 1989b									
3	Rat (Sprague-Dawley) 12	12 days 7 days/week (GO)	0, 40, 200, 1,000	CS, BW, FI, FX, DX, GN, OW, HP	Death			1,000	6/12 males and 5/12 females died in first 12 days dosing
					Neuro	200		1,000	Tremors, clonic convulsions
BSRC 2011									
4	Mouse (CD-1 ICR) 10 M,10 F	Once (GO)	NS	CS, LE	Death			1,373 M	LD_{50}
Borzelleca et al. 1985a, 1985b									
5	Mouse (ICR) 10 F	Once (GO)	0, 700, 1,050, 1,575	CS, LE, OW	Death			1,050 F	1/10 mice died
Shi et al. 2013									
INTERMEDIATE EXPOSURE									
6	Rat (Sprague-Dawley) 4–6 M	4–8 weeks 7 days/week (GO)	0, 0.64, 1.28, 5.2	HP, BC	Hepatic	0.64 M			Foamy cytoplasm and clustering of mitochondria and endoplasmic reticulum in hepatocytes not considered adverse
Phornchirasilp et al. 1989b									

Table 2-3. Levels of Significant Exposure to 4-Chlorophenol – 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)	Effects
7	Rat (Sprague-Dawley) 12/sex	28 days 7 days/week (GO)	0, 20, 100, 500	BW, CS, HE, BI, GN, OW, HP	Bd wt	500			
					Neuro	100		500	Increased incidence of tremors (23/24), rapid breathing (20/24), and salivation (17/24)
					Repro	500			No effect on histopathology of testes, epididymides, ovaries, or uteri
Hasegawa et al. 2005									
8	Rat (Sprague-Dawley) 12/sex	PNDs 4–21 (GO)	0, 12, 60, 300, 500	BW, CS, HE, BI, GN, OW, HP, DX	Death			500	4/4 males and 3/4 females died in dose range-finding study
					Resp	300			
					Cardio	300			
					Hemato	300			
					Hepatic	300			
					Renal	300			
					Endocr	300			
					Neuro	60		300	Increased incidence of tremors (24/24)
					Develop	300			
Hasegawa et al. 2005									

Table 2-3. Levels of Significant Exposure to 4-Chlorophenol – 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)	Effects
9	Rat (Sprague-Dawley) 12	41–53 days 7 days/week (GO)	0, 40, 200, 1,000	CS, BW, FI, FX, DX, GN, OW, HP	Repro	40[b]	200		Significantly reduced number live births ($BMDL_{1SD}$ =85.77 mg/kg/day); reduced number implantation sites
					Develop	200			
Biosciences Research Laboratory 2011									

[a]The number corresponds to entries in Figure 2-10; differences in levels of health effects and cancer effects between male and females are not indicated in the figure. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive a provisional intermediate-duration oral MRL of 0.9 mg/kg/day using BMD analysis. The $BMDL_{1SD}$ of 85.77 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). See Appendix A for details.

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; BMD = benchmark dose; BMDL = benchmark dose, lower confidence limit; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental effects; Endocr = endocrine; F = female(s); FI = food intake; FX = fetal toxicity; (G) = gavage; (GO) = gavage in oil; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; LD_{50} = dose producing 50% death; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; SD = standard deviation

Figure 2-10. Levels of Significant Exposure to 4-Chlorophenol – Oral
Acute (≤14 days)

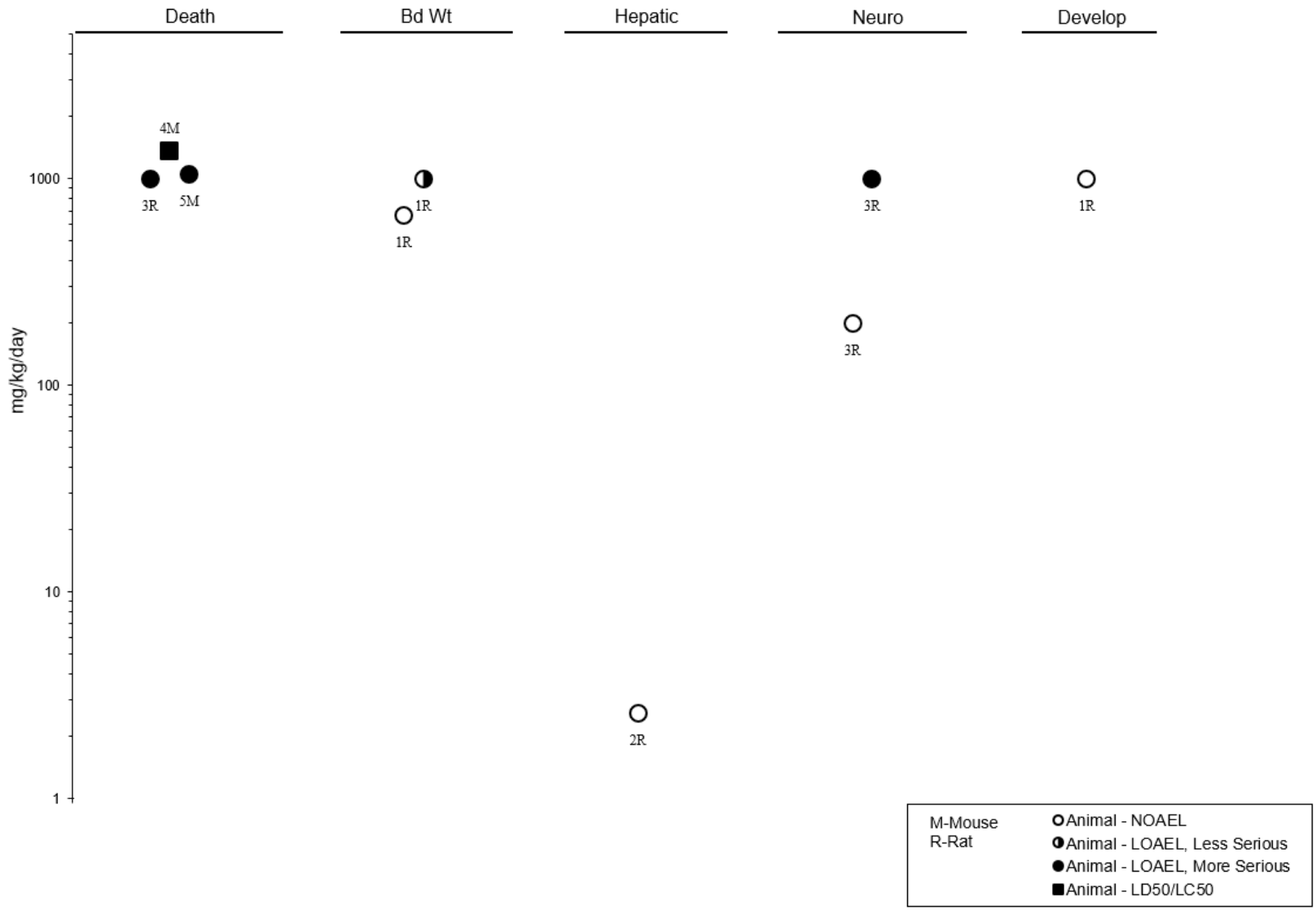


Figure 2-10. Levels of Significant Exposure to 4-Chlorophenol – Oral
Intermediate (15-364 days)

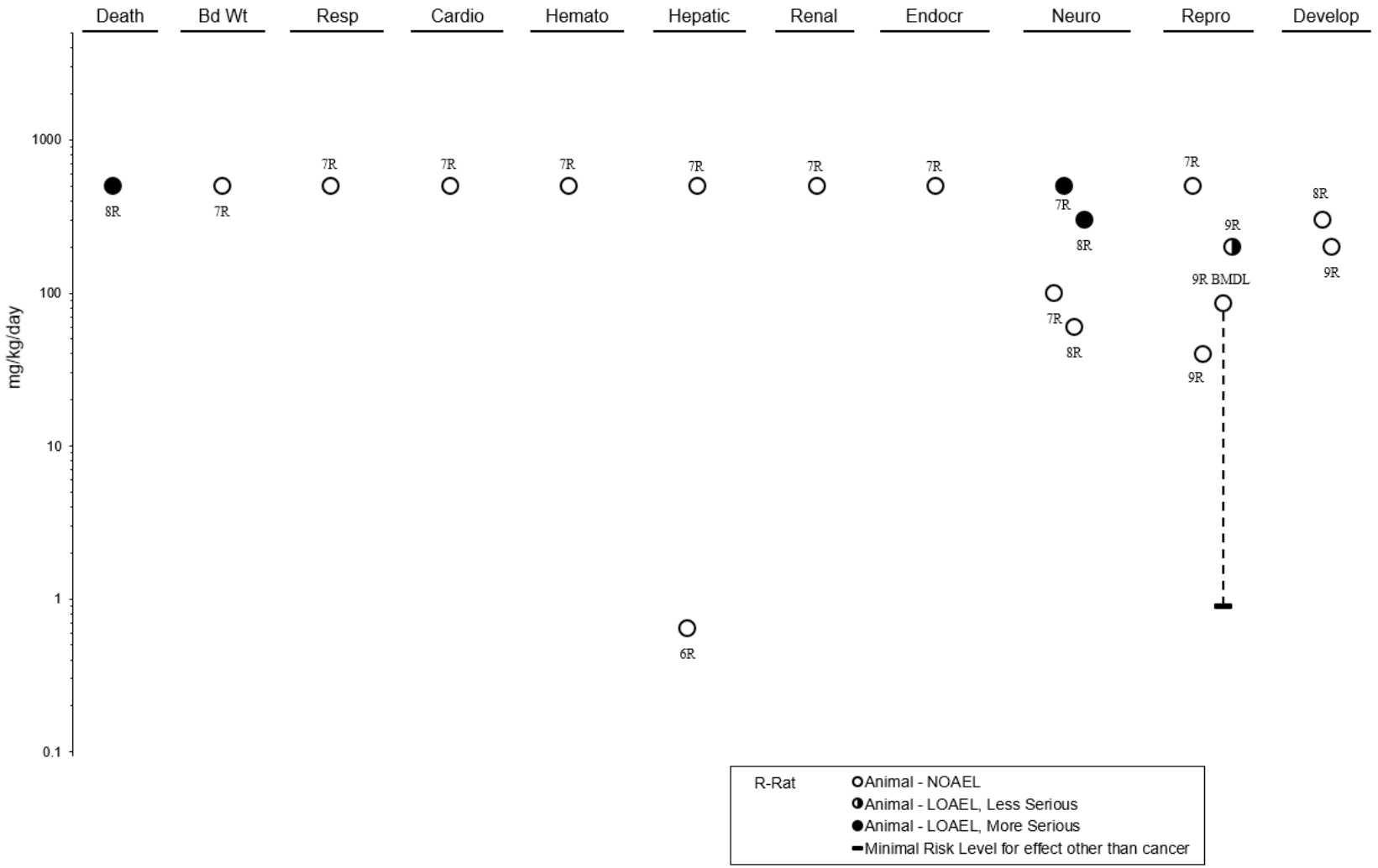


Table 2-4. Levels of Significant Exposure to 2,4-Dichlorophenol – Oral

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)	Effects
ACUTE EXPOSURE									
1	Rat (Fischer 344/N) 5 M, 5 F	14 days (F)	0, 125, 250, 500, 1,000, 2,000	BW, FI, GN, CS, LE	Bd wt	500 M	1,000 M	2,000 M	19% decrease in body weight at 1,000 mg/kg/day; 52% decrease in body weight at 2,000 mg/kg/day
NTP 1989									
2	Rat (Fischer 344) 27–31 F	10 days GDs 6–15 (GO)	0, 200, 375, 750	FX, DX, MX, CS	Death			750 F	4/34 maternal deaths
					Bd wt			375 F	23% decrease in maternal weight gain
					Develop	200	750		Delayed ossification and 3% decrease in fetal body weights
Rodwell et al. 1989									
3	Mouse (CD-1) 8 M, 8 F	Once (GO)	NS	CS	Death			1,276 M	LD_{50}
Borzelleca et al. 1985a, 1985b, 1985c									
4	Mouse (ICR) 6 M, 6 F	2 doses 18 hours apart (GO)	667, 1,000, 1,500, 2,250	LE	Death			1,000	2/12 mice died
Kobayashi et al. 1972									
5	Rat (Sprague-Dawley) 6 M 6 F	2 doses 18 hours apart (GO)	2,000, 2,250, 3,000	LE	Death			1,500	1/12 rats died
Kobayashi et al. 1972									
6	Mouse (B6C3F1) 5 M, 5 F	14 days (F)	0, 325, 650, 1,300, 2,600, 5,200	BW, FI, GN, CS, LE	Death			5,200 M	1/5 deaths
					Bd wt	2,600		5,200 M	25% decreased body weight, reduced food intake
					Neuro	2,600		5,200	Lethargy
NTP 1989									

Table 2-4. Levels of Significant Exposure to 2,4-Dichlorophenol – 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)	Effects
7	Mouse (BALB/c) 6 M/group	14 days (W)	0, 270	BW, OW, BC, HP, OF	Bd wt	270 M			
					Renal	270 M			
					Repro			270 M	Increased necrotic cell counts in seminiferous tubules, >3-fold increase in percent abnormal sperm, and decreased sperm motility
Aydin et al. 2009									
INTERMEDIATE EXPOSURE									
8	Rat (Sprague-Dawley) 10 M, F	Dams: from weaning through mating at PND 90, gestation, and lactation Offspring: from conception through weaning (PND 21) and for additional 15 weeks (W)	0, 0.46, 4.6, 46	BW, DX, RX, OF, OW, HP	Bd wt	46			
					Hemato	46			
					Hepatic	4.6	46		Increased offspring liver weight (19%) at end of exposure
					Immuno	0.46[b]	4.6		Decreased delayed-type hypersensitivity ($BMDL_{1SD}$ = 2.07 mg/kg/day)
					Repro	4.6	46		Decreased litter size
					Develop	46			No effect on birth or weaning weight or survival of offspring to weaning
Exon and Koller 1985; Exon et al. 1984									
9	Rat (Fischer-344/N) 10 M, 10 F	13 weeks (F)	0, 125, 250, 500, 1,000, 2,000	BW, FI, GN, HP, CS, LE	Bd wt	500	1,000 M		20% reduction in body weight
					Resp	2,000			
					Cardio	2,000			
					Gastro	2,000			
					Hemato	250 F		500 F	Bone marrow atrophy in erythroid and myelocytic elements
					Musc/skel	2,000			
					Hepatic	2,000			
					Renal	2,000			
					Dermal	2,000			

Table 2-4. Levels of Significant Exposure to 2,4-Dichlorophenol – 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)	Effects
					Ocular	2,000			
					Endocr	2,000			
					Neuro	1,000	2,000		Hunched posture
NTP 1989									
10	Mouse (CD-1) 20 M, 20 F	90 days (W)	M: 0, 40, 114, 383; F: 0, 50, 143, 491	BW, OW, HP, BC, CS, BI, WI	Bd wt	383			
					Resp	383			
					Hemato	383			
					Hepatic	383			
					Renal	383			
Borzelleca et al. 1985a, 1985c									
11	Mouse (ICR, ddN) 10 M	6 months (F)	0, 45, 100, 230	BW, FI, HP, CS, BC, OW	Bd wt	230 M			
					Cardio	230 M			
					Hemato	230 M			
					Hepatic	100 M	230 M		Hepatocyte swelling
					Renal	230 M			
Kobayashi et al. 1972									
12	Mouse (B6C3F1) 10 M, 10 F	3 weeks (F)	0, 325, 650, 1,300, 2,600, 5,200	CS, LE	Death			5,200	20/20 died within 3 weeks
NTP 1989									
13	Mouse (B6C3F1) 10 M, 10 F	13 weeks (F)	0, 325, 650, 1,300, 2,600, 5,200	BW, FI, GN, HP, CS	Bd wt	1,300	2,600		10–15% reduction in body weight
					Resp	2,600			
					Cardio	2,600			
					Gastro	2,600			
					Hemato	2,600			
					Musc/skel	2,600			
					Hepatic		325 M	2,600 M	Minimal hepatocellular necrosis in 4/10 at 325 mg/kg/day; hepatocellular necrosis in 10/10 at 2,000 mg/kg/day

Table 2-4. Levels of Significant Exposure to 2,4-Dichlorophenol – 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)	Effects
					Renal	2,600			
					Dermal	2,600			
					Ocular	2,600			
					Endocr	2,600			
					Neuro	2,600			
NTP 1989									
14	Mouse (CD-1) 4 M	90 days (W)	0, 50, 150, 500	OF	Repro	500 M			No adverse effect on sperm motility or acrosome integrity, or ovum penetration
Seyler et al. 1984									
15	Rat (Wistar) 24/sex	28 weeks (3 generations: 10 weeks premating through gestation and lactation until weaning of 3rd generation) (F)	M: 0, 33.4, 134, 543; F: 0, 49.1, 194, 768	CS, FI, BW, RX, DX, GN, OW, BC, HP	Bd wt	134	543 M		Decreased body weights in females in P generation (6%), and males and females (8 and 13%, respectively) of the F1 generation
					Repro	768			
					Develop	194	768 F		In offspring generations (F1, F2), increased uterine weight (42%) and increased height of epithelial cells of the uterus, as well as, increased uterine growth; 12% reduction in the time to vaginal opening; reduced percentage of pups with eye opening on day 14
Aoyama et al. 2005									
CHRONIC EXPOSURE									
16	Rat (Sprague-Dawley) 10 M, F	From conception through weaning (PND 21) and for additional 10–15 weeks (W)	0, 0.44, 4.4, 44	HE, HP	Hemato	37			
Exon and Koller 1985; Exon et al. 1984									

Table 2-4. Levels of Significant Exposure to 2,4-Dichlorophenol – 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)	Effects
17	Rat (Fischer 344) 50 F, 50 M	103 weeks (F)	F: 0, 120, 250; M: 0, 210, 440	BW, FI, GN, HP, CS, LE	Bd wt	120 F	250 F		6–12% reduced body weight
					Resp			210 M	Nasal lesions; multifocal degeneration of respiratory epithelium
					Cardio	440 M			
					Gastro	440 M			
					Hemato	440 M			
					Musc/skel	440 M			
					Hepatic	440 M			
					Renal	440 M			
					Dermal	440 M			
					Ocular	440 M			
					Endocr	440 M			
					Immuno	440 M			
					Neuro	440 M			
					Repro	250 F			
						440 M			
NTP 1989									
18	Mouse (B6C3F1) 50 F, 50 M	103 weeks (F)	F: 0, 430, 820; M: 0, 800, 1,300	BW, FI, GN, HP, CS	Bd wt	430 F	820 F		Maximum 19% decrease in body weight relative to controls
					Resp	1,300 M			
					Cardio	1,300 M			
					Gastro	1,300 M			
					Hemato	1,300 M			
					Musc/skel	1,300 M			
					Hepatic	1,300 M			
					Renal	1,300 M			
					Dermal	1,300 M			
					Ocular	1,300 M			
					Endocr	1,300 M			
					Immuno	1,300 M			

Table 2-4. Levels of Significant Exposure to 2,4-Dichlorophenol – 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)	Effects
					Neuro	1,300 M			
					Repro	820 F			
						1,300 M			
NTP 1989									

[a]The number corresponds to entries in Figure 2-11; differences in levels of health effects and cancer effects between male and females are not indicated in the figure. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive an intermediate-duration oral MRL of 0.02 mg/kg/day using BMD analysis. The $BMDL_{1SD}$ of 2.07 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability). See Appendix A for details.

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; BMD = benchmark dose; BMDL = benchmark dose, lower confidence limit; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental effects; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; FX = fetal toxicity; (GO) = gavage in oil; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; Hemato = hematological; HP = histopathology; Immuno = immunological; 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; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; RX = reproductive effects; SD = standard deviation; (W) = water; WI = water intake

Figure 2-11. Levels of Significant Exposure to 2,4-Dichlorophenol – Oral
Acute (≤14 days)

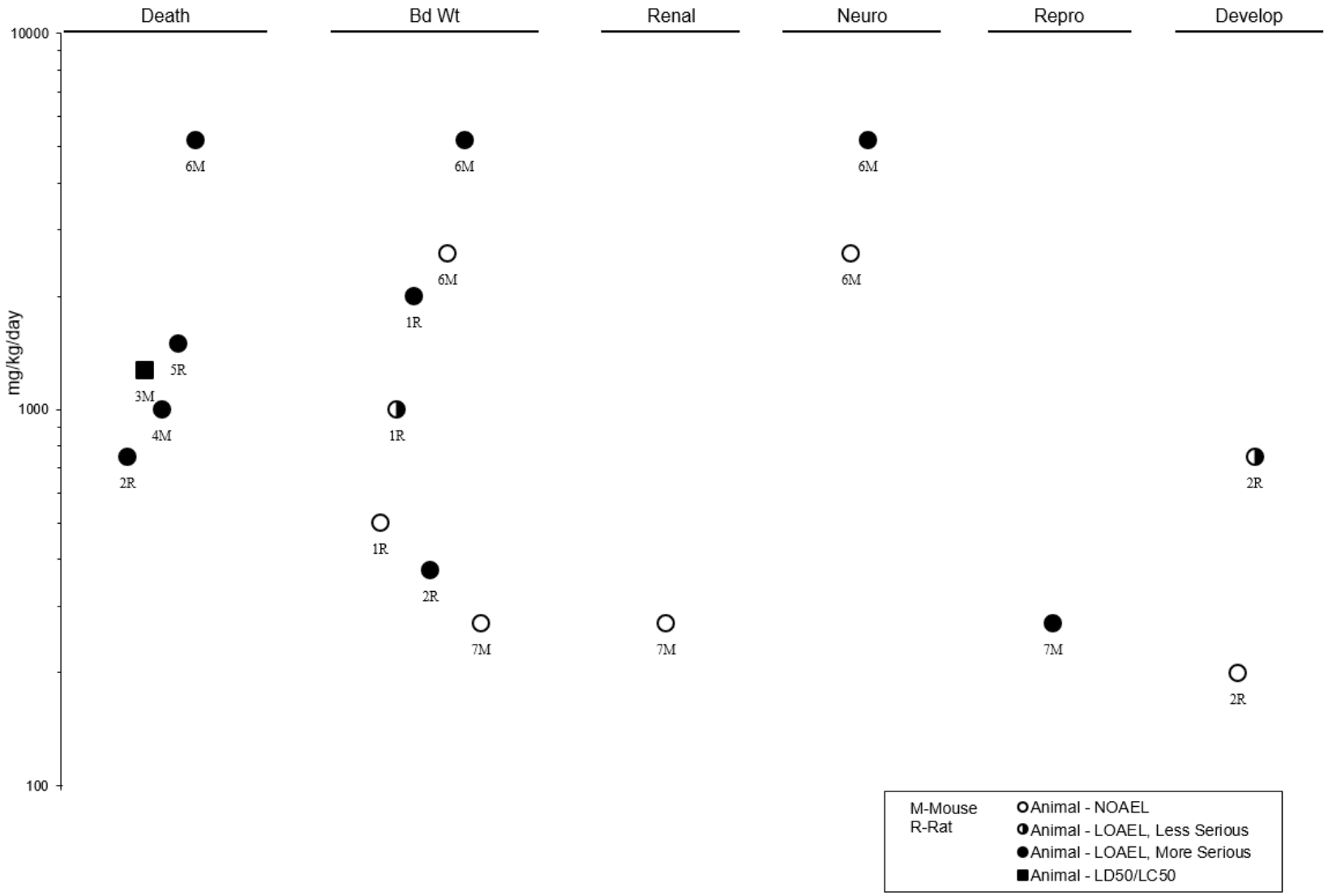


Figure 2-11. Levels of Significant Exposure to 2,4-Dichlorophenol – Oral
Intermediate (15-364 days)

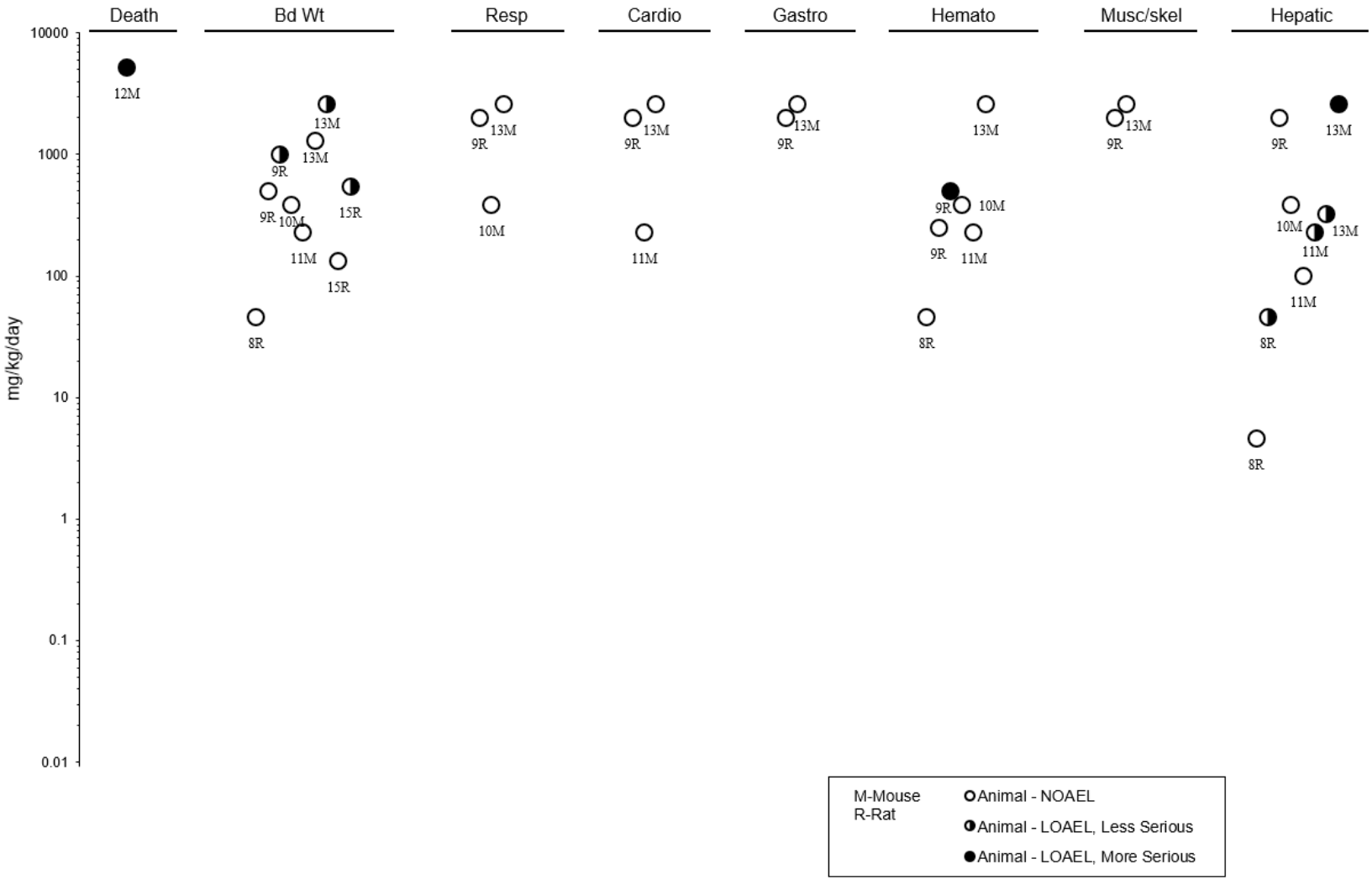


Figure 2-11. Levels of Significant Exposure to 2,4-Dichlorophenol – Oral
Intermediate (15-364 days)

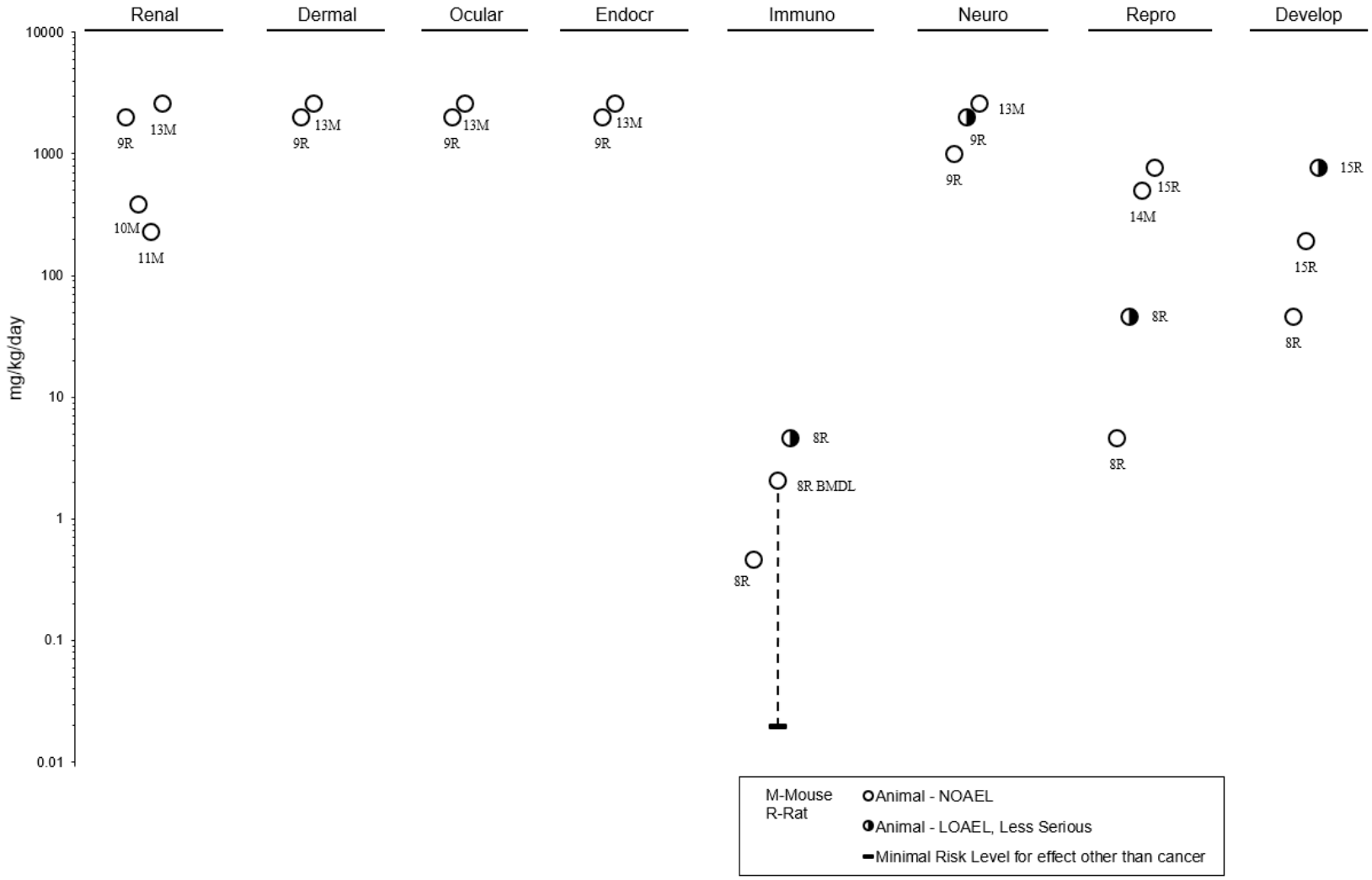


Figure 2-11. Levels of Significant Exposure to 2,4-Dichlorophenol – Oral
Chronic (≥365 days)

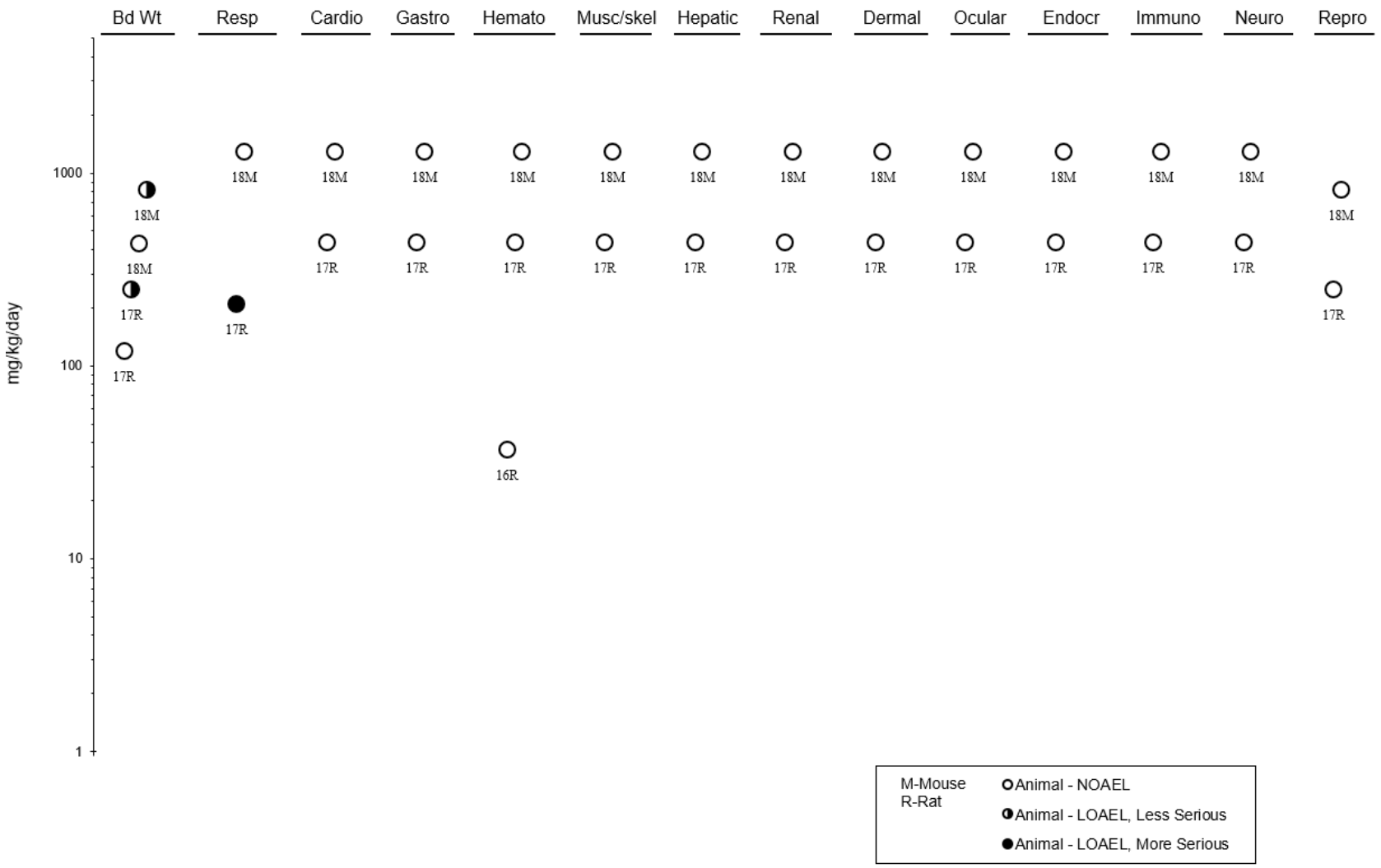


Table 2-5. Levels of Significant Exposure to 2,4,5-Trichlorophenol – Oral

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)	Effects
ACUTE EXPOSURE									
1	Rat (NS) 5 M	Once (GO)	1,000, 1,260, 1,580, 2,000, 2,520, 3,160, 3,980	LE	Death			2,960 M	LD_{50}
McCollister et al. 1961									
2	Rat (Sprague-Dawley) 6 M	14 days (GO)	0, 25, 100, 400	EA	Hepatic	400			No effect on hepatic enzyme levels
Carlson 1978									
INTERMEDIATE EXPOSURE									
3	Rat (Wistar) 10 M, 10 F	98 days (F)	0, 10, 30, 100, 300, 1,000	CS, BW, FI, HE, BC, OW, GN, HP	Bd wt	300 F		1,000 F	10% decrease in terminal body weight
					Resp	1,000			
					Cardio	1,000			
					Hemato	1,000			
					Hepatic	100[b]	300		Mild centrilobular degeneration

Table 2-5. Levels of Significant Exposure to 2,4,5-Trichlorophenol – 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)	Effects
					Renal	100[b]	300		Slight degenerative changes in convoluted tubule epithelium
					Repro	1,000			No effect on testes weight or histology
					Endocr	1,000			
McCollister et al. 1961									

[a]The number corresponds to entries in Figure 2-12; differences in levels of health effects and cancer effects between male and females are not indicated in the figure. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive an intermediate-duration oral MRL of 1.0 mg/kg/day. The NOAEL of 100 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability). See Appendix A for details.

Bd wt or BW = body weight; BC = biochemistry; Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; EA = enzyme activity; (F) = feed; F = female(s); FI = food intake; FX = fetal toxicity; (GO) = gavage in oil; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; LD_{50} = dose producing 50% lethality; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; Repro = reproductive; Resp = respiratory

Figure 2-12. Levels of Significant Exposure to 2,4,5-Trichlorophenol – Oral

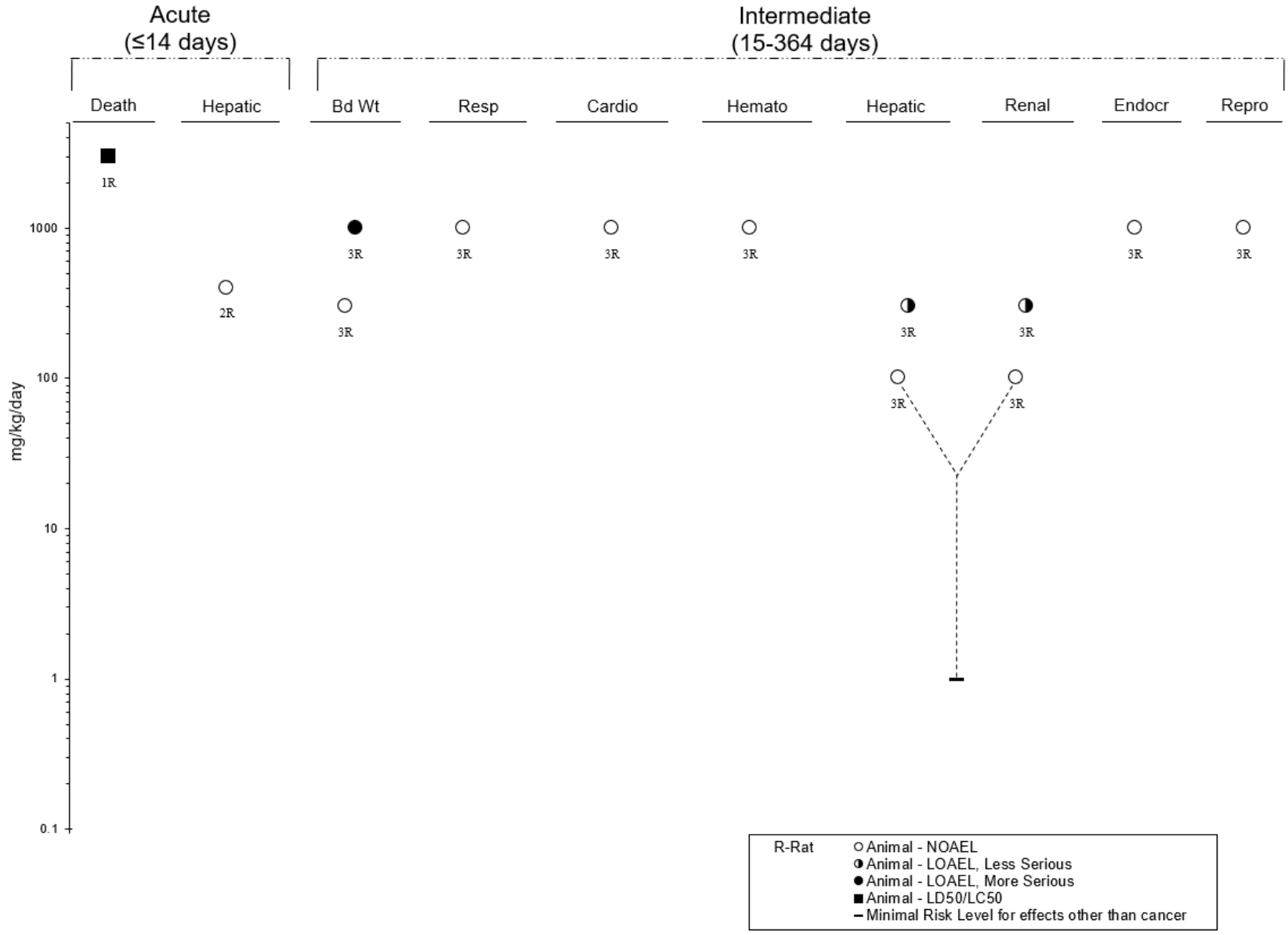


Table 2-6. Levels of Significant Exposure to 2,4,6-Trichlorophenol – Oral

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)	Effects
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 6 M	14 days (GO)	0, 25, 100, 400	BI, OF	Hepatic	400			No effect on hepatic enzyme activities
Carlson 1978									
INTERMEDIATE EXPOSURE									
2	Rat (Long-Evans hooded) 30 or 40 F	2 weeks 5 days/week; and GDs 1–21, 7 days/week (GO)	0, 100, 500, 1,000	BW, LE, CS	Bd wt	500	1,000		Reduced mean maternal body weight
					Develop	100	500		10–11% reduction in litter weight
Blackburn et al. 1986									
3	Rat (Sprague-Dawley) 10 M, 10 F	90 days (GO)	0, 80, 240, 720	CS, BW, FI, BC, OP, HE, UR, OW, GN, HP	Bd wt	720			
					Resp	720			
					Cardio	720			
					Gastro	720			
					Hemato	720			
					Hepatic	80	240 M		14% increased relative liver weight
					Renal	240	720 M		Increased kidney weight, decreased urinary pH
					Ocular	720			
					Endocr	720			
Bercz et al. 1990									
4	Rat (Long-Evans hooded) 15–25 M	11 weeks 5 days/week (GO)	0, 100, 500, 1,000	CS, LE, RX, OW, BW, GN	Death			1,000 M	8/25 died
					Bd wt	1,000 M			
					Resp	1,000 M			
					Cardio	1,000 M			
					Hepatic	1,000 M			
					Renal	1,000 M			

Table 2-6. Levels of Significant Exposure to 2,4,6-Trichlorophenol – 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)	Effects
					Endocr	1,000 M			
					Repro	1,000 M			
Blackburn et al. 1986									
5	Rat (Fischer 344) 5 M, 5 F	7 weeks, 7 days/week (F)	0, 500, 735, 1,075, 1,575, 2,300	BW, LE, HP	Bd wt	500	735	1,075	11–16% decrease in body weight at 735 mg/kg/day; 27% decrease in body weight at 1,075 mg/kg/day
					Hemato	1,575	2,300		Increased splenic hematopoiesis
					Hepatic	1,575	2,300 M		Midzonal vacuolation of hepatocytes
NCI 1979									
6	Rat (Sprague-Dawley) 10–14 NS	Dams: from weaning through mating at PND 90, gestation, and lactation Offspring: from conception through weaning (PND 21) and for additional 15 weeks (W)	0, 0.46, 4.6, 46	BW, OW	Bd wt	46			
					Hemato	46			
					Hepatic	0.46[b]	4.6		Increased liver weight (15%)
					Immuno	4.6	46		Increased spleen weight
					Repro	4.6	46		Decreased mean litter size
					Develop	46			No effect on birth or weaning weight or survival to weaning
Exon and Koller 1985									
7	Mouse (B6C3F1) 5 M, 5 F	7 weeks 7 days/week (F)	0, 884, 1,300, 1,911, 2,795, 4,095	HP, BW, GN, CS, LE	Death			4,095	4/10 died
NCI 1979									

Table 2-6. Levels of Significant Exposure to 2,4,6-Trichlorophenol – 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)	Effects
CHRONIC EXPOSURE									
8	Rat (Fischer 344) 50 M, 50 F	107 weeks 7 days/weeks (F)	0, 250, 500	BW, GN, HP, CS, LE	Bd wt		250 F	500 F	Approximate 10% decrease in body weight at 250 mg/kg/day; approximate 29% decrease in body weight at 500 mg/kg/day
					Resp	500			
					Cardio	500			
					Gastro	500			
					Hemato			250 M	Bone marrow hyperplasia
					Hepatic	500			
					Renal	500			
					Dermal	500			
					Endocr	500			
					Immuno	500			
					Neuro	500			
					Repro	500			
					Cancer			250 M	CEL: monocytic leukemia 23/50
NCI 1979									
9	Mouse (B6C3F1) 50 M, 50 F	105 weeks 7 days/week (F)	M: 0, 650, 1,300; F: 0, 678, 1,356 (TWA)	BW, GN, HP, CS	Bd wt			658 F	Approximately 24% decrease in body weight
					Resp	1,300 M			
					Cardio	1,300 M			
					Gastro	1,300 M			
					Hemato	1,300 M			
					Hepatic			650 M	Hepatic hyperplasia
					Renal	1,356			
					Dermal	1,356			
					Endocr	1,356			
					Neuro	1,356 F			

Table 2-6. Levels of Significant Exposure to 2,4,6-Trichlorophenol – 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)	Effects
					Repro	1,356 F 1,300 M			
					Cancer			650 M	CEL: 7/47 hepatocellular carcinomas or adenomas
NCI 1979									

[a]The number corresponds to entries in Figure 2-13; differences in levels of health effects and cancer effects between male and females are not indicated in the figure. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive a provisional intermediate-duration oral MRL of 0.005 mg/kg/day. The NOAEL of 0.46 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). See Appendix A for details.

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; BMD = benchmark dose; BMDL = benchmark dose, lower confidence limit; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental effects; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; (GO) = gavage in oil; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OP = ophthalmology; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; RX = reproductive effects; SD= standard deviation; TWA = time-weighted average; UR = urinalysis; (W) = water

Figure 2-13. Levels of Significant Exposure to 2,4,6-Trichlorophenol – Oral

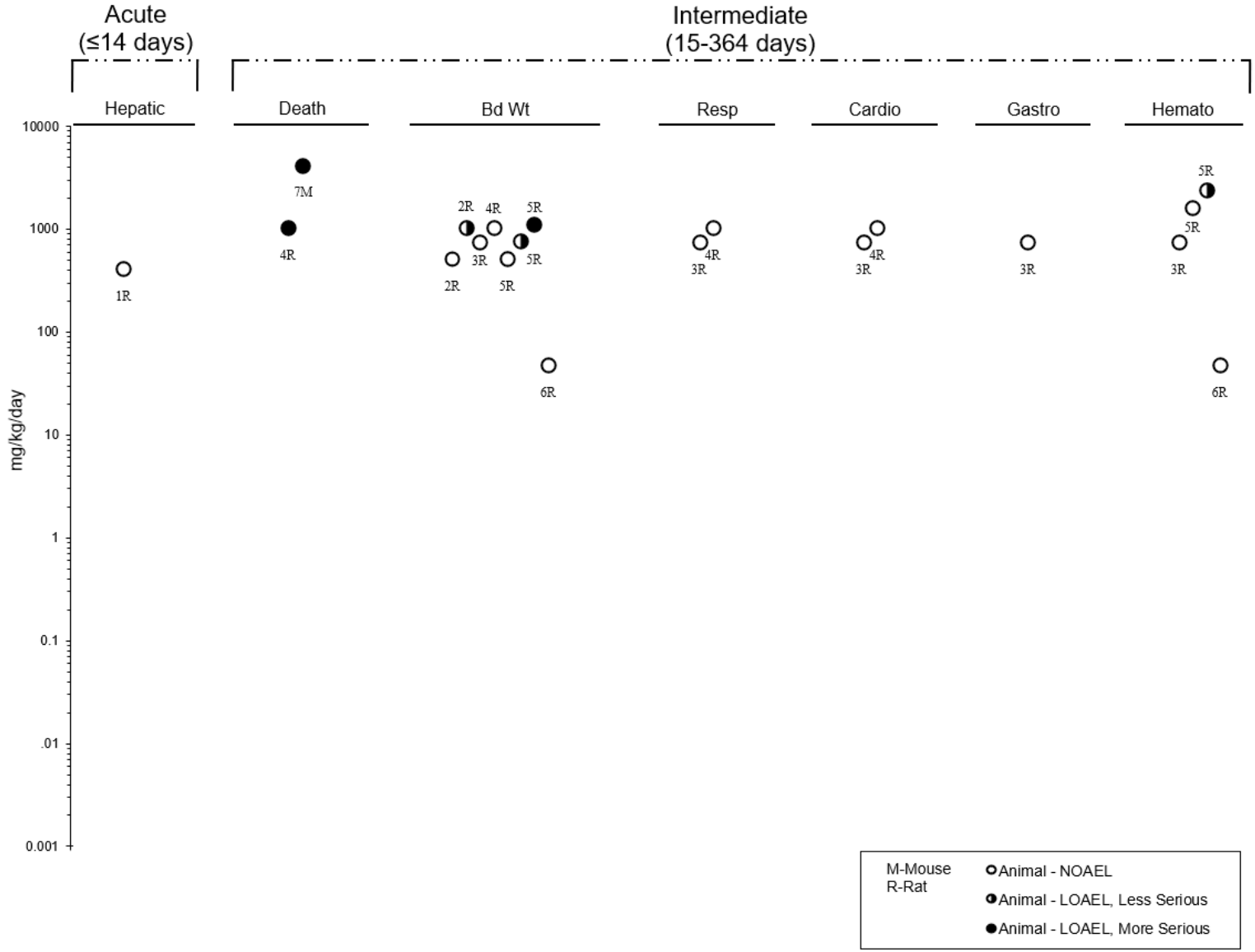


Figure 2-13. Levels of Significant Exposure to 2,4,6-Trichlorophenol – Oral
Intermediate (15-364 days)

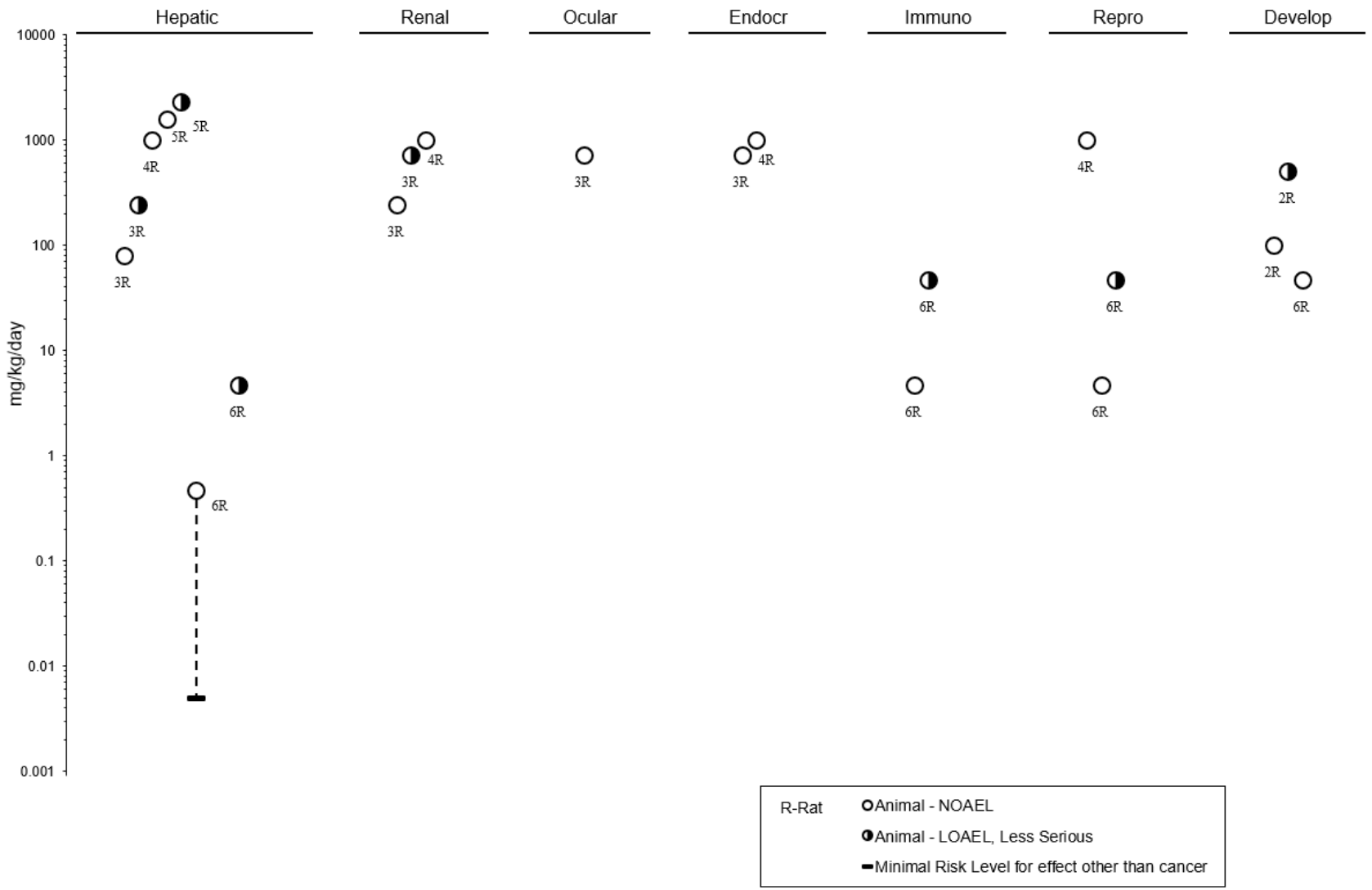


Figure 2-13. Levels of Significant Exposure to 2,4,6-Trichlorophenol – Oral
Chronic (≥365 days)

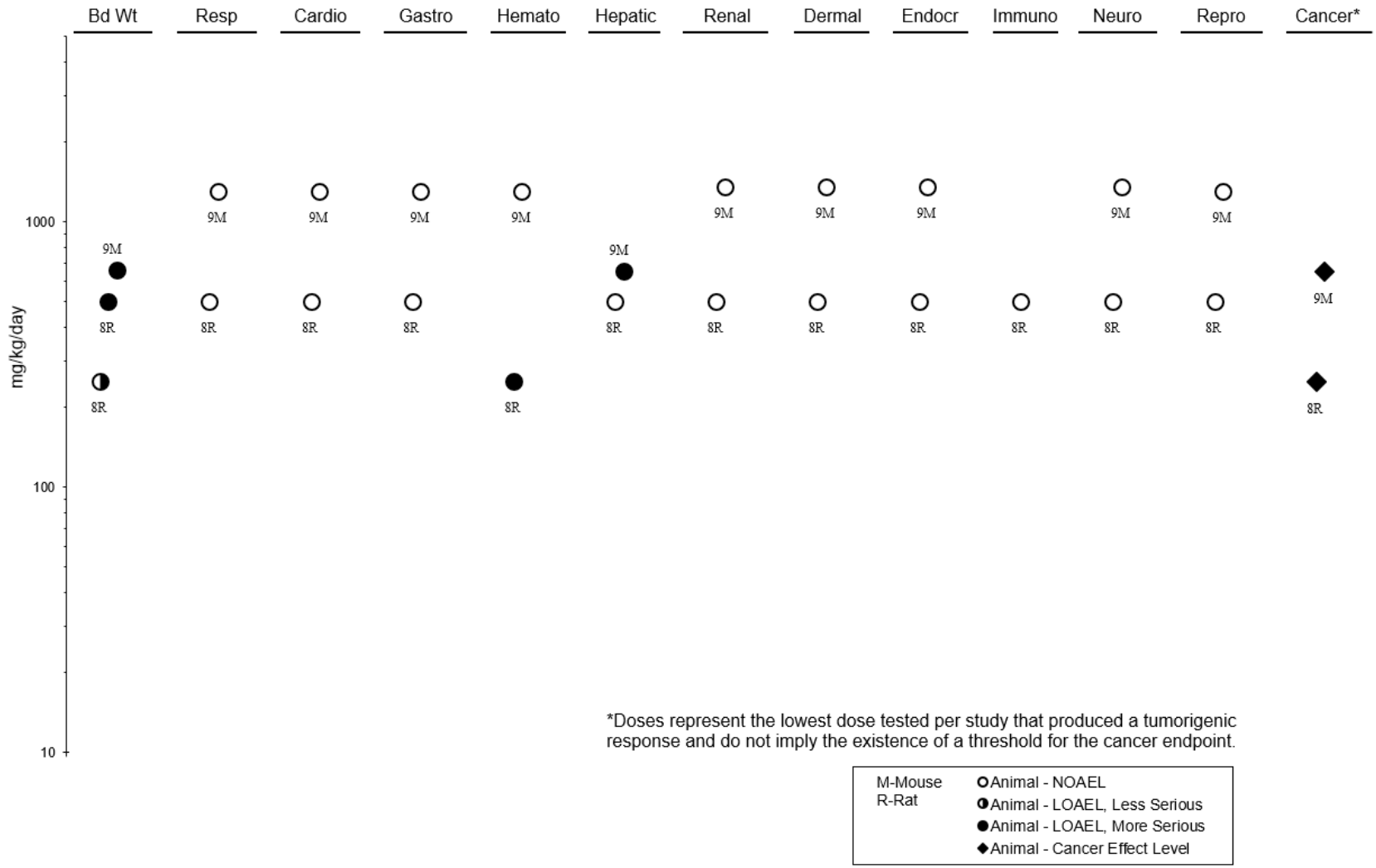


Table 2-7. Levels of Significant Exposure to 2,3,4,6-Tetrachlorophenol – Oral

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)	Effects
ACUTE EXPOSURE									
1	Gerbil (NS) NS F	Once (G)	NS	LE	Death			698 F	LD_{50}
Ahlborg and Larsson 1978									
2	Rat (Wistar) 10 NS	Once (GO)	0, 300, 360, 410, 432, 518, 632	HP	Gastro	410	432	632	Mild necrosis at 432 mg/kg/day; mucosal hyperemia of stomach, severe necrosis of intestine at 632 mg/kg/day
					Musc/skel	632			
					Renal	632			
Hattula et al. 1981									
3	Rat (CD) 18–22 F	GDs 6–15 (GO)	0, 25, 100, 200	BW, FX, DX, MX, FI, GN	Bd Wt	25 F	100 F	200 F	Decrease in corrected maternal body weight gain: 13% at 100 mg/kg/day; 26% at 200 mg/kg/day
					Develop	200			
EPA 1987a, 1987b									
4	Rat (Sprague-Dawley) 10 M	5 days (GO)	0, 10, 25, 50, 100, 200	CS, BW, BC, OW, HP	Bd wt	200 M			
					Hepatic	100 M	200 M		23 and 26% increases in absolute and relative liver weights; increased incidence of centrilobular hypertrophy and low incidence of necrosis
Dodd et al. 2012									
5	Rat (Sprague-Dawley) 10 M	2 weeks, 7 days/week (GO)	0, 10, 25, 50, 100, 200	CS, BW, BC, OW, HP	Bd wt	200 M			
					Hepatic	10[b] M	25 M		15 and 14% increases in absolute and relative liver weights; low incidence of vacuolation ($BMDL_{1SD}$ = 8.45 mg/kg/day)
Dodd et al. 2012									
6	Mouse (C57 black) 4 M, 4 F	Once (G)	NS	LE	Death			131 F	LD_{50}
Ahlborg and Larsson 1978									

Table 2-7. Levels of Significant Exposure to 2,3,4,6-Tetrachlorophenol – 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)	Effects
INTERMEDIATE EXPOSURE									
7	Rat (Wistar) NS	55 days, 7 days/week (GO)	0, 10, 50, 100	HP, BW, FI, HE	Bd wt	100			
					Gastro	50	100		Focal necrosis of small intestine
					Musc/skel	100			
					Hepatic	10		50	Necrosis, thrombosed veins
Hattula et al. 1981									
8	Rat (Sprague-Dawley) 245 M (10/group)	13 weeks, 7 days/week (GO)	0, 10, 25, 50, 100, 200	CS, BW, BC, OW, GN, HP	Bd wt	50 M	100 M		12% decrease in body weight
					Hepatic		10[c] M		27 and 18% increases in absolute and relative liver weights; increased incidences and/or severity of centrilobular vacuolation and hypertrophy ($BMDL_{10}$ = 1.02 mg/kg/day)
Dodd et al. 2012									
9	Rat (Sprague-Dawley) 10 M	4 weeks, 7 days/week (GO)	0, 10, 25, 50, 100, 200	CS, BW, BC, OW, HP	Bd wt	200 M			
					Hepatic	10 M	25 M		Increased incidences of hepatic centrilobular vacuolation and hypertrophy
Dodd et al. 2012									
10	Rat (Sprague-Dawley) 30 M, 30 F	90 days, 7 days/week (GO)	0, 25, 100, 200	LE, HP, CS, BW, FI, OW, GN, BI, HE	Bd wt	100	200 M		Body weight gain decreased by 11%
					Resp	200			
					Cardio	200			
					Gastro	200			
					Hemato	200			
					Musc/skel	200			
					Hepatic	25	100		Increased liver weights and centrilobular hypertrophy
					Renal	25	100		Increased kidney weights
					Ocular	200			

Table 2-7. Levels of Significant Exposure to 2,3,4,6-Tetrachlorophenol – 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)	Effects
					Endocr	200			
					Immuno	200			
					Neuro	200			
					Repro	200			

EPA 1986 (formerly cited as American Biogenics)

[a]The number corresponds to entries in Figure 2-14; differences in levels of health effects and cancer effects between male and females are not indicated in the figure. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive a provisional acute-duration oral MRL of 0.08 mg/kg/day using BMD analysis. The $BMDL_{1SD}$ of 8.45 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). See Appendix A for details.
[c]Used to derive a provisional intermediate-duration oral MRL of 0.01 mg/kg/day using BMD analysis. The $BMDL_{10}$ of 1.02 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). See Appendix A for details.

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; BMD = benchmark dose; BMDL = benchmark dose, lower confidence limit; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental effects; Endocr = endocrine; 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; LD_{50} = dose producing 50% death; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = muscular/skeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; Repro = reproductive; Resp = respiratory; SD = standard deviation

Figure 2-14. Levels of Significant Exposure to 2,3,4,6-Tetrachlorophenol – Oral
Acute (≤14 days)

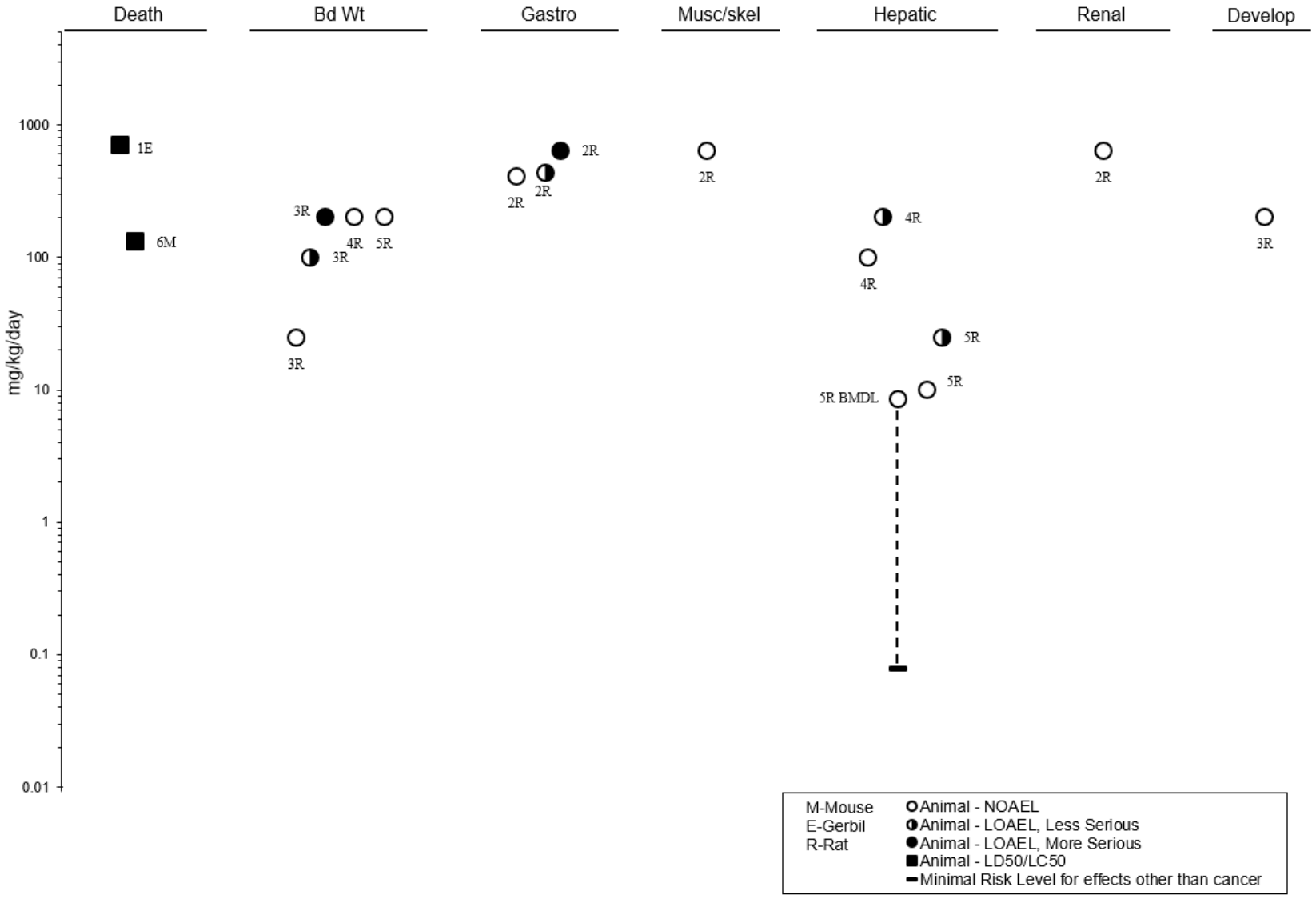


Figure 2-14. Levels of Significant Exposure to 2,3,4,6-Tetrachlorophenol – Oral
Intermediate (15-364 days)

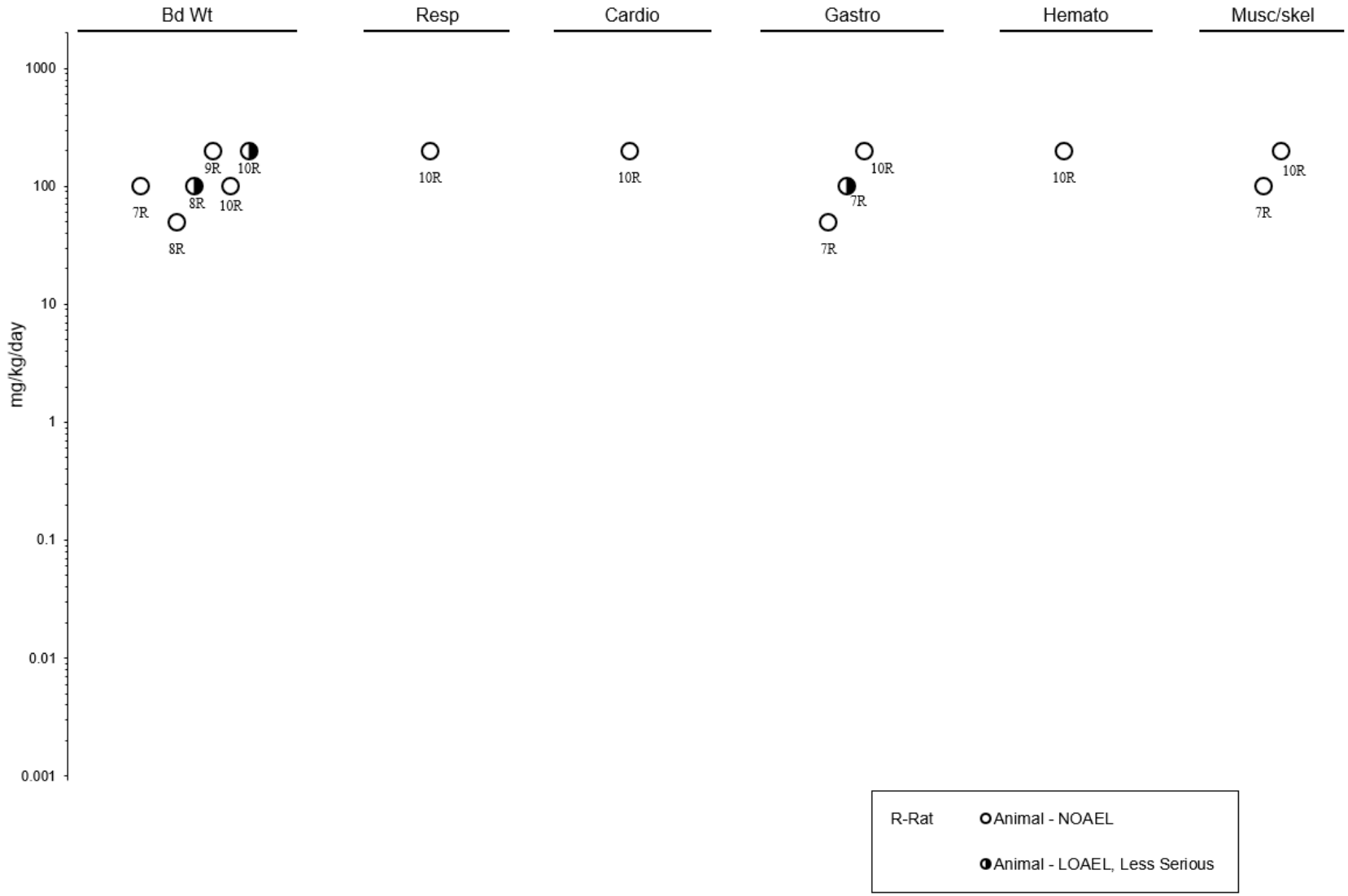


Figure 2-14. Levels of Significant Exposure to 2,3,4,6-Tetrachlorophenol – Oral
Intermediate (15-364 days)

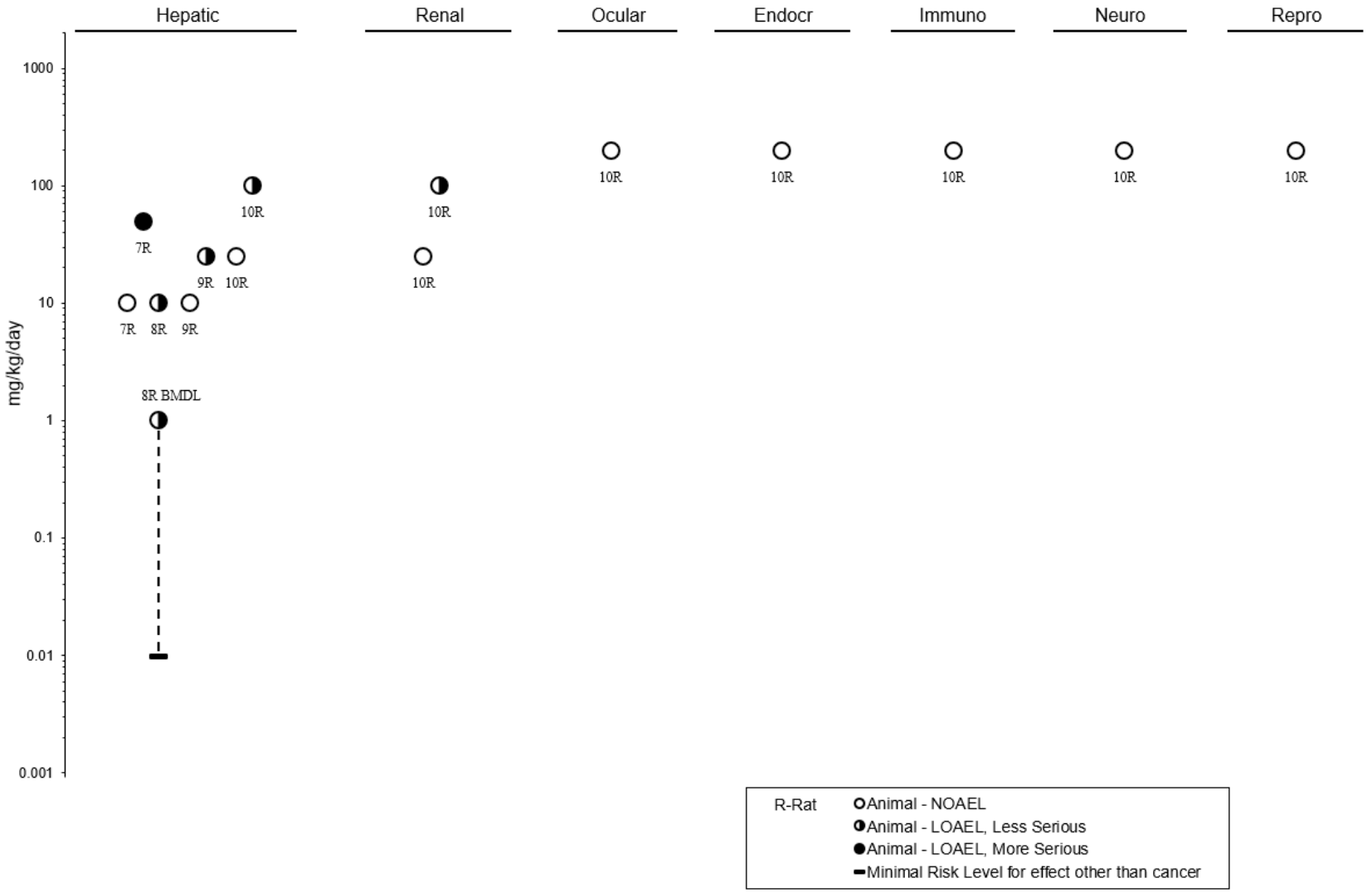


Table 2-8. Levels of Significant Exposure to Other Chlorophenols – Oral

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)	Effects
ACUTE EXPOSURE									
1	Mouse (CD-1) 8 M, 8 F	Once (GO)	NS	LE	Death			2,376 F	LD_{50}
2,3-Dichlorophenol Borzelleca et al. 1985b									
2	Mouse (CD-1) 8 M, 8 F	Once (GO)	NS	LE	Death			946 F	LD_{50}
2,5-Dichlorophenol Borzelleca et al. 1985b									
3	Mouse (CD-1) 8 M, 8 F	Once (GO)	NS	LE	Death			1,685 M	LD_{50}
3,4-Dichlorophenol Borzelleca et al. 1985b									
4	Mouse (CD-1) 8 M, 8 F	Once (GO)	NS	CS	Death			2,389 F	LD_{50}
3,5-Dichlorophenol Borzelleca et al. 1985b									
5	Gerbil (NS) NS F	Once (G)	NS	LE	Death			979 F	LD_{50}
2,3,5,6-Tetrachlorophenol Ahlborg and Larsson 1978									
6	Gerbil (NS) NS F	Once (G)	NS	LE	Death			533 F	LD_{50}
2,3,4,5-Tetrachlorophenol Ahlborg and Larsson 1978									

Table 2-8. Levels of Significant Exposure to Other Chlorophenols – 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)	Effects
7	Mouse (C57 black) 4 F, 4 M	Once (G)	NS	LE	Death			89 M	LD_{50}
2,3,5,6-Tetrachlorophenol Ahlborg and Larsson 1978									
8	Mouse (C57 black) 4 M, 4 F	Once (G)	NS	LE	Death			400 F	LD_{50}
2,3,4,5-Tetrachlorophenol Ahlborg and Larsson 1978									

[a]The number corresponds to entries in Figure 2-15; differences in levels of health effects and cancer effects between male and females are not indicated in the figure. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

Bd wt or BW = body weight; CS = clinical signs; Develop = developmental; DX = developmental effects; (F) = feed; F = female(s); FX = fetal toxicity; (G) = gavage; (GO) = gavage in oil; GD = gestation day; LD_{50} = dose producing 50% lethality; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified

Figure 2-15. Levels of Significant Exposure to Other Chlorophenols – Oral
Acute (≤14 days)

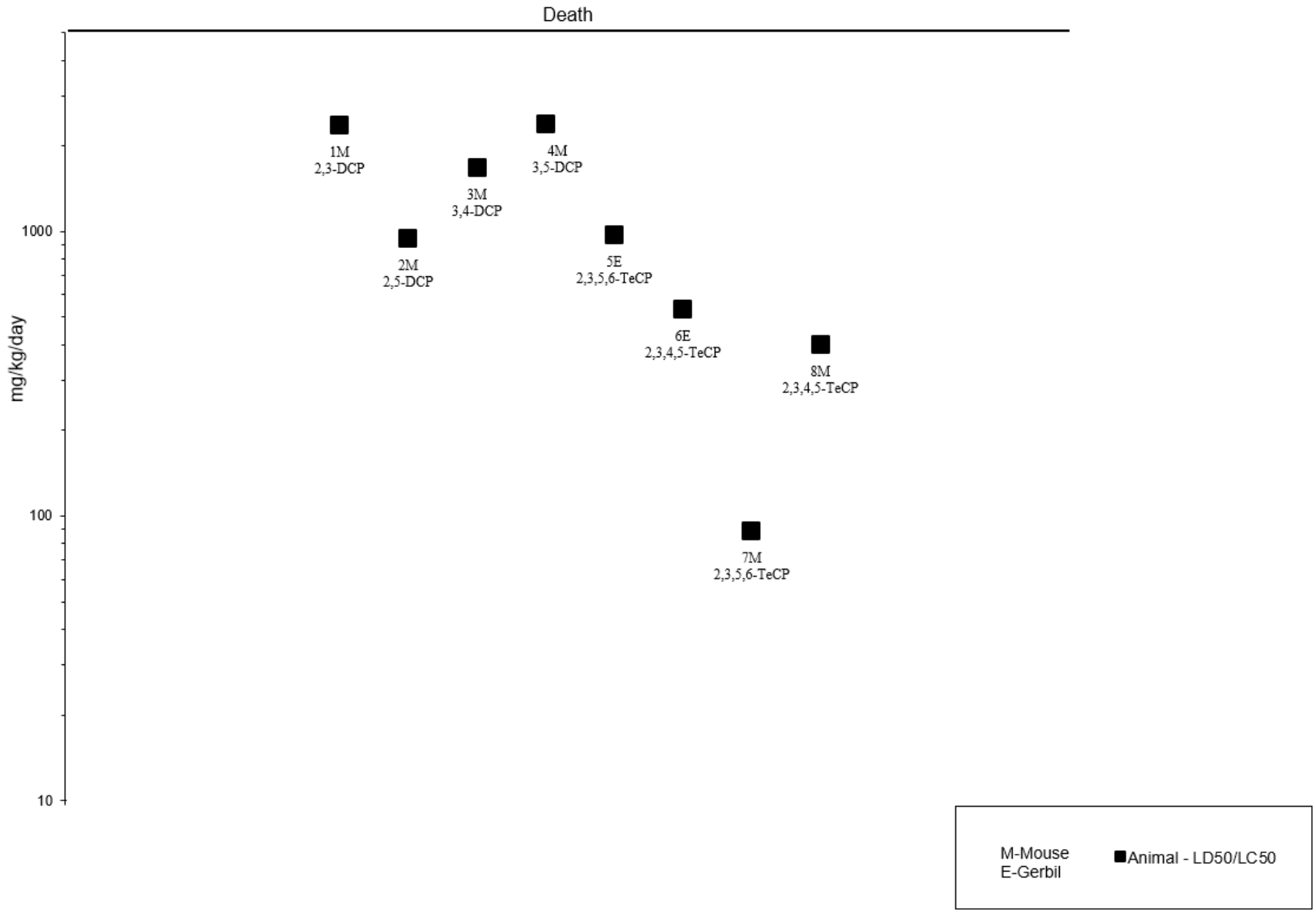


Table 2-9. Levels of Significant Exposure to Chlorophenols – Dermal

Species (strain) No./group	Exposure parameters	Doses (mg/kg)	Parameters monitored	Endpoint	NOAEL (mg/kg)	Less serious LOAEL (mg/kg)	Serious LOAEL (mg/kg)	Effects
ACUTE EXPOSURE								
Rabbit (New Zealand White) 1 M and/or F	24 hours	631, 1,000, 1,580	LE, CS, GN	Death			1,580	2/2 rabbits died
2-Chlorophenol Monsanto 1975								
Mouse (dd) 10–20 M	6 hours	2.5, 5, 10, 25, 50, 100	OW	Immuno	100 M			No effect on ear weight
4-Chlorophenol Dohi et al. 1989								
Rabbit (New Zealand albino) 2 F	24 hours	200, 398	LE, CS, HP, BW	Dermal		200 F		Moderate to marked erythema, edema, and necrosis
2,4-Dichlorophenol Hencke and Lockwood 1978								
Rabbit (New Zealand albino) 2 M	24 hours	250, 500, 1,000, 2,000, 4,000	CS, LE	Death			1,414 M	LD_{50}
				Dermal		250 M		Moderate to marked erythema, slight to marked edema and necrosis
				Neuro		250 M		Lethargy
2,4-Dichlorophenol Carreon et al. 1980b								
Rat (Sprague-Dawley) 10 M, 10 F	24 hours	2,000	LE	Death			2,000 M	1/10 died
2,3,4,5-Tetrachlorophenol Shen et al. 1983								
Rat (Swiss-Webster)	24 hours	485 (M); 565 (F)	LE	Death			485 M	LD_{50}
2,3,4,6-Tetrachlorophenol Shen et al. 1983								

Table 2-9. Levels of Significant Exposure to Chlorophenols – Dermal

Species (strain) No./group	Exposure parameters	Doses (mg/kg)	Parameters monitored	Endpoint	NOAEL (mg/kg)	Less serious LOAEL (mg/kg)	Serious LOAEL (mg/kg)	Effects
Rat (Sprague-Dawley) 10 M, 10 F	24 hours	2,000	LE	Death			2,000 F	2/10 died
2,3,5,6-Tetrachlorophenol								
Shen et al. 1983								

BW = body weight; CS = clinical signs; (F) = feed; F= female(s); GN = gross necropsy; HP = histopathology; LD_{50} = dose producing 50% death; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurotoxicity; NOAEL = no-observed-adverse-effect level; OW = organ weight

2.2 DEATH

Mortality studies of workers at phenoxy herbicide factories where exposure to 2,4,5-TCP, 2,4,6-TCP, and/or 2,4-DCP occurred have not shown increased mortality from any cause (Coggon et al. 1991; Kogevinas et al. 1997; Ott et al. 1987). Occupational studies that focus on cancer-related deaths are discussed in Section 2.19. Case reports of mortalities among workers exposed to 2,4-DCP are discussed below in the section for that chlorophenol.

Acute oral LD_{50} values from animal studies are compared across species, sex, vehicle, and compound in Table 2-10. The data indicate little to no differences in oral LD_{50} values between sexes or species. Vehicle was an important determinant of LD_{50} values for 2,3,4,6- and 2,3,5,6-TeCP, with lower values obtained when these tetrachlorophenols were administered in ethanol compared with propylene glycol. For 2,3,4,5-TeCP, vehicle did not appear to influence LD_{50}. Among compounds tested under the same conditions, there were no marked differences in potency, with the exception of the greater potency (lower LD_{50} values) of 2,3,4,6- and 2,3,5,6-TeCP compared with 2,3,4,5-TeCP when administered in ethanol to mice.

Table 2-10. Comparisons Among Oral LD_{50} Values for Chlorophenols

	Oral LD_{50} (mg/kg)									
Species	Rats		Mice							Gerbils
Sex	NS	Male	Male			Female				Female
Vehicle Compound	Olive oil[a]	Corn oil[b]	diH_20[c]	Corn oil[c]	40% Ethanol[d]	diH_20[c]	Corn oil[c]	40% Ethanol[d]	Propylene glycol[d]	Propylene glycol[d]
2-CP	670	–	347	–	–	345	–	–	–	–
4-CP	670	–	–	1,373	–	–	1,422; 1,640[e]	–	–	–
2,3-DCP	–	–	–	2,585	–	–	2,376	–	–	–
2,4-DCP	–	–	–	1,276	–	–	1,352	–	–	–
2,5-DCP	–	–	–	1,600	–	–	946	–	–	–
3,4-DCP	–	–	–	1,685	–	–	2,046	–	–	–
3,5-DCP	–	–	–	2,643	–	–	2,389	–	–	–
2,4,5-TCP	–	2,960	–	–	–	–	–	–	–	–
2,3,4,5-TeCP	–	–	–	–	572	–	–	400	677	533

Table 2-10. Comparisons Among Oral LD_{50} Values for Chlorophenols

	Oral LD_{50} (mg/kg)									
Species	Rats		Mice							Gerbils
Sex	NS	Male	Male			Female				Female
Vehicle Compound	Olive oil[a]	Corn oil[b]	diH_20[c]	Corn oil[c]	40% Ethanol[d]	diH_20[c]	Corn oil[c]	40% Ethanol[d]	Propylene glycol[d]	Propylene glycol[d]
2,3,4,6-TeCP	–	–	–	–	163	–	–	131	735	698
2,3,5,6-TeCP	–	–	–	–	89	–	–	109	543	979

[a]Deichmann and Mergard 1948
[b]McCollister et al. 1961
[c]Borzelleca et al. 1985b
[d]Ahlborg and Larsson 1978
[e]Shi et al. 2013

CP = chlorophenol; DCP = dichlorophenol; TCP = trichlorophenol; TeCP = tetrachlorophenol

2-CP. In two studies with limited experimental details, nose-only exposure of male and female Wistar rats to 2-CP for 4 hours to a concentration of 908 ppm (Rhone-Poulenc 1991) and whole-body exposure of Sprague-Dawley rats to 2-CP for 6 hours at 620 ppm (Monsanto 1975) did not result in any deaths. In a dose-range-finding study of neonatal Sprague-Dawley rats (postnatal day [PND] 4) given 2-CP by gavage, all animals given 500 mg/kg/day died by the 9th day of exposure, while all survived doses up to 300 mg/kg/day for 18 days in the main study (Hasegawa et al. 2005). When male and female ICR mice were administered daily gavage doses of 35, 69, or 175 mg/kg/day 2-CP in corn oil for 14 days, no exposure-related deaths occurred at the two lower treatment levels, while all mice exposed at 175 mg/kg/day died (Borzelleca et al. 1985a).

Results of a contract laboratory study indicate that the dermal LD_{50} of 2-CP in rabbits is between 1,000 and 1,580 mg/kg (Monsanto 1975). Antemortem observations included increasing weakness, tremors, collapse, and coma. Gross necropsy in the rabbit studies indicated hemorrhage in the lungs, liver discoloration, gastrointestinal inflammation, darkened spleens and kidneys, and enlarged gall bladders. The study data do not clearly indicate whether mortality resulted from any of these effects. Conclusions from this study are limited by small test groups and/or the lack of information regarding experimental methodology.

4-CP. Daily gavage doses of 1,000 mg/kg/day were lethal to 6/12 male and 5/12 female Crl:CD (SD) rats within 12 days of the first dose in a 42–53-day reproductive/developmental toxicity screening study; no deaths occurred at any time at doses up to 200 mg/kg/day (BSRC 2011). Based on clinical signs observed

prior to death, the mortalities were attributed to irritant and central nervous system effects (BSRC 2011). All male and three of four female Sprague-Dawley rats given 500 mg/kg/day 4-CP by gavage beginning on PND 4 died (timing of deaths not reported), while there were no deaths at 300 mg/kg/day in the main study (18 days of exposure, PNDs 4 –21) (Hasegawa et al. 2005).

The acute oral LD_{50} for 4-CP in female ICR mice observed for 7 days after dosing was 1,640 mg/kg/day (Shi et al. 2013). The authors noted that the mice expired within 3 hours of dosing at the highest of the three tested doses (1,575 mg/kg).

2,3-DCP. Borzelleca et al. (1985b) reported acute oral LD_{50} values of 2,585 and 2,376 mg/kg for male and female mice, respectively, given 2,3-DCP as a single dose in corn oil.

2,4-DCP. Four fatalities were reported among chemical workers following acute accidental exposures to 2,4-DCP (CDC 2000). In all cases, the predominant exposure route was dermal, but some effects in lungs and stomach were noted to have been caused by inhalation. A 29-year-old male chemical plant worker lost consciousness almost immediately and died 1 hour after being sprayed with 2,4-DCP on his forearms, right knee, right thigh, and face. CDC (2000) did not report the volume of fluid, concentration of 2,4-DCP in the fluid, or duration of skin contact with the fluid. Pulmonary edema and chemical burns of exposed skin surfaces were the only findings during autopsy. 2,4-DCP levels detected in this patient's blood and urine samples were 13.1 and 6.2 mg/L, respectively. The cause of death was reported as "acute 2,4-dichlorophenol intoxication." A 45-year-old male chemical worker died after being sprayed with steam containing 2,4-DCP (volume and/or concentration not reported). Prior to death, the worker experienced loss of consciousness and convulsions. The time elapsed from exposure to death was not reported. Thermal burns from steam exposure were observed on the skin, mouth, and upper airway, and chemical burns were also observed on the skin. Postmortem findings included pulmonary and laryngeal congestion, alveolar hemorrhage, and hepatocellular fatty change. 2,4-DCP concentrations in biological fluids were not reported. The cause of death was reported as "acute steam and dichlorophenol exposure." A 33-year-old chemical worker died approximately 90 minutes after he was splashed over 60–65% of his body with a solution containing 51% 2,4-DCP. Prior to death, the worker experienced loss of consciousness and convulsions. The autopsy revealed significant damage to the lungs with hemorrhagic fluid in both lungs and in the stomach, as well as intense congestion and petechial hemorrhages in the brain (CDC 2000). Finally, a 64-year-old chemical worker died 20 minutes after 2,4-DCP was splashed on his head and neck (volume and/or concentration not reported). No additional information was reported.

A worker who splattered pure 2,4-DCP on portions of his right arm and leg while disposing of industrial waste collapsed and experienced a seizure within 20 minutes of the accident and died shortly thereafter (CDC 2000; Kintz et al. 1992). Postmortem examination revealed blood and urine 2,4-DCP concentrations of 24.3 and 5.3 mg/L, respectively; concentrations in bile and stomach were 18.7 and 1.2 mg/L, respectively. The identity of 2,4-DCP was confirmed by mass spectrometry, and a screen for other drugs including ethanol, organic solvents, tranquilizers, and drugs of abuse was negative.

When treated on gestation days (GDs) 6–15 with gavage doses of 2,4-DCP in corn oil (750 mg/kg/day), 4 of 34 pregnant Fischer-344 rats died (Rodwell et al. 1989), while all nonpregnant rats treated with 2,000 mg/kg/day in the diet for 14 days survived (NTP 1989). Although pregnant rats may be more susceptible, the difference in effect may also be a result of differences in the rate of exposure between gavage and dietary dosing. All rats and mice exposed to 2,4-DCP in the diet for 13 weeks at doses of 2,000 or 2,600 mg/kg/day survived (NTP 1989). However, all mice died when exposed to 5,200 mg/kg/day for 3 weeks (NTP 1989). In a 2-year study, decreased survival was not observed in rats fed 2,4-DCP in the diet at doses up to 440 mg/kg/day or in mice fed 2,4-DCP in the diet at doses up to 1,300 mg/kg/day for 103 weeks (NTP 1989).

A dermal LD_{50} of 1,415 mg/kg has been reported for male rabbits exposed to 2,4-DCP for 24 hours (Carreon et al. 1980b). Because there were only two rabbits per dose group, the 95% confidence interval (CI) on this value is very large (236–8,455 mg/kg).

2,5-DCP. Oral LD_{50} values of 1,600 and 946 mg/kg were reported for male and female mice, respectively, administered single doses of 2,5-DCP in corn oil (Borzelleca et al. 1985b).

3,4-DCP. In mice given a single dose of 3,4-DCP in corn oil, acute LD_{50} values in males and females were 1,685 and 2,046 mg/kg, respectively (Borzelleca et al. 1985b).

3,5-DCP. Acute oral LD_{50} values of 2,643 and 2,389 mg/kg were reported for male and female mice, respectively, given 3,5-DCP in corn oil as a single dose (Borzelleca et al. 1985b).

2,4,5-TCP. No deaths were observed among rats treated by gavage (18 doses in olive oil) or in the diet with 2,4,5-TCP at doses up to 1,000 mg/kg/day for 90 days (McCollister et al. 1961). In addition, no

deaths were observed in rabbits treated with 20 gavage doses of 500 mg/kg/day 2,4,5-TCP over 28 days (McCollister et al. 1961).

2,4,6-TCP. Deaths were observed during the first 4 weeks of treatment among female (3/40) and male rats (8/25) exposed to 2,4,6-TCP in corn oil by gavage for 11 weeks at 1,000 mg/kg/day, but not at 500 mg/kg/day (Blackburn et al. 1986). The females were treated 2 weeks prior to pregnancy and then throughout gestation. No deaths were observed in rats treated by gavage with 2,4,6-TCP in corn oil at 720 mg/kg/day for 90 days (Bercz et al. 1990). In a 7-week dietary study, 1 of 5 rats died at 1,075 mg/kg/day and 4 of 10 mice died at 4,095 mg/kg/day, with no deaths observed at 735 mg/kg/day among rats or at 2,795 mg/kg/day among mice (NCI 1979). In a chronic study, no increased mortality trend was observed in rats or mice treated with 2,4,6-TCP in the diet at concentrations up to 500 mg/kg/day for 106–107 weeks for rats and 1,356 mg/kg/day for 105 weeks for mice (NCI 1979).

2,3,4,5-TeCP. As shown in Table 2-10, acute oral lethality studies of 2,3,4,5-TeCP resulted in a narrow range of LD_{50} estimates between 400 and 677 mg/kg in male and female mice and female gerbils (Ahlborg and Larsson 1978). Vehicle did not appear to significantly influence the oral lethality of 2,3,4,5-TeCP, in contrast to other tetrachlorophenols: the LD_{50} values in female mice exposed to 2,3,4,5-TeCP were 400 mg/kg when administered in 40% ethanol and 677 mg/kg when administered in propylene glycol (Ahlborg and Larsson 1978).

Unoccluded dermal application of 2,000 mg/kg 2,3,4,5-TeCP resulted in 1 out of 20 deaths in Sprague-Dawley rats (Shen et al. 1983). Clinical signs preceding death included initial hyperactivity followed by hypoactivity, neuromuscular weakness, and convulsions (Shen et al. 1983).

2,3,4,6-TeCP. Oral LD_{50} values for 2,3,4,6-TeCP appear to depend on the vehicle in which it is administered. When administered in ethanol, LD_{50} values of 163 and 131 mg/kg were obtained in male and female mice, respectively (Ahlborg and Larsson 1978). In contrast, when administered in propylene glycol, the LD_{50} values were 735 mg/kg in female mice and 698 mg/kg in female gerbils (Ahlborg and Larsson 1978). No deaths were observed in rats treated by gavage with 200 mg/kg/day 2,3,4,6-TeCP in olive oil during gestation (EPA 1987a, 1987b) or for 90 days (EPA 1986).

In Sprague-Dawley rats, dermal LD_{50} values for commercial tetrachlorophenol, consisting primarily of the 2,3,4,6- isomer (at least 90%), were 485 mg/kg in males and 565 mg/kg in females (Shen et al. 1983).

Prior to death, the rats exhibited initial hyperactivity followed by hypoactivity, neuromuscular weakness, and convulsions.

2,3,5,6-TeCP. In Sprague-Dawley rats exposed by unoccluded dermal application of 2,000 mg/kg 2,3,5,6-TeCP, 2 out of 20 animals died after exhibiting hyperactivity followed by hypoactivity, neuromuscular weakness, and convulsions (Shen et al. 1983).

2.3 BODY WEIGHT

No studies were located regarding body weight effects in humans following exposure to any of the chlorophenols discussed in this profile. In animals, acute-duration oral exposures resulted in adverse effects on body weight at doses as low as 69 mg/kg/day 2-CP in mice (Borzelleca et al. 1985a) and 1,000 mg/kg/day 2,4-DCP in rats (NTP 1989). Higher doses of 2,4-DCP (≥2,000 mg/kg) resulted in serious body weight decrements (more than 25% compared with controls) in both rats and mice (NTP 1989). After intermediate-duration oral exposure, biologically significant decreases in body weight were noted in rats after exposure to ≥100 mg/kg/day 2,3,4,6-TeCP (Dodd et al. 2012; EPA 1986), ≥735 mg/kg/day 2,4,6-TCP (Blackburn et al. 1986; NCI 1979), or 1,000 mg/kg/day 2,4-DCP (NTP 1989), and in mice exposed to 2,600 mg/kg/day 2,4-DCP (NTP 1989). In the few available chronic oral studies in animals, doses of ≥250 mg/kg 2,4-DCP or 2,4,6-TCP in rats resulted in body weight decreases of at least 10% (NCI 1979; NTP 1989). In mice, body weight decreases of up to 19% compared with controls were seen after chronic oral exposure to 820 mg/kg/day 2,4-DCP (NTP 1989).

2-CP. No changes in body weight were observed during the 15-day observation period after rats were exposed (nose only) to 2-CP at 908 ppm for 4 hours in an acute lethality study with no controls (Rhone-Poulenc 1991). In a 14-day study, both sexes of mice receiving 69 mg/kg/day 2-CP had body weight decrements of unspecified magnitude (Borzelleca et al. 1985a); the NOAEL was 35 mg/kg/day. In Sprague-Dawley rats administered 2-CP by gavage at doses up to 257 mg/kg/day for 10 days, no significant effect on body weight was observed (Daniel et al. 1993). Gavage doses up to 1,000 mg/kg/day 2-CP administered to young (5–6 weeks old) Sprague-Dawley rats for 28 days did not result in body weight changes (Hasegawa et al. 2005).

When Sprague-Dawley rats received 2-CP by gavage for 90 days, doses of 150 mg/kg/day resulted in modestly increased body weights at the end of the experiment (11 and 7% higher than controls in males and females, respectively) (Daniel et al. 1993). No effects on body weight were observed in rats treated

with 2-CP in drinking water at doses of 50 mg/kg/day during gestation and lactation (at doses up to 76 mg/kg/day) or up to 7 months of age (at doses up to 62 mg/kg/day) (Exon and Koller 1982, 1983b).

4-CP. Single-day oral exposure of pregnant Sprague-Dawley rats to 1,000 mg/kg 4-CP resulted in significant body weight loss (Kavlock 1990). By 72 hours after dosing, the body weight difference was no longer statistically significantly different from controls. Doses ≤667 mg/kg/day did not inhibit body weight gain (Kavlock 1990). Gavage doses up to 500 mg/kg/day 4-CP administered to young (5–6 weeks old) Sprague-Dawley rats for 28 days did not result in body weight changes (Hasegawa et al. 2005). At 1,000 mg/kg/day for 42–53 days, 4-CP induced significant reductions in body weight and food consumption; this dose was also lethal to about half of exposed rats (Bioscience Research Center 2011).

2,4-DCP. Body weights of pregnant animals treated on GDs 6–15 were reduced at 375 mg/kg/day, but not at 200 mg/kg/day (Rodwell et al. 1989). No body weight effects were observed in BALB/c mice receiving 2,4-DCP in drinking water (~260 mg/kg/day) for 14 days (Aydin et al. 2009). Studies with rats and mice fed diets containing 2,4-DCP for acute, intermediate, and chronic durations revealed dose-related decreases in food intake and body weight that were attributed to poor palatability of the treated diets (NTP 1989). Body weights were not affected in mice treated with 2,4-DCP in the diet at doses up to 230 mg/kg/day (Kobayashi et al. 1972) or in drinking water at doses up to 491 mg/kg/day (in females) or 383 mg/kg/day (in males) (Borzelleca et al. 1985a, 1985c). To improve palatability in drinking water, Borzelleca et al. (1985a, 1985c) added a 1:9 emulphor:water solution (modified vegetable oil). Body weights were not affected in Sprague-Dawley rats exposed to 2,4-DCP from conception through weaning and for an additional 15 weeks in drinking water at doses up to 44 mg/kg/day (Exon and Koller 1985; Exon et al. 1984).

Body weight effects were observed in a 2-generation reproductive toxicity study in Wistar-Hanover rats (Aoyama et al. 2005). Groups of 24 rats/sex/group were administered a diet containing 2,4-DCP at 0, 500, 2,000 or 8,000 ppm, which corresponded to 0, 33.4, 134, or 543 mg/kg/day for males and 0, 49.1, 194, or 768 mg/kg/day for females. Feed aversion was apparent since body weight gain and feed consumption were significantly decreased in mid-dose P generation females at the end of the pre-mating, and during the gestational periods, and in high-dose P and F1 generation males and females throughout exposure (Aoyama et al. 2005).

2,4,5-TCP. Treatment of rats by gavage with 2,4,5-TCP for 18 or 24 days at 1,000 mg/kg/day had no effect on body weight (McCollister et al. 1961). In contrast, treatment with 2,4,5-TCP in the diet at

1,000 mg/kg/day for 90 days resulted in a 24% decrease in body weight gain in female rats, but not in male rats (McCollister et al. 1961). No effects on food intake were measured.

2,4,6-TCP. Treatment of rats with 2,4,6-TCP by gavage at 1,000 mg/kg/day for 2 weeks before mating and throughout gestation resulted in reduced body weights through GD 14 (Blackburn et al. 1986). Body weights on GD 21 were not significantly different from those of the controls. No effect on body weight was observed in rats treated by gavage with 2,4,6-TCP at 1,000 mg/kg/day for 90 days (Bercz et al. 1990) or 11 weeks (Blackburn et al. 1986), suggesting that pregnant animals may be more sensitive to effects on body weight following treatment with 2,4,6-TCP. No effect on body weight was observed in rats treated with 2,4,6-TCP in drinking water at 44 mg/kg/day from conception through weaning and for an additional 10–15 weeks (Exon and Koller 1985). Body weights were significantly reduced in rats treated with 2,4,6-TCP in the diet for 7 weeks at 735 mg/kg/day, but not at 500 or 250 mg/kg/day, for 105 weeks (NCI 1979). Body weights were also significantly decreased in mice fed 2,600 mg/kg/day 2,4,6-TCP in the diet for 7 weeks and at 658 mg/kg/day for 105 weeks (NCI 1979). No effects on body weight were observed in mice fed 1,300 mg/kg/day 2,4,6-TCP for 7 weeks (NCI 1979). Food intake data were not provided in the NCI (1979) study. The fact that 2,4,6-TCP affected body weight following dietary intake but had little effect at similar doses following gavage treatment suggests that 2,4,6-TCP may have caused the food to be less palatable and reduced food intake in mice at the concentrations used in the NCI (1979) study. Therefore, decreased body weight may be an effect of decreased food intake rather than an effect of 2,4,6-TCP treatment.

2,3,4,6-TeCP. Acute-duration exposure to 2,3,4,6-TeCP at doses up to 200 mg/kg/day for 5 days did not result in any body weight changes (Dodd et al. 2012). In the same study, treatment for 2 or 4 weeks at 200 mg/kg/day similarly had no effect on body weight (Dodd et al. 2012). Body weight was significantly decreased in rats treated by gavage with 2,3,4,6-TeCP at 100 mg/kg/day for 90 days (Dodd et al. 2012; EPA 1986), but not 100 mg/kg/day for 55 days (Hattula et al. 1981).

2.4 RESPIRATORY

Human data on respiratory effects of chlorophenols are limited by confounding by co-exposures, poor exposure characterization, and small numbers of exposed subjects. No repeated-exposure animal studies of chlorophenol exposure by inhalation were located. In oral animal studies, only one (NTP 1989) reported respiratory system effects. Nasal lesions were seen in male rats fed 210 mg/kg/day 2,4-DCP in

feed for 103 weeks, but not in female rats or in mice fed as much as 1,300 mg/kg/day. It is possible that the lesions occurred from aspiration while eating.

When compared to 260 unexposed referents, 281 workers involved in the production of sodium trichlorophenol (2,4,5-TCP) and its derivatives for 18 years had no increased incidence of chronic bronchitis, chronic obstructive pulmonary disease, or altered measures of pulmonary function (Calvert et al. 1991). Occupational exposure of seven workers to an unspecified trichlorophenol isomer, in addition to other chemicals, by chronic inhalation for 2–10 years was associated with adverse upper airway and chest symptoms (cough, chronic bronchitis, chest wheezing), altered pulmonary function (reduced expiratory flow rate of the lung, increased closing volume of the lung, increased elastic recoil pressure of the lung), and pulmonary lesions (interstitial densities) (Alexandersson and Hedenstierna 1982). The air exposure concentrations were characterized as 0.003 mg/L (0.02 ppm) trichlorophenol or less, with potential for considerable variability. The study was also limited by the very small number of subjects (seven), which included three smokers. It is, therefore, not possible to determine whether the exposure to trichlorophenol alone induced the reported respiratory effects or whether smoking was a contributing factor.

Lumber mill workers (40 exposed and 40 controls) exposed to a mixture of tetrachlorophenols (specific isomers not stated) and pentachlorophenol reported upper respiratory tract irritation more frequently than unexposed workers (Kleinman et al. 1986). Tetrachlorophenol air concentrations ranged from 0.8 to 12.2 μg/m^3, and pentachlorophenol concentrations were below the limit of detection (0.5 μg/m^3).

In a cross-sectional study of 2,125 children and adults participating in NHANES (2005–2006) (Jerschow et al. 2014), urinary levels of 2,5-DCP were associated with increased odds of all self-reported measures of asthma (told by doctor; prescribed medication for wheezing; missed work due to wheeze; and wheezing during exercise; odds ratios (ORs) for 3rd tertile compared to 1st tertile ranged from 2.2 to 10.0, and p-value for trend <0.05 for all measures) among atopic wheezers (n=156). Urinary 2,4-DCP was associated only with an increased odds of missing work due to wheezing (OR 11.4 for 3rd tertile compared to 1st tertile; p-value for trend <0.01) among atopic wheezers (Jerschow et al. 2014). Among non-atopic wheezers (n=94), none of the asthma metrics were clearly increased with urinary concentrations (Jerschow et al. 2014). In a study of 3,617 adult NHANES (2007–2010) participants (Rooney et al. 2018), no association between prevalence of respiratory diseases (asthma, chronic bronchitis, or emphysema) and urinary 2,4- or 2,5-DCP levels was observed.

2-CP. In a 4-hour inhalation (nose only) exposure to 2-CP, tachypnea was observed in one of five male, but not female, rats at 908 ppm (Rhone-Poulenc 1991). Dark red foci were observed in the lungs (right caudal, median, or left lobe) of male and female rats exposed to 17 (2/5 males, 2/5 females) or 104 ppm (4/5 males, 2/5 females) but were not found at 908 ppm (Rhone-Poulenc 1991). No controls were used in this study. There were no treatment-related changes in lung weights or gross or microscopic pathology findings in the lungs of Sprague-Dawley rats administered 2-CP by gavage at doses up to 257 mg/kg/day for 10 days (Daniel et al. 1993), up to 1,000 mg/kg/day for 28 days (Hasegawa et al. 2005), or up to 150 mg/kg/day for 90 days (Daniel et al. 1993).

4-CP. When young (5–6 weeks old) Sprague-Dawley rats were administered 4-CP at doses up to 500 mg/kg/day by gavage for 28 days, lung weights were not affected, and no treatment-related microscopic pathology findings were noted in the lungs (Hasegawa et al. 2005). BSRC (2011) reported dyspnea and abnormal respiratory noises in male rats given 1,000 mg/kg/day 4-CP by gavage for 42 days; this dose was lethal to 6/12 males.

2,4-DCP. Lung hemorrhaging occurred in rats treated with a single lethal gavage dose of 2,4-DCP (Wil Research Laboratories 1982). Nasal lesions were noted in male but not female rats fed 210 mg/kg/day for 103 weeks; however, no nasal lesions were observed in mice fed as much as 1,300 mg/kg/day for the same duration (NTP 1989). Therefore, this effect may be specific to the male rat or may have been a result of aspiration while eating. Histopathological changes have not been observed in the lungs of rats exposed to 2,4-DCP at doses up to 5,200 mg/kg/day in feed (NTP 1989). In chronic-duration studies, neither rats nor mice exhibited treatment-related microscopic changes in the lungs after exposure to 2,4-DCP in the diet for 103 weeks at doses up to 440 mg/kg/day (rats) or 1,300 mg/kg/day (mice) (NTP 1989).

2,4,5-TCP. No lung weight changes or histopathological changes in the lungs were observed in rats given 2,4,5-TCP by gavage at doses up to 1,000 mg/kg/day for 18 exposures over 24 days, in rabbits given doses up to 500 mg/kg/day for 20 exposures over 28 days, or in rats exposed for 98 days via the diet at concentrations up to 1% in feed (about 1,000 mg/kg/day) (McCollister et al. 1961).

2,4,6-TCP. Histopathological changes were not observed in the lungs of rats or mice following oral administration of 2,4,6-TCP for 5–13 weeks at doses up to 1,000 mg/kg/day (Bercz et al. 1990; Blackburn et al. 1986; NCI 1979) or for 103 weeks at doses up to 500 mg/kg/day (rats) or 1,356 mg/kg/day (mice) (NCI 1979)

2,3,4,6-TeCP. No histopathological changes were observed in the lungs of rats orally exposed to 2,3,4,6-TeCP (doses up to 2,000 mg/kg/day by daily gavage) for 90 days (EPA 1986).

2.5 CARDIOVASCULAR

No adequate studies of cardiovascular effects in humans exposed to chlorophenols by any route were located. A number of cross-sectional studies of chlorophenols in urine and cardiovascular endpoints in humans have been published. However, these studies are of limited utility for hazard identification because exposures are measured at the same time or after the health effect is assessed, and because chlorophenols in urine can occur as a result of metabolism of other compounds such as chlorinated benzenes (see Section 3.3.1 for further information). In available studies of animals exposed orally to chlorophenols, no effects on heart weights or cardiac histopathology were reported.

Electrocardiograms were normal in three individuals who developed chloracne following occupational exposure (inhalation and dermal) to chlorophenols and other compounds during the manufacture of 2,4-DCP and 2,4,5-TCP (Bleiberg et al. 1964).

Available cross-sectional studies have not shown associations between urinary concentrations of 2,4-DCP and obesity, overweight, body mass index (BMI), waist circumference, serum triglycerides or cholesterol, or blood pressure in children or adults (Parastar et al. 2018; Shiue 2014; Shiue and Hristova 2014). Similarly, no association between urinary 2,4-DCP levels and cardiovascular disease (coronary heart disease, heart attack, chronic heart failure, or stroke) prevalence was observed in a study of 3,617 adult NHANES (2007–2010) participants (Rooney et al. 2018). In a study in Iran, urinary levels of 2,5-DCP were associated with higher BMI z-score and waist circumference in 6–18-year-old children and adolescents and with lower systolic blood pressure in 6–11-year-old children (Parastar et al. 2018). However, urinary 2,5-DCP was not associated with high blood pressure in studies of adult NHANES participants (Shiue 2014; Shiue and Hristova 2014). Rooney et al. (2018) observed positive associations between urinary 2,5-DCP concentrations and coronary heart disease, but not with chronic heart failure or stroke in adult NHANES (2007–2010) participants. Parastar et al. (2018) observed a positive association between urinary 2,4,5-TCP and waist circumference among 12–18-year-old adolescents in Iran, and inverse associations between 2,4,5-TCP and high-density lipoprotein (HDL) cholesterol in both 6–11- and 12–18-year-old children and adolescents.

2-CP. In Sprague-Dawley rats administered up to 257 mg/kg/day 2-CP by gavage for 10 days, no treatment-related changes in heart weight or histopathology were observed (Daniel et al. 1993). Heart weights were not affected, and no microscopic heart changes were seen in Sprague-Dawley rats after 28 days of exposure (beginning at 5–6 weeks of age) to gavage doses up to 1,000 mg/kg/day 2-CP (Hasegawa et al. 2005). In a 90-day study by Daniel et al. (1993), neither cardiac weight nor microscopic findings in the heart were affected in Sprague-Dawley rats receiving doses up to 150 mg/kg/day 2-CP.

4-CP. When young Sprague-Dawley rats were given up to 500 mg/kg/day 4-CP by gavage for 28 days of exposure (beginning at 5–6 weeks of age), neither heart weight nor histology was affected by exposure (Hasegawa et al. 2005).

2,4-DCP. Heart weights of mice fed doses of up to 230 mg/kg/day 2,4-DCP for 6 months were not changed (Kobayashi et al. 1972). Studies of intermediate and chronic durations of 2,4-DCP-fed rats (fed 2,000 and 440 mg/kg/day, respectively) and mice (fed 2,600 and 1,300 mg/kg/day, respectively) showed no effect on histopathological examination of the heart (NTP 1989).

2,4,5-TCP. No heart weight nor histologic changes were observed in rats treated by gavage with 1,000 mg/kg/day of 2,4,5-TCP for 18 (out of 24) days, nor were histological changes observed in the hearts of rats treated with up to 1,000 mg/kg/day 2,4,5-TCP in the diet for 98 days (McCollister et al. 1961).

2,4,6-TCP. Treatment of rats orally administered doses as high as 1,000 mg/kg/day 2,4,6-TCP showed no change in heart weight over an intermediate (10 or 13 weeks) exposure period (Bercz et al. 1990; Blackburn et al. 1986). No treatment-related lesions were evident upon histopathologic examination of the hearts of rats and mice exposed to doses of 2,4,6-TCP as high as 720 mg/kg/day for 90 days (Bercz et al. 1990) and 1,356 mg/kg/day for 105 weeks (NCI 1979).

2,3,4,6-TeCP. No changes in heart weight or histology were observed in rats treated with 2,3,4,6-TeCP for 90 days (EPA 1986).

2.6 GASTROINTESTINAL

The self-reported prevalence of gastrointestinal disease was not increased among 281 TCP production workers with elevated serum markers of exposure (TCDD) (Calvert et al. 1992). However, the long lag time (at least 15 years) between exposure and examination of gastrointestinal symptoms compared with the rapid elimination of chlorophenols may invalidate the results. Few animal studies have indicated gastrointestinal effects after oral exposure to chlorophenols; when effects were observed, they typically followed gavage administration of high doses (≥1,000 mg/kg). The one exception is 2,3,4,6-TeCP; necrosis in the intestines was reported in Wistar rats given ≥100 mg/kg/day 2,3,4,6-TeCP by gavage for 55 days (Hattula et al. 1981).

2-CP. Sprague-Dawley rats exposed by gavage for 10 days to 2-CP doses up to 257 mg/kg/day or for 90 days to doses up to 150 mg/kg/day exhibited no treatment-related effects on gastrointestinal tract histology (Daniel et al. 1993).

4-CP. Histopathology findings consisting of squamous epithelial hyperplasia in the forestomach and erosion or ulcers in the esophagus and forestomach were observed in rats given 1,000 mg/kg/day 4-CP by gavage for up to 53 days; mortalities at this dose were partially attributed to these gastrointestinal effects (BSRC 2011). There were no histopathology examinations in the gastrointestinal tracts of animals receiving lower doses, so a NOAEL could not be identified.

2,4-DCP. Mild catarrhal enteritis was observed in female Sprague-Dawley albino rats given a single gavage dose of 316–5,000 mg/kg 2,4-DCP in corn oil and sacrificed 24 hours later (Hencke and Lockwood 1978). In another study, gross necropsy revealed reddened hindstomach and intestines in Fischer-344 rats given a single gavage dose of 2,400 mg/kg/day 2,4-DCP in corn oil (Wil Research Laboratories 1982). Following 2,4-DCP exposure in feed, no significant histopathological changes were observed in the gastrointestinal tracts of Fischer-344 rats fed 2,000 mg/kg/day, mice fed 2,600 mg/kg/day for 13 weeks, rats fed 440 mg/kg/day, or mice fed 1,300 mg/kg/day for 103 weeks (NTP 1989).

Diarrhea was observed in one of two female rabbits the day after a dermal exposure to a single dose of 398 mg/kg 2,4-DCP (Hencke and Lockwood 1978). This limited study suggests that either dermally applied 2,4-DCP, or the stress of being exposed to a skin irritant, can result in gastrointestinal effects in rabbits.

2,4,6-TCP. McCollister et al. (1961) reported diarrhea in rats given single gavage doses (≥1,000 mg/kg) of 2,4,5-TCP in an acute lethality study. These authors also reported wet abdominal areas among rats receiving 2,4,5-TCP at doses ≥300 mg/kg/day in the diet for 3 months, and suggested that the rats probably had diarrhea (McCollister et al. 1961).

2,4,6-TCP. In a 90-day study, no significant histopathological changes were observed in the gastrointestinal tracts of rats treated by gavage with 2,4,6-TCP at 720 mg/kg/day (Bercz et al. 1990). Histopathologic examination of the stomach and intestines of rats and mice exposed for 2 years to doses as high as 500 and 1,356 mg/kg/day 2,4,6-TCP, respectively, revealed no treatment-related lesions (NCI 1979).

2,3,4,6-TeCP. Wistar rats administered a single gavage dose of 632 mg/kg 2,3,4,6-TeCP had eosinophilic granulocyte infiltration in the stomach, mucosal hyperemia of the small intestine, and severe necrosis of the large intestine (Hattula et al. 1981). At doses of 432 and 518 mg/kg, mild necrosis was observed in the large intestines of 1/10 rats (each), with 70% of animals showing necrosis at 622 mg/kg; no effects on the large intestine were observed at 410 mg/kg. Focal necrosis of the small intestines was observed in Wistar rats treated by gavage for 55 days with 100 mg/kg/day2,3,4,6-TeCP, but not 10 mg/kg/day (Hattula et al. 1981). In contrast, no histopathological changes were observed in the gastrointestinal tracts of Sprague-Dawley rats treated with 2,3,4,6-TeCP at 200 mg/kg/day for 90 days (EPA 1986). 2,3,4,6-TeCP was administered in olive oil in both the Hattula et al. (1981) (concentrations not reported) and EPA (1986) studies (maximum concentration of 20 mg/mL). Because olive oil was used as a vehicle for both studies, the difference in gastrointestinal tract effects may be due to dosing solution concentrations or rodent strain.

2.7 HEMATOLOGICAL

Human data are inadequate to assess the hematological effects of chlorophenols, while animal studies do not indicate that the hematopoietic system is a sensitive target of oral exposure to chlorophenols. Clinical assessment of two patients occupationally exposed during the manufacture of 2,4-DCP- and 2,4,5-TCP-based herbicides showed hematology and blood chemistry parameters (blood counts, bleeding and clotting time, serum bilirubin, blood urea nitrogen [BUN], and others) to be within normal ranges (Bleiberg et al. 1964).

2-CP. Groups of mice (12/sex) were administered up to 69 mg/kg/day 2-CP daily by gavage in corn oil for 14 days. No adverse effects on standard hematological parameters, including total and differential white blood cells, red blood cells, platelets, hematocrit, hemoglobin, and coagulation measures were reported relative to unexposed controls (Borzelleca et al. 1985a). In a 10-day study, Daniel et al. (1993) found that doses up to 257 mg/kg/day 2-CP resulted in increased red blood cell count (12%) and hematocrit (28%) in male, but not female, Sprague-Dawley rats. However, the investigators indicated that the values remained within normal ranges for laboratory rats.

No hematologic changes (both erythrocyte and leukocyte parameters were measured) were observed in Sprague-Dawley rats exposed to 2-CP at doses up to 1,000 mg/kg/day for 28 days (Hasegawa et al. 2005). In a subchronic (90 day) study, doses up to 150 mg/kg/day 2-CP administered by gavage resulted in increased red blood cell count and hematocrit in females and increased mean corpuscular volume in males at 150 mg/kg/day (Daniel et al. 1993). Intermediate-duration pre- and postnatal (from conception through weaning at PND 21) exposure to 2-CP in drinking water (up to 73 mg/kg/day 2-CP) did not adversely affect red blood cell count, hematocrit, mean corpuscular volume, white cell count, or hemoglobin concentration (Exon and Koller 1982). However, pre- and postnatal exposure to 62 mg/kg/day 2-CP in drinking water for up to 24 months or until death resulted in increased (>10%) erythrocyte count and hemoglobin concentration and an increase in packed cell volume (Exon and Koller 1985). The investigators speculated that the increase may be secondary to effects on liver enzymes or hematopoietic stem cells and did not consider these effects biologically significant (Exon and Koller 1985).

4-CP. No changes to erythrocyte or leukocyte parameters were observed when Sprague-Dawley rats were given 4-CP by gavage (up to 500 mg/kg/day) for 28 days (Hasegawa et al. 2005).

2,4-DCP. Groups of 12 male and 12 female mice administered up to 638 mg/kg/day 2,4-DCP (by gavage in corn oil vehicle) for 14 days showed no adverse effects on hematological parameters, including total and differential white blood cells, red blood cells, platelets, hematocrit, hemoglobin, and coagulation measures relative to unexposed controls (Borzelleca et al. 1985a). However, when groups of 20 male and 20 female mice were dosed with up to 383 mg/kg/day of 2,4-DCP (male) and 49 mg/kg/day (female) in drinking water (containing 10% Emulphor) for 90 days, the number of white blood cells was increased in the high-dose males (Borzelleca et al. 1985a, 1985c). No changes in red or white blood cell counts were noted in mice exposed to 2,4-DCP at doses up to 230 mg/kg/day for 6 months (Kobayashi et al. 1972). In an NTP 13-week study (NTP 1989), bone marrow atrophy was observed in male rats treated with 2,4-DCP in the diet at 1,000 mg/kg/day and in female rats at 500 mg/kg/day. The atrophy resulted in

depletion of both erythroid and myeloid elements, with no effects observed at 250 mg/kg/day. No hematological effects were noted in mice treated with up to 2,600 mg/kg/day 2,4-DCP in the diet for 13 weeks or in rats or mice treated with 440 or 1,300 mg 2,4-DCP/kg/day, respectively, for 103 weeks (NTP 1989).

Chronic prenatal and postnatal exposure to 44 mg/kg/day 2,4-DCP resulted in increased (>10%) erythrocyte count and hemoglobin concentration, and an increase in packed cell volume (Exon and Koller 1985). As discussed above for 2-CP, the investigators believed these results to be secondary effects that were not biologically significant.

2,4,5-TCP. Treatment of rats with 2,4,5-TCP in the diet at doses up to 1,000 mg/kg/day for 98 days resulted in no changes in hematocrit, hemoglobin, or white blood cell counts (McCollister et al. 1961).

2,4,6-TCP. Administration of up to 720 mg/kg/day 2,4,6-TCP by gavage to rats for 90 days resulted in no adverse effects on erythrocyte count, leukocyte count, corrected leukocyte count, hemoglobin, hematocrit, platelet count, or a differential analysis of leukocytes (Bercz et al. 1990). Rats exposed orally for 7 weeks to 4,600 mg/kg/day 2,4,6-TCP exhibited a “moderate to marked increase” in splenic hematopoiesis (NCI 1979). A high incidence of bone marrow hyperplasia, leukocytosis, and monocytosis occurred in rats chronically exposed to 2,4,6-TCP in their diet at 250 or 500 mg/kg/day (NCI 1979). Further discussion of these hematological effects in rats can be found in Section 2.19. No hematological effects were evident in mice exposed chronically to 2,4,6-TCP in their diet at doses up to 1,300 mg/kg/day (NCI 1979).

2,3,4,6-TeCP. Treatment of rats by gavage with doses of 200 mg/kg/day 2,3,4,6-TeCP for 90 days significantly ($p<0.05$) reduced hemoglobin and hematocrit in both sexes (EPA 1986). Although the effects were statistically significant, the investigators did not consider the effects to be toxicologically significant because the group mean data were within the normal range of reference control data for the laboratory where the study was conducted. In addition, no gross or histopathologic evidence was found to support the decreases in hemoglobin and hematocrit.

2.8 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans. Studies of musculoskeletal endpoints after oral exposure to these chlorophenols were limited to muscle and bone histopathology examinations in studies of 2-CP, 2,4-DCP, and 2,3,4,6-TeCP. No treatment-related effects were reported.

2-CP. No microscopic lesions were identified in the skeletal muscle or bones of Sprague-Dawley rats given 2-CP by gavage at doses up to 257 mg/kg/day for 10 days or up to 150 mg/kg/day for 90 days (Daniel et al. 1993).

2,4-DCP. Ninety-day (up to 2,600 mg/kg/day) and 2-year (up to 1,300 mg/kg/day) dietary exposures of rats and mice to 2,4-DCP did not result in any histopathological changes in the muscle or ribs (NTP 1989).

2,3,4,6-TeCP. Single-dose (up to 632 mg/kg) and 55-day (up to 100 mg/kg/day) exposures to 2,3,4,6-TeCP produced no adverse histopathological effects on muscle in Wistar rats (Hattula et al. 1981).

2.9 HEPATIC

The limited available data on the hepatic effects of chlorophenols in exposed humans are potentially confounded by coexposures to other chemicals and alcohol use, rendering them of little utility for hazard identification. The liver is a well-established target of chlorophenol toxicity in laboratory animals exposed orally. Hepatic effects including clinical chemistry changes, increased liver weight, hepatocellular hypertrophy, and necrosis have been observed in rats and mice after acute, intermediate, and/or chronic oral exposure to 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP (Aydin et al. 2009; Bercz et al. 1990; BSRC 2011; Dodd et al. 2012; Exon and Koller 1985; Exon et al. 1984; Hasegawa et al. 2005; Kobayashi et al. 1972; McCollister et al. 1961; NCI 1979; NTP 1989).

Porphyria cutanea tarda (a skin condition caused by markedly decreased uroporphyrinogen decarboxylase activity in the liver) has been reported in workers employed in the manufacture of 2,4-DCP and 2,4,5-TCP (Bleiberg et al. 1964). Exposure to chlorophenols and intermediates was likely through inhalation and dermal contact. In a survey of 29 workers, 11 cases of porphyria were identified, based on urinary porphyrin excretion and 2 were studied in more detail. In the two cases, elevated serum transaminase levels and evidence of liver damage, e.g., regeneration of liver cells and hemofuscin (a

brownish-yellow pigment that results from the decomposition of hemoglobin) deposition, were detected from liver biopsies indicating the exposure was related to liver injury. No definitive conclusions regarding the connection between the porphyria or liver injury and exposure to chlorophenols in this group of workers can be made because the workers were exposed to a variety of chlorinated compounds, including a highly volatile chlorinated phenolic ether with six chlorines formed during the manufacturing process. Information on exposure to other liver toxicants, including the chronic ingestion of alcohol, was not obtained.

The results of a cross-sectional study of 281 trichlorophenol exposed production workers (and 260 controls) indicated an increased risk of elevated gamma-glutamyltransferase (GGT) activity in these workers (OR 2.27; CI 1.17–4.39, not adjusted for confounding factors) (Calvert et al. 1992). Statistical evaluation of interactions indicated elevated risk was restricted to workers with a history of alcohol consumption. Risk of increased GGT activity in workers with a history of alcohol consumption correlated with increased exposure (Calvert et al. 1992). Because the effect was seen only in those workers who consumed alcohol, and because the workers were also exposed to other compounds (including TCDD), and other hepatic enzymes were not increased, the utility of this study for hazard identification is limited.

In a cross-sectional study of 3,617 adult NHANES (2007–2010) participants (Rooney et al. 2018), no associations were observed between the prevalence of self-reported nonneoplastic liver conditions (not further specified) and urinary 2,4-DCP or 2,5-DCP levels.

2-CP. In a 10-day study in Sprague-Dawley rats exposed by gavage, no changes in liver weight, serum chemistry, or histology were observed at doses up to 257 mg/kg/day (Daniel et al. 1993). Mice administered doses up to 69 mg/kg/day 2-CP in corn oil by gavage for 14 days exhibited a significant decrease in liver weights in females with no effects on serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT); liver microsomal proteins; cytochrome P-450; cytochrome b5; activities of liver aminopyrine demethylase, aniline hydroxylase, or aryl hydrocarbon hydroxylase; or gross pathology findings (Borzelleca et al. 1985a). The results of the study were reported qualitatively, and histopathology examinations were not performed, so the toxicological significance of the liver weight decrease is not known.

Sprague-Dawley rats administered 1,000 mg/kg/day 2-CP by gavage for 28 days exhibited increased incidences of slight centrilobular hepatocellular hypertrophy (6/6 males and 5/6 females, compared with

0/6 male and 0/6 female controls) (Hasegawa et al. 2005). There were no microscopic findings in the livers of animals receiving lower doses (up to 500 mg/kg/day) (Hasegawa et al. 2005). An intermediate-duration study conducted by Daniel et al. (1993) showed no effects on liver weight, serum chemistry, or liver histopathology in Sprague-Dawley rats after 90 days of exposure to 2-CP at doses as high as 150 mg/kg/day (Daniel et al. 1993).

4-CP. Seven days after a single gavage dose up to 1,575 mg/kg 4-CP, liver weights of female ICR mice were not different from controls (Shi et al. 2013). In Sprague-Dawley rats, twice daily administration of as little as 0.32 mg/kg 4-CP for 2 weeks (0.64 mg/kg/day) resulted in significant activation of hepatic enzymes including cytochrome P-450, as well as elevated levels of microsomal protein and cytochrome P-450, without altering the liver/body weight ratio (Phornchirasilp et al. 1989b). The magnitude of increase in liver microsomal protein and cytochrome P-450 content over 2 weeks declined at doses >0.64 mg/kg/day. Following additional experiments in which treatment was given 2 times/day, both a 2-week exposure to 2.58 mg/kg/day and a ≥4-week exposure to 0.64 mg/kg/day resulted in morphological changes in hepatic ultrastructure (foamy cytoplasm and the proliferation and clustering of mitochondria and endoplasmic reticulum). The electron microscopic changes were not observed in the livers of rats treated at 1.28 mg/kg/day for 2 weeks. In separate studies, similar treatment doses of 4-CP had no effect on relative liver weights, microsomal zoxazolamine 6-hydroxylase activity, or serum lipids and lipoprotein concentrations, but did increase fasting glucose levels (Phornchirasilp et al. 1989a).

When Sprague-Dawley rats received 4-CP by gavage for 28 days, no liver histopathology findings were seen by light microscopy at doses up to 500 mg/kg/day (Hasegawa et al. 2005). In a reproductive/developmental toxicity screening study, rats given 1,000 mg/kg/day for 42–53 days exhibited increased incidences of centrilobular hepatocellular hypertrophy (Bioscience Research Center 2011). Histopathology examinations of the liver were not performed at lower doses in this study, so a NOAEL could not be determined.

In a study examining the role of oxidative stress on hepatic effects of 4-CP, ICR mice were given 0, 1, 10, or 100 mg/kg/day in corn oil by gavage for 28 days, and hepatic levels of superoxide dismutase (SOD), catalase (CAT), and malondialdehyde (MDA) (all normalized to protein levels in the liver) were measured (Shi et al. 2013). A significant increase in MDA was observed at the highest dose, suggesting that 4-CP may induce oxidative stress in the livers of mice. No apical endpoints were evaluated in this study.

2,4-DCP. In a 2-week study focused on male reproductive toxicity, significantly increased AST, ALT, and lactate dehydrogenase (LDH) were observed in BALB/c mice given 1,000 ppm 2,4-DCP in drinking water (~260 mg/kg/day) (Aydin et al. 2009). No changes in liver weight were reported. No other hepatic parameters were evaluated in this study. When guinea pigs were administered 40 mg/kg 2,4-DCP orally 3 times/week for 2 weeks, lipid peroxidation was increased in the liver (Clerhata et al. 1996). A high intake of ascorbic acid (50 mg/animal/day) significantly decreased lipid peroxidation in the liver in comparison to guinea pigs with low ascorbic acid intake (2 mg/kg/day). 2,4-DCP accumulation was also decreased in the liver of animals with high ascorbic acid intake.

Sprague-Dawley rats dosed at 44 mg/kg/day of 2,4-DCP *in utero* and through lactation (via maternal exposure in the drinking water) and postweaning in the drinking water for about 15 weeks exhibited increased absolute liver weights (19% higher than controls) (Exon et al. 1984). When mice were fed 383 or 230 mg/kg/day for 90 days or 6 months, respectively, no effects were noted on serum AST or ALT activities (Borzelleca et al. 1985a, 1985c; Kobayashi et al. 1972). One of 10 mice exposed to 230 mg/kg/day 2,4-DCP for 6 months had hepatocellular hyperplasia. No liver effects were observed at 100 mg/kg/day (Kobayashi et al. 1972). No histopathological changes were observed in the livers of Fischer-344 rats fed 2,4-DCP in the diet at doses up to 2,000 mg/kg/day for 13 weeks or 400 mg/kg/day for 103 weeks (NTP 1989). Liver weights or liver enzymes released to the serum were not measured in the NTP (1989) study. Mice fed 325 mg/kg/day of 2,4-DCP for 13 weeks had dose-related increases in hepatocellular necrosis (not further described) and multinucleated hepatocytes (NTP 1989). Diffuse syncytial alterations occurred in male mice given 800 mg/kg/day 2,4-DCP in the diet for 103 weeks (NTP 1989). The number of cells affected was small, and the affected cells were scattered within the histologic sections.

A single intraperitoneal injection of 2,4-DCP (120 mg/kg) to male Kunming mice resulted in significant increases in serum ALT and AST as well as histologic changes including inflammatory cell infiltration, central venous congestion, and abnormal morphology (not further detailed) in the livers at sacrifice 1, 3, or 5 days after dosing (Fu et al. 2016). These authors observed endoplasmic reticulum (ER) stress (measured as increased expression of Bip and CHOP messenger ribonucleic acid [mRNA] and proteins) in the livers of exposed mice on days 1 and 3 postdosing. Coupled with the observation that pretreatment with sodium tauroursodeoxycholate (TUDCA, an inhibitor of ER stress) reduced the effects of 2,4-DCP on serum ALT and AST (as well as Bip and CHOP mRNA levels), these data suggest that ER stress induction plays a role in the hepatic effects of 2,4-DCP. *In vitro* assays confirmed the effects of 2,4-DCP on Bip and CHOP mRNA and protein expression in human hepatocytes (HL7702 cells). Because ER

stress can trigger apoptosis, the authors performed additional *in vitro* assays to assess apoptosis. In cultured hepatocytes, 2,4-DCP exposure (0, 0.5, 0.75, or 1.0 mM) resulted in dose-dependent reductions in mitochondrial membrane potential (MMP) and increases in the percentages of apoptotic cells, providing further evidence for the role of ER stress and apoptosis in 2,4-DCP induced hepatic effects.

2,4,5-TCP. A dose of 400 mg/kg/day 2,4,5-TCP decreased microsomal cytochrome c-reductase activity and cytochrome P-450 activity in rats exposed for 14 days; ethyl-*p*-nitrophenylphosphonothionate detoxification was not affected (Carlson 1978). A similar experiment at 200 mg/kg/day 2,4,5-TCP showed no change in glucuronyltransferase activity in exposed rats (Carlson 1978). In another rat study, Kitchin and Brown (1988) examined the effects of a single gavage dose of 2,4,5-TCP on ornithine decarboxylase activity in the liver and serum ALT activity. At a 2,4,5-TCP dose of 164 mg/kg, no effects were observed on these parameters. Histologic changes in the liver were not observed when rats were treated by gavage with 2,4,5-TCP in corn oil at doses up to 1,000 mg/kg/day for 18 times in 24 days (McCollister et al. 1961). Slight pathologic changes, which were not further described, were noted in the livers of rabbits treated by gavage with 2,4,5-TCP in 5% gum acacia solution 20 times in 28 days (McCollister et al. 1961). Over a 98-day period, a dose of 300 mg/kg/day given to rats in the diet resulted in mild centrilobular degeneration and focal necrosis, with no effects observed at 100 mg/kg/day (McCollister et al. 1961).

2,4,6-TCP. The treatment of rats with 2,4,6-TCP by gavage at doses up to 400 mg/kg/day for 14 days had no effect on ethyl-*p*-nitrophenylphosphonothionate detoxification or microsomal enzyme activities (cytochrome c-reductase, cytochrome P-450, or glucuronyltransferase) (Carlson 1978). Kitchin and Brown (1988) observed a significant increase in liver ornithine decarboxylase activity, but no significant change in serum ALT in rats given a single oral dose of 2,4,6-TCP (500 mg/kg).

Increased liver weight and midzonal vacuolation of hepatocytes were evident in rats exposed orally for 7 weeks to 2,300 mg/kg/day 2,4,6-TCP (NCI 1979). Concentration-related increases in absolute liver weight occurred in weanling Sprague-Dawley rats exposed to 4.6 or 46 mg/kg/day 2,4,6-TCP from conception through weaning and in drinking water for an additional 12 weeks (Exon and Koller 1985). The investigators did not examine functional or anatomical hepatic parameters. Increased relative liver weights and increased serum albumin and total protein were found in groups of male rats (Sprague-Dawley) exposed to 240 and 720 mg/kg/day and female rats exposed to 720 mg/kg/day of 2,4,6-TCP for 90 days (Bercz et al. 1990). Males administered 720 mg/kg/day also had increased serum ALT. The investigators attributed clinical chemistry results to either an altered hydration status or dysfunctional

hepatic activity; no treatment-related histopathological evidence of tissue damage was noted in either sex (Bercz et al. 1990). The investigators considered 240 mg/kg/day as a LOAEL for hepatic effects and the next lower dose, 80 mg/kg/day, as a NOAEL for intermediate-duration exposure. In contrast to effects seen in Sprague-Dawley rats, increased liver weight and histopathologic lesions were not evident in Long-Evans or F344 rats exposed to 2,4,6-TCP over intermediate or chronic periods at doses up to 1,000 and 500 mg/kg/day, respectively (Blackburn et al. 1986; NCI 1979).

Microscopic examination revealed hepatic hyperplasia and other signs of hepatocellular damage (e.g., liver cell abnormalities, focal areas of cellular alteration) in mice exposed chronically to 2,4,6-TCP in the diet at doses as low as 650 mg/kg/day (NCI 1979).

The differing hepatic effects of 2,4,6-TCP in available studies may, in part, be a result of the different methodologies used for exposure, variations in experimental design (including different species and strains), and/or possible differences in gastrointestinal absorption because of the nature of the vehicle. In the intermediate oral studies by Bercz et al. (1990) and Blackburn et al. (1986), 2,4,6-TCP was administered in corn oil by gavage. Interpretation of the Blackburn et al. (1986) data is further complicated by the investigators' failure to report sample sizes used in the statistical analysis. The NCI (1979) studies administered 2,4,6-TCP in the diet, while 2,4,6-TCP was administered in drinking water in the Exon and Koller (1985) study, rendering direct comparisons uncertain.

2,3,4,6-TeCP. In the study by Kitchin and Brown (1988), 2,3,4,6-TeCP administration as a single dose (193 mg/kg) to rats induced an increase in ornithine decarboxylase activity in the liver without a significant change in serum ALT. In a comprehensive examination of the hepatic effects of 2,3,4,6-TeCP, Sprague-Dawley rats were administered up to 200 mg/kg/day 2,3,4,6-TeCP by gavage (5 days/week) for 13 weeks, with interim sacrifices after 5 days (acute) and 2 and 4 weeks (intermediate) (Dodd et al. 2012). After 5 days of exposure, an increase in liver weight was seen at 100 and 200 mg/kg/day, and an increased incidence of centrilobular hypertrophy was noted at 200 mg/kg/day group. After 2 weeks of exposure, significant increases (≥14% compared to controls) in absolute and relative liver weight were observed at doses ≥25 mg/kg/day, and statistically significant increased incidences of histopathology changes in the liver (centrilobular hypertrophy and necrosis) were observed at ≥50 mg/kg/day. After 4 weeks, increased incidences of hepatic centrilobular vacuolation and hypertrophy were seen at doses ≥25 mg/kg/day, and significant (≥21%) increases in absolute and relative liver weights occurred at ≥50 mg/kg/day. At the end of the study after 13 weeks of exposure, significant (≥41%) increases in absolute and relative liver weight were reported at all but the lowest dose. Centrilobular vacuolation was

seen in all groups including controls (4/12), but the incidence and severity increased with dose such that all animals were affected at doses ≥25 mg/kg/day. Hypertrophy was not seen in controls, but the incidence increased with dose from 4/10 at 10 mg/kg/day to all animals (9/9 or 10/10) at doses of at least 50 mg/kg/day. Necrosis was observed at doses of ≥50 mg/kg/day, from 3/9 at 50 mg/kg/day to 10/10 at 200 mg/kg/day. Incidences of other histopathology lesions were not reported in tables. All high-dose (200 mg/kg/day) rats exhibited bile duct hyperplasia, as did 20% of rats in the 100 and 25 mg/kg/day groups. Finally, centrilobular and/or periportal fibrosis was observed at 10% incidence in groups exposed to 25 and 100 mg/kg/day and at 40–60% incidence in the 200 mg/kg/day group (Dodd et al. 2012).

In a study sponsored by the EPA (1986), increased liver weights (>20 and >16% for absolute and relative weights, respectively) in males and centrilobular hypertrophy were observed in rats administered 100 or 200 mg/kg/day 2,3,4,6-TeCP by gavage for 90 days. No effects were observed at 25 mg/kg/day. In an intermediate-duration study (55 days) with limited reporting, gavage administration of 100 mg/kg/day to Wistar rats resulted in moderate to severe hepatic damage (consisting of bile duct proliferation, focal necrosis, and polymorphonuclear leukocyte infiltration or large necroses with dilated and thrombosed veins; incidences not reported). At 50 mg/kg/day, 1 out of 10 rats showed severe damage, and at 10 mg/kg/day, no liver effects were seen (Hattula et al. 1981).

2.10 RENAL

No studies were located regarding renal effects in humans after exposure to any of the chlorophenols discussed in this profile. Animal studies suggest that acute- and intermediate-duration oral exposures to mono- and dichlorophenols have little effect on kidney endpoints. Intermediate-duration studies indicated effects on the kidneys (mild degenerative changes on the tubular epithelium or increased kidney weights) in rats exposed to 2,4,5-TCP (McCollister et al. 1961) or 2,3,4,6-TeCP (EPA 1986).

2-CP. In mice, daily administration of 35 or 69 mg/kg/day 2-CP for 14 days had no adverse effects on measures of renal function, including BUN, total protein, albumin/globulin ratio, or electrolyte balance (Borzelleca et al. 1985a). No significant compound-related adverse effects were noted in the kidney at necropsy; however, a dose of 175 mg/kg/day was lethal to all exposed mice. When Sprague-Dawley rats were exposed to 2-CP by gavage for 10 days (at doses up to 257 mg/kg/day) or 90 days (at doses up to 150 mg/kg/day), no effects on BUN, serum creatinine, kidney weight, or kidney histology were noted (Daniel et al. 1993).

No exposure-related effects on serum chemistry, urinalysis parameters, kidney weight, or microscopic kidney findings were observed in Sprague-Dawley rats given 2-CP by gavage at doses up to 1,000 mg/kg/day for 28 days (Hasegawa et al. 2005). By contrast, neonatal rats given 300 mg/kg/day 2-CP for 18 days exhibited increased incidences of basophilic renal tubules, in the absence of changes in serum chemistry, urinalysis, or kidney weight (discussed further in Section 2.17).

4-CP. An increase in relative kidney weight, in the absence of effects on body weight, was observed in female ICR mice 7 days after a single gavage dose of 1,575 mg/kg 4-CP; 4/10 mice receiving this dose died (Shi et al. 2013). In a 28-day study, Sprague-Dawley rats exposed to 4-CP by gavage at doses up to 500 mg/kg/day exhibited no treatment-related effects on serum chemistry, urinalysis parameters, kidney weight, or kidney histology (Hasegawa et al. 2005).

2,4-DCP. No significant changes in serum BUN or creatinine were observed in BALB/c mice given 1,000 ppm 2,4-DCP (270 mg/kg/day) in drinking water for 14 days (Aydin et al. 2009). Except for renal tubular necrosis in mice that died following treatment with 2,4-DCP in the diet for 3 weeks at 5,200 mg/kg/day (NTP 1989), kidney effects have not been observed in intermediate-duration studies of animals treated with 2,4-DCP. Based on histological examinations, the NOAELs for kidney effects after dietary exposure to 2,4-DCP are 2,000 and 440 mg/kg/day for rats exposed for 13 and 103 weeks, respectively (NTP 1989); and 230, 2,600, and 1,300 for mice exposed for 90 days, 13 weeks, and 103 weeks, respectively (Kobayashi et al. 1972; NTP 1989). Treatment of mice for 90 days with 2,4-DCP in drinking water at doses up to 491 mg/kg/day (in females) or 383 mg/kg/day (in males) had no effect on kidney weights or clinical chemistry values including urine protein, phosphorus, calcium, sodium, chloride, potassium, or creatinine levels; histopathological examinations were not completed (Borzelleca et al. 1985a, 1985c).

2,4,5-TCP. Treatment of rats with 2,4,5-TCP (1,000 mg/kg/day by gavage) for 18 days resulted in a significant increase in kidney weight, with no histopathologic changes or changes in BUN (McCollister et al. 1961). Slight pathologic changes (not further described) were observed in rabbits given 20 gavage doses of 100 or 500 mg/kg/day, with no effects noted at 10 mg/kg/day (McCollister et al. 1961). In a 98-day study, 2,4,5-TCP administered in the diet at 300 mg/kg/day resulted in mild degenerative changes in the renal epithelium of the convoluted tubules and in proliferation of the interstitial tissue (McCollister et al. 1961). No kidney effects were observed at 100 mg/kg/day.

2,4,6-TCP. Administration of 720 mg/kg/day 2,4,6-TCP in corn oil by gavage for 90 days resulted in increased absolute and relative kidney weights in male, but not female, Sprague-Dawley rats, as well as decreased urinary pH in both sexes. No other effects on clinical parameters of renal function were observed (Bercz et al. 1990). Renal weight was not increased in Long-Evans rats administered 2,4,6-TCP in corn oil by gavage at doses as high as 1,000 mg/kg/day for 11 weeks, 5 days/week (Blackburn et al. 1986). Strain differences and daily treatment as opposed to treatment 5 times/week may account for the differences in renal effects in the Bercz et al. (1990) and Blackburn et al. (1986) studies. No treatment-related lesions were evident upon histopathologic examination of the kidney in rats and mice exposed to dietary 2,4,6-TCP for 2 years at doses as high as 500 and 1,356 mg/kg/day, respectively (NCI 1979).

2,3,4,6-TeCP. Neither a single dose nor 55-day repeated exposure to 2,3,4,6-TeCP at doses up to 632 mg/kg or 100 mg/kg/day, respectively, induced adverse effects on the histological appearance of the kidneys of rats (Hattula et al. 1981). Increased kidney weights without any histopathologic changes were observed in rats treated by gavage with 2,3,4,6-TeCP at 100 mg/kg/day, but not at 25 mg/kg/day, for 90 days (EPA 1986).

2.11 DERMAL

Chloracne and evidence of acquired porphyria, hyperpigmentation, and hirsutism have been observed in workers employed in the manufacture of 2,4-DCP- and 2,4,5-TCP-based herbicides (Bleiberg et al. 1964; Bond et al. 1989). The chloracne incidence was greatest in young employees exposed in trichlorophenol production and in chlorophenol production and finishing procedures (Bond et al. 1989). In this study, workers exposed to the highest concentration of the contaminant TCDD were at the greatest risk of developing chloracne.

The results of available animal studies indicate that chlorophenols are damaging to epithelial tissue.

2-CP and 4-CP. Severe effects have been reported at exposure levels of 242–2,000 mg/kg of 2-CP or 4-CP applied directly to rabbit skin (Rhone-Poulenc 1978, 1981). Corrosion (not further described) was typically accompanied by other signs of severe skin injury, including erythema, edema, and discoloration. A single dermal application of a lower dose (100 mg/kg) of 4-CP to one ear of a mouse did not increase ear weight relative to the untreated ear (Dohi et al. 1989).

2,4-DCP. Dermal lesions were caused by a single direct application of as little as 200 mg/kg 2,4-DCP to bare abdominal skin of New Zealand White rabbits (Carreon et al. 1980a, 1980b; Hencke and Lockwood 1978; Monsanto 1976). The dose-related dermal damage observed was described as mild-to-moderate erythema and mild-to-marked edema, followed by necrosis and scabbing.

2,3,4,5-TeCP. Dermal application of 20 mL/kg (32 g/kg) 2,3,4,5-TeCP on the shaved skin of female rats resulted in dermatosis associated with scar formation. Rats treated with a sodium hydroxide-extracted fraction of 2,3,4,5-TeCP had no dermatological lesion, indicating that the adverse effects were attributable to the chlorophenol rather than contaminants, such as dioxins (Shen et al. 1983).

Mechanisms. Corrosive skin damage resulting from high-concentration chlorophenol exposure has been attributed to protein denaturation by protein-solute complexes (Roberts et al. 1977). In this study, various concentrations of 2-CP and 4-CP were applied to samples of human abdominal skin maintained in a diffusion chamber. The estimated threshold concentrations for damage (the aqueous concentration at which the transmembrane permeability coefficient began to increase) were 0.8 and 0.75%, respectively, for these two isomers. The investigators proposed that the extent of damage was related to the concentration of the solute partitioned into the stratum corneum, the diffusivity of the solute, and the pK of the applied compound.

2.12 OCULAR

Lumber mill workers exposed to a mixture of tetrachlorophenols (specific isomers not stated) and pentachlorophenol reported eye irritation more frequently than unexposed workers (Kleinman et al. 1986). The eye irritation may have resulted from contact of the eye with the airborne chemicals or contact with contaminated surfaces (e.g., hands, clothing). Animal studies indicate that direct application of chlorophenols to the eyes can induce severe damage, but oral exposure does not affect the eyes.

2-CP. Severe discomfort and corrosion was reported to occur 1 minute after the application of 33 mg/kg undiluted 2-CP to rabbit eyes (Monsanto 1975).

4-CP. When 0.6 mg/kg 4-CP (as a 1% solution) was applied to the corneas of rabbits, slight hyperemia was noted (Harrison and Madonia 1971). At 1.2 mg/kg, rabbits had more severe hyperemia, with edematous swelling, corneal cloudiness, and exudation. The maximum response occurred 5 hours after application, and inflammation was no longer apparent at 96 hours (Harrison and Madonia 1971).

2,4-DCP. Severe corneal damage occurred in the eyes of rabbits after a single direct application of 0.1 mL 2,4-DCP (Hencke and Lockwood 1978). Careful washing of the eye 30 seconds after application did not prevent this damage.

In rats and mice treated with 2,4-DCP in the diet for intermediate or chronic durations, histopathologic examination of the eyes did not reveal any adverse effect (NTP 1989).

2,4,6-TCP. Ophthalmoscopic examinations did not reveal any treatment-related effects in rats treated with 2,4,6-TCP by gavage at doses up to 720 mg/kg/day for 90 days (Bercz et al. 1990).

2,3,4,6-TeCP. Histopathologic examination of the eyes did not reveal any adverse effect in rats exposed to 2,3,4,6-TeCP by gavage at doses up to 200 mg/kg/day for 90 days (EPA 1986).

2.13 ENDOCRINE

Available human studies of endocrine effects of chlorophenols have used urinary levels of chlorophenols to assess exposure. However, chlorophenols in urine can occur as a result of metabolism of other compounds such as chlorinated benzenes (see Section 3.3.1 for further information); thus, the relevance of these studies to hazard identification is uncertain. In animals exposed orally to chlorophenols have not shown effects on endocrine organ weights or microscopic findings in these organs.

In a nested case-control study of pregnant women participating in the Lifecodes longitudinal birth cohort, urine and blood samples were collected 4 times during pregnancy for measurement of dichlorophenols and thyroid hormone levels, respectively (Aker et al. 2018). Repeated measures analyses showed no associations between 2,4-DCP or 2,5-DCP in urine and serum levels of thyroid stimulating hormone (TSH), free thyroxine (FT4), thyroxine (T4), or triiodothyronine (T3) (Aker et al. 2018). When results were stratified by gestational age, urinary 2,4-DCP levels showed associations with decreased T3 and marginally increased TSH at 21–30 weeks of gestation, as well as marginally decreased TSH at <21 weeks of gestation (Aker et al. 2018). Marginal associations between 2,5-DCP and serum TSH were observed, but the direction of change was not consistent across gestational periods. In a similar study, concentrations of 2,4-DCP in urine measured twice during pregnancy were inversely associated with free T4 in maternal serum, but not with total T4 in maternal serum or with TSH levels in serum of mothers or their neonates in a study of 338 mothers participating in a longitudinal birth cohort study (Center for the

Health Assessment of Mothers and Children of Salinas or CHAMACOS) (Berger et al. 2018). Urinary 2,5-DCP levels were not associated with these endpoints (Berger et al. 2018).

Urinary concentrations of 2,5-, but not 2,4-DCP were associated with higher prevalence of hypothyroidism among 618 adolescents (ages 12–19 years) participating in NHANES surveys during 2007–2008 and 2011–2012 (Wei et al. 2016). The authors noted that urinary 2,5-DCP was considered to be a reliable biomarker for *p*-dichlorobenzene exposure; thus, the relationship to hazard identification for 2,5-DCP is uncertain. No association was observed between serum concentrations of 2,4,5,6-TeCP and transthyretin-bound thyroxin in a cross-sectional study of 120 adult (ages 18–39 years) Inuit women (Audet-Delage et al. 2013). Rooney et al. (2018) did not observe an association between urinary 2,4- or 2,5-DCP levels and thyroid problems (not further specified) in a cross-sectional study of 3,617 adult NHANES (2007–2010) participants.

2-CP. In Sprague-Dawley rats given 2-CP by gavage, no changes in adrenal weight or histology of adrenal glands, pancreas, pituitary, or thyroid/parathyroid glands were observed at doses up to 257 mg/kg/day for 10 days or up to 150 mg/kg/day for 90 days (Daniel et al. 1993). Likewise, 28-day exposure of Sprague-Dawley rats to doses up to 1,000 mg/kg/day via gavage did not result in changes in the weights or histology of adrenal, pituitary, or thyroid glands (Hasegawa et al. 2005).

4-CP. When Sprague-Dawley rats received doses up to 500 mg/kg/day 4-CP by gavage for 28 days, there were no changes in endocrine organ weights (adrenal, pituitary, and thyroid glands) or microscopic findings in these organs (Hasegawa et al. 2005).

2,4-DCP. Histopathologic examinations did not reveal any changes in the endocrine glands (adrenals, pituitary, thyroid, pancreas) of rats or mice treated with 2,4-DCP in the diets at doses up to 2,000 (rats) or 2,600 (mice) mg/kg/day for 13 weeks, or at doses up to 440 (rats) or 1,300 (mice) mg/kg/day for 103 weeks (NTP 1989).

2,4,5-TCP. No histopathologic changes were observed in the adrenals of rats exposed to 2,4,5-TCP in the diet at 1,000 mg/kg/day for 98 days (McCollister et al. 1961).

2,4,6-TCP. Female rats treated by gavage with 720 mg/kg/day of 2,4,6-TCP for 90 days had slightly, but statistically significant, increases in adrenal weights compared to untreated controls, without concomitant histopathological changes (Bercz et al. 1990). Adrenal gland weights were not increased in male rats

treated by gavage with 2,4,6-TCP at 1,000 mg/kg/day for 11 weeks (Blackburn et al. 1986). Histopathologic changes were not observed in the adrenal glands, thyroid, pancreas, or parathyroid glands in rats or mice treated with 2,4,6-TCP in the diet at doses of 500 (rats) or 1,356 (mice) mg/kg/day for 105 weeks (NCI 1979).

2,3,4,6-TeCP. Treatment of rats by gavage with 2,3,4,6-TeCP for 90 days at doses up to 200 mg/kg/day had no effect on the histologic appearance of the adrenal glands, pituitary, pancreas, or thymus (EPA 1986).

Mechanisms. The potential for 2,4-DCP to affect thyroid hormone functions was evaluated in an *in vitro* study using isolated T3, recombinant protein disulfide isomerase (PDI; an intracellular thyroid hormone binding protein that assists in protein folding), and recombinant nuclear thyroid hormone receptor (Okada et al. 2005). 2,4-DCP produced dose-dependent inhibition of PDI activity, PDI-T3 binding, and T3-nuclear thyroid hormone receptor binding. Results indicate that 2,4-DCP may alter thyroid function through changes in intracellular processing of T3 (Kim et al. 2005). None of the three chlorophenols (2-CP, 2,4-DCP, and 2,4,6-TCP) tested for agonistic and antagonistic activity in a thyroid receptor β transcriptional assay exhibited any activity.

2.14 IMMUNOLOGICAL

Available human studies of immunological effects of chlorophenols have used urinary 2,4- and 2,5-DCP levels to measure exposure. However, as noted earlier, urinary chlorophenols may result from metabolism of other compounds, and in particular 2,5-DCP in urine is considered to be a reliable biomarker for exposure to *p*-dichlorobenzene (Yoshida et al. 2002). Of the three chlorophenols (2-CP, 2,4-DCP, and 2,4,6-TCP) tested for sensitive measures of immunotoxicity in animals exposed orally, only 2,4-DCP showed evidence of adverse effects. In rats, 2,4-DCP exposure (≥4.6 mg/kg/day in drinking water) resulted in decreased delayed-type hypersensitivity, and higher doses induced increased serum antibodies to keyhole limpet hemocyanin (Exon and Koller 1985; Exon et al. 1984).

Two studies (Aung et al. 2019; Watkins et al. 2015) evaluated whether urinary levels of 2,4- or 2,5-DCP in pregnant women were associated with serum markers of inflammation. Watkins et al. (2015) included a total of 54 subjects (participants in the Puerto Rico Testsite for Exploring Contamination Threats or PROTECT project) who provided urinary samples three times and blood samples twice during pregnancy. Linear mixed models were used to account for intraindividual correlation across sampling times. No

association was observed between serum measures of inflammation (interleukins [IL-1β, IL-6, IL-10], tumor necrosis factor [TNF-α], or C-reactive protein [CRP]) and specific gravity-adjusted levels of 2,4- or 2,5-DCP in urine (Watkins et al. 2015). Aung et al. (2019) evaluated the same inflammatory markers in a nested preterm birth case-control study (participants in the LIFECODES prospective birth cohort) of 130 cases and 352 controls, each of whom provided urine samples four times and blood samples five times during pregnancy. Linear mixed models analysis did not indicate any association between serum IL-1β, IL-6, IL-10, TNF-α, or CRP and urinary concentrations of 2,4- or 2,5-DCP (Aung et al. 2019). Serum CRP levels were positively associated (10% increase in serum CRP with interquartile increase in urinary concentration) with urinary 2,5-DCP, but not urinary 2,4-DCP, in this study (Aung et al. 2019).

2-CP. Mice fed 69 mg/kg/day 2-CP for 14 days showed no changes in humoral or cell-mediated immunological assays (Borzelleca et al. 1985a). Statistically significant decreases in spleen weight were noted at 69 mg/kg/day, but no gross abnormalities in spleen morphology were observed (Borzelleca et al. 1985a). At the next higher dose (175 mg/kg/day), all mice died prematurely. A 10-day exposure to 2-CP via gavage (at doses up to 257 mg/kg/day) in Sprague-Dawley rats did not alter spleen or thymus weights or histology (Daniel et al. 1993).

Rats fed 73 mg/kg/day 2-CP from conception through weaning and for an additional 10 weeks showed no changes in humoral or cell-mediated immunological assays including tests for antibody production, delayed-type hypersensitivity, or phagocytic activity of peritoneal exudate cells (Exon and Koller 1983b, 1985). Furthermore, neither thymus nor spleen weights were affected by exposure (Exon and Koller 1983b, 1985). Similarly, no effects on thymus or spleen weights or histopathology were noted in Sprague-Dawley rats given gavage doses up to 1,000 mg/kg/day 2-CP for 28 days (Hasegawa et al. 2005) or up to 150 mg/kg/day 2-CP for 90 days (Daniel et al. 1993).

4-CP. Spleen and thymus weights were not affected by exposure to 4-CP doses up to 300 mg/kg/day for 28 days in Sprague-Dawley rats, and there were no histopathology findings in these organs (Hasegawa et al. 2005).

2,4-DCP. Sensitive tests have demonstrated immune system effects in animals exposed to low doses of 2,4-DCP administered for 15 weeks. Decreased delayed-type hypersensitivity occurred in rats exposed to 4.6 mg/kg/day of 2,4-DCP in drinking water, and increased serum antibodies to keyhole limpet hemocyanin were found in the blood of rats during similar exposures to 46 mg/kg/day (Exon and Koller 1985; Exon et al. 1984). Macrophage function, measured by the *in vitro* phagocytosis of sheep red blood

cells, showed no effect from 2,4-DCP treatment. No immune system effects occurred with exposure to 0.46 mg/kg/day (Exon and Koller 1985; Exon et al. 1984).

In contrast, organ weight and histopathology examinations have not generally shown evidence of alterations in the immune system after intermediate-duration exposure. Spleen weights were nearly doubled (compared to controls) but thymus weights were not significantly affected in rats that received 46 mg 2,4-DCP kg/day from conception through weaning (via maternal dosing) and for an additional 15 weeks in drinking water (Exon and Koller 1983b, 1985). Histopathological examination of lymph nodes, spleen, and thymus did not reveal any effects in rats or mice treated with 2,4-DCP in the diet at doses up to 2,000 mg/kg/day (rats) and 2,600 mg/kg/day (mice) for 13 weeks (NTP 1989). Bone marrow atrophy was observed in rats treated at 500 mg/kg/day, but not 250 mg/kg/day, for 13 weeks (NTP 1989). Because both erythroid and myeloid elements were affected, this study is also discussed in Section 2.7 (Hematological). No changes in spleen weight were observed in mice treated with 2,4-DCP in the diet at 230 mg/kg/day for 6 months (Kobayashi et al. 1972), and no changes in spleen or thymus weight were noted in mice treated with 2,4-DCP in the drinking water at doses up to 491 mg/kg/day (in females) or 383 mg/kg/day (in males) for 90 days (Borzelleca et al. 1985a, 1985c).

Chronic (103 week) exposure to 2,4-DCP in the diet did not induce histopathological changes in the lymph nodes, spleen, or thymus in rats or mice treated at doses up to 440 (rats) and 1,300 mg/kg/day (mice) (NTP 1989).

2,4,5-TCP. In rats treated with 2,4,5-TCP in the diet at doses of 1,000 mg/kg/day for 98 days, spleen weight and histological appearance were not altered by treatment (McCollister et al. 1961).

The murine local lymph node assay, which is predictive of skin sensitization potential, was completed in mice treated with 2,4,5-TCP (Kimber and Weisberger 1991). A single dermal exposure of 50 mL of 2,4,5-TCP was applied on one shaved flank; 5 days later, the mice were given three daily doses (140–560 mg/kg/day) applied to the ear. A positive response was observed at all doses, suggesting that 2,4,5-TCP can be a skin sensitizer. This study is limited since only three mice were used in each group and a statistical analysis of the data was not completed.

2,4,6-TCP. No changes in spleen weight or histological appearance were observed in rats treated by gavage with 720 mg/kg/day 2,4,6-TCP for 90 days (Bercz et al. 1990). Spleen weights were significantly increased in rats exposed to 2,4,6-TCP in the drinking water both pre- and postnatally (~15 weeks

postweaning) at doses of 46 mg/kg/day, while no significant effects on immune function (antibody levels, delayed-type hypersensitivity, macrophage numbers) were observed (Exon and Koller 1985). Treatment of rats and mice with 2,4,6-TCP in the diet for 2 years at doses up to 500 mg/kg/day for rats and 1,356 mg/kg/day for mice did not reveal any significant gross or histopathological changes in the spleen, lymph nodes, or thymus (NCI 1979).

2,3,4,6-TeCP. Administration of a single gavage dose 632 mg/kg of 2,3,4,6-TeCP in Wistar rats resulted in "slight stasis" in the spleens of rats (Hattula et al. 1981); the toxicological significance of this finding is unknown. No histological changes were observed in the spleen, lymph nodes, or thymus of rats treated with 2,3,4,6-TeCP by gavage at doses up to 200 mg/kg/day for 90 days (EPA 1986).

2.15 NEUROLOGICAL

Data pertaining to neurological effects of chlorophenols in humans are subject to the same limitations noted for other endpoints; these include potential confounding by coexposures to other compounds, poor exposure characterization, and/or use of nonspecific, unreliable biomarkers (e.g., urinary chlorophenol levels) to assess exposure. Lumber mill workers exposed to a mixture of tetrachlorophenols (specific isomers not stated) and pentachlorophenol reported headaches more frequently than unexposed workers (Kleinman et al. 1986). Monitoring of air and urinary concentrations of tetrachlorophenols suggested that exposure was principally through the skin, with some possibility of oral ingestion. An industrial waste worker who accidentally splashed pure 2,4-DCP on portions of his right arm and leg, experienced a seizure within 20 minutes of the exposure, and died shortly thereafter (Kintz et al. 1992).

Several cross-sectional studies examined relationships between di- or trichlorophenol levels in urine and prevalence of self-reported neurological effects on olfaction, vision, hearing, balance, or attention deficit hyperactivity disorder (ADHD) among NHANES participants. In a study of 10,122 adults >50 years participating in the 2003–2004 NHANES survey, Shiue (2013) evaluated self-reported vision, hearing, and balance problems. After adjustment for covariates, an increased odds of self-reported balance problems (dizziness, falling) was observed with higher urinary 2,4,5-TCP, and an increased odds of reporting ringing, roaring, or buzzing in the ears was associated with higher urinary 2,4-DCP. No association with vision, hearing, or balance problems was observed for 2,5-DCP or 2,4,6-TCP (Shiue et al. 2013). Among respondents in the 2013–2014 NHANES survey who participated in an odor detection test (the NHANES Pocket Smell Test), an increased odds of hyposmia (scoring 4–5 on the test) was associated with higher urinary levels of 2,4-DCP when compared with levels among those scoring as

normal (scores of 6–8) (Bello and Dumancas 2017; Noel et al. 2017). Urinary concentrations of 2,4-DCP were not reported, nor were results for other chlorophenols. Xu et al. (2011) evaluated the association between trichlorophenol exposure and attention deficit disorders in 2,546 children aged 6–15 years participating in the 1999–2004 NHANES survey. The results showed that children with low (<3.58 μg/g) and high (≥3.58 μg/g) levels of 2,4,6-TCP in urine samples had higher risks of parent-reported attention deficit disorder than children with urinary 2,4,6-TCP levels below the levels of instrumentation detection. No association was seen with urinary levels of 2,4,5-TCP (Xu et al. 2011).

As described below, high doses of chlorophenols have resulted in clinical signs of neurotoxicity in animals. Lethargy, tremors, convulsions, and/or central nervous system depression have been reported in animals exposed orally or dermally to 2- and 4-CP and 2,4-DCP (Borzelleca et al. 1985a; Carreon et al. 1980a, 1980b; Hasegawa et al. 2005; Monsanto 1976; NTP 1989; Phornchirasilp et al. 1989b; Rhone-Poulenc 1991; Spencer and Williams 1950) or to tetrachlorophenols via single dermal application (Shen et al. 1983). The lowest dose associated with neurotoxicity after exposure for any duration was 35 mg/kg/day 2-CP in an acute-duration study of mice (Borzelleca et al. 1985a). No studies evaluating more sensitive measures of neurological function in animals exposed to any of the subject chlorophenols were identified in the available literature.

2-CP. In an LD_{50} study, single oral doses (unspecified) of 2-CP caused motor weakness, tremors, convulsions, and central nervous system depression in rats and mice (Borzelleca et al. 1985a, 1985b). The actual doses used in the study (Borzelleca et al. 1985b) were not stated. Single oral doses of 2-CP >300 mg/kg resulted in distress and twitching in rabbits (Spencer and Williams 1950). Clinical signs were not observed and neither brain weight nor sciatic nerve histology was affected by exposure in Sprague-Dawley rats treated by gavage to doses up to 257 mg/kg/day 2-CP for 10 days (Daniel et al. 1993).

When rats were exposed by nose-only inhalation for 4 hours to 908 ppm 2-CP, signs of toxicity included restlessness, a hunched posture, and ruffled fur (Rhone-Poulenc 1991). These effects were not observed at 104 ppm.

Newborn rats (12/sex/group) administered 2-CP in olive oil by gavage at or 300 mg/kg/day on PNDs 4–21 (18 days total) exhibited significant increases in the incidence of tremors (11/12 males, 12/12 females); few signs of hypoactivity or abnormal gait were observed (Hasegawa et al. 2005). Although one female exhibited tremors at 50 mg/kg/day, no other animals exposed to lower doses (up to 100 mg/kg/day)

exhibited clinical signs of neurotoxicity. The clinical signs of neurotoxicity appeared within 5 minutes of dosing and vanished approximately 4 hours post-exposure (Hasegawa et al. 2005). In a related experiment reported in the same publication, young (5–6 weeks old) Sprague-Dawley rats treated with 1,000 mg/kg/day 2-CP in olive oil for 28 days showed tremors (9/24), hypoactivity (13/24), and abnormal gait (11/24). The signs of neurotoxicity appeared approximately 3 hours after dosing; times to disappearance of symptoms were not reported (Hasegawa et al. 2005). Neither newborn nor young rats exhibited effects on brain weight or microscopic findings related to 2-CP exposure in these experiments (Hasegawa et al. 2005). Sprague-Dawley rats exposed by gavage to doses up to 150 mg/kg/day 2-CP for 90 days showed no changes in brain weight or histopathology in the brain or sciatic nerve (Daniel et al. 1993).

In male and female ICR mice, repeated oral administration of 35 and 69 mg/kg/day 2-CP for 14 days resulted in hyperactivity and decreased brain weight, respectively, but the brain tissue appeared grossly normal (Borzelleca et al. 1985a).

4-CP. Single oral doses (unspecified) of 4-CP administered to rats and mice to assess acute lethality caused motor weakness, tremors, convulsions, and central nervous system depression (Borzelleca et al. 1985a, 1985b). A single oral dose of 514 mg/kg 4-CP produced seizures immediately followed by death in male ICR mice (Phornchirasilp et al. 1989b). Spencer and Williams (1950) reported distress and twitching in rabbits after administration of single (unspecified, but reported to be >300 mg/kg) oral doses of 4-CP.

Newborn rats (12/sex/group) were administered 4-CP at doses of 0, 12, 60, or 300 mg/kg/day in olive oil by gavage on PNDs 4–21 (Hasegawa et al. 2005). Rats of both sexes treated with 300 mg/kg of 4-CP exhibited tremors (24/24), rapid breathing, and salivation; the animals were not affected at 60 mg/kg/day. Tremors occurred approximately 15–60 minutes after dosing and disappeared within 4 hours post-exposure. In a companion experiment, young (5–6 weeks old) Sprague-Dawley rats of both sexes treated with 500 mg/kg/day 4-CP by gavage for 28 days showed clinical signs of toxicity, which included tremors, rapid breathing, and salivation. The onset of symptoms occurred approximately 5–30 minutes after dosing, and the time to disappearance of symptoms was not reported (Hasegawa et al. 2005). No change in brain weight or histology was noted in either of these experiments (Hasegawa et al. 2005). In an intermediate-duration (42–53 days) reproductive/developmental toxicity screening study in rats exposed by gavage, clinical signs of neurotoxicity, including ataxia, tremors, and clonic convulsions were observed within 30 minutes of dosing with 1,000 mg/kg/day; this dose was also lethal in about half of

exposed animals (BSRC 2011). Signs of neurotoxicity were not observed at lower doses in this study (40 and 200 mg/kg/day).

2,4-DCP. Rabbits given single dermal applications of 250 mg/kg 2,4-DCP or more became lethargic (Carreon et al. 1980a, 1980b; Monsanto 1976), and two rabbits in the 2,000-mg/kg group and one in the 4,000-mg/kg group became anorexic (Carreon et al. 1980b). Lethargy was also seen in mice treated with 2,4-DCP in the diet at 5,200 mg/kg/day for 14 days; one out of five male mice died after exposure to this dose (NTP 1989).

In intermediate- and chronic-duration studies, there was little evidence for neurotoxicity after exposure to 2,4-DCP. Hunched posture was observed in rats treated with 2,4-DCP in the diet at 2,000 mg/kg/day for 13 weeks (NTP 1989) with no histopathological changes in the brain, sciatic nerve, or spinal cord. In mice treated with 2,4-DCP in the diet at doses up to 2,600 mg/kg/day for 13 weeks, no histopathological changes were observed in the brain, sciatic nerve, or spinal cord (NTP 1989). No effect on brain weight was observed in mice treated for 90 days with 2,4-DCP in the drinking water at doses up to 491 mg/kg/day (in females) or 383 mg/kg/day (in males) (Borzelleca et al. 1985a, 1985c). No clinical signs of neurological effects were reported in rats or mice fed doses up to 440 mg/kg/day for rats and 1,300 mg/kg/day for 2 years, and histopathologic examination of the brains of these animals did not reveal any effects (NTP 1989).

2,4,5-TCP. No changes in brain weight or histological appearance of the brain were observed in rats treated with 2,4,5-TCP in the diet at doses up to 1,000 mg/kg/day for 98 days (McCollister et al. 1961).

2,4,6-TCP. Histopathologic examination of the brain (cerebrum and cerebellum) of rats and mice exposed repeatedly to 2,4,6-TCP at oral doses as high as 720 and 1,356 mg/kg/day, respectively, revealed no treatment-related effects (Bercz et al. 1990; NCI 1979).

2,3,4,5-TeCP. When 20 Sprague-Dawley rats were exposed by unoccluded dermal application of 2,000 mg/kg 2,3,4,5-TeCP, one rat died after exhibiting clinical signs including hyperactivity, neuromuscular weakness, and convulsions (Shen et al. 1983).

2,3,4,6-TeCP. In Wistar rats exposed to a single dose of up to 632 mg/kg 2,3,4,6-TeCP (Hattula et al. 1981), or repeatedly to 200 mg/kg/day 2,3,4,6-TeCP for 90 days, no histopathological effects in the brain were observed (EPA 1986). In a single-dose dermal study of 2,3,4,6-TeCP and other tetrachlorophenols

in rats, clinical signs observed before death were hyperactivity, neuromuscular weakness, and convulsions; the dermal LD_{50} values for 2,3,4,6-TeCP were 468 mg/kg in males and 565 mg/kg in females (Shen et al. 1983).

2,3,5,6-TeCP. A single dermal application of 2,000 mg/kg 2,3,5,6-TeCP, which was lethal to 2 of 20 (male and female) Sprague-Dawley rats, resulted in the following clinical signs before death: hyperactivity, neuromuscular weakness, convulsions, and death (Shen et al. 1983).

Mechanisms. Limited data were located on the mechanism of phenol- or chlorophenol-induced convulsions. Inhibition of oxidative phosphorylation and cellular respiration (discussed further in Section 2.18) is one possible mechanism.

Phenol administration in cats facilitated effects on central synaptic transmission at both excitatory and inhibitory synapses (Banna and Jabbur 1970). The authors proposed that certain phenols increase the amount of neurotransmitter released during synaptic transmission, resulting in convulsions. After intraperitoneal injection of several chlorophenols, convulsions predominated in those mice receiving the 2- and 4-CP compounds (Farquharson et al. 1958). Because these compounds have pK values ≥8.65 and would not be in the ionic form at physiologic pH, the investigators attributed the observed effect to the chlorophenol rather than the ion.

2.16 REPRODUCTIVE

Studies of reproductive effects in humans exposed to chlorophenols are limited to assessments using urinary levels of di- or trichlorophenols to assess exposure. Urinary levels are not considered to be reliable biomarkers of chlorophenol exposure; in fact, as noted earlier, urinary 2,5-DCP is used as a biomarker for exposure to *p*-dichlorobenzene. In animals exposed to chlorophenols by oral administration, decreases in implantations, litter size, and/or live births per litter have been reported after intermediate-duration exposure to 4-CP (200 mg/kg/day) (BSRC 2011), 2,4-DCP (46 mg/kg/day) (Exon and Koller 1985; Exon et al. 1984), and 2,4,6-TCP (46 mg/kg/day) (Exon and Koller 1985). Adverse effects on the male reproductive system (including increases in the percentage of abnormal sperm and decreased sperm motility) were observed after acute-duration exposure to 2,4-DCP in mice (Aydin et al. 2009).

Harley et al. (2019) observed an association between decreased age at menarche and prenatal concentration of 2,4-DCP in maternal urine (mean shift of -0.8 months, 95% CI 1.6–0.0) in 179 girls followed as part of a longitudinal birth cohort study in California (CHAMACOS). No association was observed between maternal or peripubertal 2,4-DCP concentration and thelarche or pubarche in this group of girls. 2,5-DCP in children's urine (peripubertal) was associated with delayed pubarche in girls (mean shift +1.0 month, 95% CI 0.1–1.9) in this study (Harley et al. 2019). No association was observed between urinary 2,4- or 2,5-DCP and gonadarche or pubarche among 159 boys in the same cohort (Harley et al. 2019). In contrast, a cross-sectional analysis of 440 adolescent girls ages 12–16 years who participated in the NHANES survey (2003–2008) found that age at menarche was not associated with urinary 2,4-DCP levels (Buttke et al. 2012). However, in the latter study, menarche occurred prior to exposure measurement (urine sampling) in some participants; thus, a temporal relationship between the two could not be evaluated in the study.

A longitudinal study of chemical exposure and reproductive hormones was conducted in a sample of 143 healthy, premenopausal women recruited at a research center in New York state (Pollack et al. 2018). Each participant provided between three and five urine samples at key points over two menstrual cycles for chemical analysis (including 2,4-DCP, 2,5-DCP, 2,4,5-TCP, and 2,4,6-TCP). Blood samples were collected from participants at several phases of the ovulatory cycle: the early follicular phase, at ovulation, and mid-luteal phase in cycle 1 and at ovulation in cycle 2. Serum levels of estradiol, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were measured. Urinary concentrations ranged between 0.03 and 38.6 ng/mL for 2,4-DCP; 0.1–803.5 ng/mL for 2,5-DCP; 0.04–2.8 ng/mL for 2,4,5-TCP; and 0.03–8.5 ng/mL for 2,4,6-TCP. More than 49% of samples showed 2,4,5-TCP levels below the limit of detection, so this compound was not included in the analyses. In linear mixed models analysis of log-transformed hormone levels examining single chemicals, urinary 2,4-DCP was positively associated with progesterone levels (β 0.14, 95% CI 0.06–0.21) and inversely associated with FSH (β -0.08, 95% CI -0.11 to -0.04) after adjustment for covariates. No association was seen between 2,4-DCP and estradiol or LH, or between urinary 2,5-DCP or 2,4,6-TCP and any reproductive hormone (Pollack et al. 2018). Limitations of this study include the small sample size and relatively low prevalence of detectable 2,4-DCP (>35% of samples were below the detection limit).

2-CP. In a single-generation reproductive toxicity study using Sprague-Dawley rats exposed to 2-CP via drinking water from weaning through mating and parturition, the only difference from control was a marginal decrease ($p<0.10$) in litter size at the highest dose (76 mg/kg/day); no effects were seen at lower exposures (Exon and Koller 1985). This study was limited by assessment of few endpoints (percent

fertile, litter size, numbers of live fetuses, birth and weaning weights, and survival to weaning); in addition, the fetus, not the litter, was the unit of statistical analysis.

No treatment-related histopathology findings were noted in the testes, epididymides, ovaries, or uteri of Sprague-Dawley rats given 2-CP (up to 1,000 mg/kg/day) by gavage for 28 days (Hasegawa et al. 2005).

4-CP. Exposure of Sprague-Dawley rats to 4-CP by gavage at doses up to 300 mg/kg/day for 28 days did not result in treatment-related histopathology findings in the testes, epididymides, ovaries, or uteri (Hasegawa et al. 2005). In a screening-level reproductive/developmental toxicity study (BSRC 2011), rats exposed to doses up to 200 mg/kg/day showed no effects on sperm parameters, estrous cyclicity, copulation, fertility, or gestation length. The number of implantation sites was reduced at this dose (14.6 versus 15.8 in controls). Although the difference from control was not statistically significant, the number of offspring delivered was also lower, and the number of live offspring was significantly decreased ($p<0.05$) at 200 mg/kg/day (BSRC 2011). At 1,000 mg/kg/day (a dose that was lethal to 5/12 rats during the 14-day premating period), reduced numbers of implantations, offspring, and live offspring were also noted (but the changes were not statistically significant). No reproductive effects were noted at 40 mg/kg/day.

2,4-DCP. The effects of 2,4-DCP exposure were assessed in a 2-generation study in Wistar-Hanover rats (Aoyama et al. 2005). Groups of 24 rats/sex/group were administered a diet containing 2,4-DCP at concentrations of 0, 500, 2,000, or 8,000 ppm, which corresponded to doses of 0, 33.4, 134, or 543 mg/kg/day for males and 0**,** 49.1, 194, or 768 mg/kg/day for females. The parental generation (P) was exposed for 10 weeks prior to mating and through the gestation and lactation periods, then sacrificed upon weaning of their offspring. Offspring of the P generation (F1) were exposed to 2,4-DCP from weaning through mating, gestation, and lactation and were sacrificed upon weaning of their offspring. Offspring of the F1 generation (F2) were sacrificed at weaning. A statistically significant decrease in the number of implantation sites per female was detected in high-dose F1 rats, but not in the parental generation or in F1 rats receiving lower doses. No treatment-related changes in estrous cycle length, incidence of normal estrous cycles, number of primordial ovarian follicles, mating index, fertility index, gestation index, gestation length, pup number, viability at birth, or sex ratio, or pup viability during lactation were observed in the P or F1 generations. In addition, no treatment-related changes were observed in serum hormones that affect the reproductive system (FSH, LH, prolactin, estradiol, and progesterone) in female rats (assessed in F1 rats only) or in sperm parameters (number of testicular or epididymis sperm, sperm motility, and sperm morphology) in P and F1 males.

A teratogenicity study in which pregnant rats were treated with 2,4-DCP by gavage on GDs 6–15 at doses that caused maternal deaths and decreased body weight gain showed neither postimplantation loss nor changes in the numbers of resorptions and viable fetuses (Rodwell et al. 1989). When female Sprague-Dawley rats received 2,4-DCP in drinking water at doses up to 46 mg/kg/day from weaning through mating and parturition (~13 weeks total), the only exposure-related effect was a marginal decrease ($p<0.10$) in litter size (Exon and Koller 1985). The study examined few endpoints (percent fertile, litter size, numbers of live fetuses, birth and weaning weights, and survival to weaning); in addition, the fetus, not the litter, was the unit of statistical analysis.

Aydin et al. (2009) reported significant effects on the male reproductive system, including increased necrotic cell counts in the seminiferous tubules, increased percent abnormal sperm (>3-fold increase in percent abnormal), and decreased sperm motility, in BALB/c mice receiving 1,000 ppm 2,4-DCP in drinking water (~260 mg/kg/day) for 14 days. However, sperm from male CD-1 mice fed 500 mg/kg/day 2,4-DCP for 90 days in drinking water did not exhibit impaired ability to fertilize ova (Seyler et al. 1984). The 2-generation study in rats (Aoyama et al. 2005) reported no effects on sperm parameters in parental or F1 males receiving dietary doses up 543 mg/kg/day 2,4-DCP.

No reproductive organ pathology was observed in rats or mice of either sex fed up to 2,000 or 2,600 mg/kg/day 2,4-DCP, respectively, for 13 weeks (NTP 1989). Reproductive organ pathology was not observed in male rats fed 440 mg/kg/day, in female rats fed 250 mg/kg/day, in male mice fed 1,300 mg/kg/day, or in female mice fed 8,210 mg/kg/day 2,4-DCP for 2 years (NTP 1989).

2,4,5-TCP. Gavage treatment of rats with 2,4,5-TCP at doses up to 1,000 mg/kg/day for 98 days had no effect on the weights of the testes or ovaries (McCollister et al. 1961). No other data pertaining to reproductive effects of 2,4,5-TCP were located.

2,4,6-TCP. A marginal ($p<0.10$) decrease in litter size was reported at the highest dose (46 mg/kg/day) in a single-generation reproductive toxicity study of 2,4,6-TCP (Exon and Koller 1985). In this study, female Sprague-Dawley rats received 2,4,6-TCP in drinking water (0, 3, 30, or 300 ppm) beginning at weaning and extending through mating (with untreated males) and parturition for a total duration of ~13 weeks. This study was limited by evaluation of few endpoints (percent fertile, litter size, numbers of live fetuses, birth and weaning weights, and survival to weaning); in addition, the fetus, not the litter, was the unit of statistical analysis.

Blackburn et al. (1986) observed no reproductive toxicity in a cross-mating study of 2,4,6-TCP administered by gavage at doses up to 1,000 mg/kg/day. Male and female rats were exposed for 2 weeks prior to mating for up to 10 days with untreated animals. Female rats continued exposure throughout gestation. Despite the fact that exposure-related deaths occurred in both sexes at 1,000 mg/kg/day, exposure had no effects on breeding success, litter size, or litter survival regardless of the sex treated. In a study of male reproductive effects in the same publication, gavage doses up to 1,000 mg/kg/day 10 weeks prior to mating with untreated females did not influence copulatory behavior, sperm count, motility, or morphology, nor were there any changes in weights of the testes, prostate, or seminal vesicles (Blackburn et al. 1986).

In a subchronic toxicity study, no effects were observed on the weights of the testes or ovaries in rats treated by gavage with 2,4,6-TCP doses up to 720 mg/kg/day (Bercz et al. 1990). Chronic (2-year) dietary exposure to 2,4,6-TCP in the diet likewise did not result in histologic changes in the testes, prostates, uteri, or ovaries of rats receiving doses up to 500 mg/kg/day or mice receiving doses up to 1,356 mg/kg/day (NCI 1979).

2,3,4,6-TeCP. An exposure-related trend in percent preimplantation loss, suggesting an effect on the process of implantation or early postimplantation viability, was observed when pregnant rats were treated with 2,3,4,6-TeCP by gavage at doses up to 200 mg/kg/day on GDs 6–l 5 (EPA 1987a, 1987b). However, because the study was not designed to examine the preimplantation/ implantation phase of reproduction, this finding requires confirmation. No histopathological changes were observed in the testes, ovaries, or uterus and cervix of rats treated by gavage with 2,3,4,6-TeCP at doses up to 200 mg/kg/day for 90 days (EPA 1986).

Mechanisms. The potential for chlorophenols to perturb estrogen and androgen activities has been evaluated in *in vitro* studies (Harris et al. 2005; Kim et al. 2005; Okada et al. 2005; Yu et al. 2019). In vitro testing of 2-CP, 2,4,-DCP, and 2,4,6-TCP for estrogenic and antiestrogenic activities in the ER α transactivation assay showed that 2,4,6-TCP showed antagonistic activity, but only at the highest concentration tested (10^{-5} M); the other compounds were inactive as agonists or antagonists (Yu et al. 2019). Several chlorophenols were evaluated for their potential to inhibit isolated estrogen sulfotransferase (Harris et al. 2005). Sulfonation of estrogen, which results in a pharmacologically inactive substance, is an important process in the attenuation of the steroid-hormone signal in endometrial, mammary, and testicular tissues. 2,3-, 2,4-, 2,5-, and 2,6-DCP were potent inhibitors of

isolated estrogen sulfotransferase. Other chlorophenols, such as 3,4-and 3,5-DCP and 4-CP, inhibited estrogen sulfotransferase, but with a lower relative potency. The authors suggested that chlorophenol-induced inhibition of estrogen sulfotransferase could lead to increased intracellular levels of estrogen and thereby potentially alter estrogen-mediated cellular functions.

The potential for 2,4-DCP to potentiate 5α-dihydrotestosterone (DHT) action, as assessed by cell proliferation, was evaluated in human prostate cancer cells (lines AR expressed 22v1 and PC3) (Kim et al. 2005). Co-administration of 10 nano-molar (nM) 2,4-DCP enhanced the androgenic activity of DHT by 1.6-fold in comparison to 10 nM DHT alone. Translocation of the androgen receptor complex to the nucleus was increased in the presence of 2,4-DCP, suggesting that 2,4-DCP has the potential to alter androgen-induced transcriptional activity.

Limited *in vitro* data suggest that 2,4,6-TCP could affect reproductive function by interfering with steroidogenesis. In human adrenocortical H295R cells incubated with 2,4,6-TCP (10^{-7}–10^{-5} M, or 0.1–10 μM), significant, concentration-related decreases in CYP17 mRNA levels were detected (by reverse transcription-polymerase chain reaction [RT-PCR]) at all concentrations (Yu et al. 2019). In another study using the same test system, 2,4,6-TCP concentrations ≥1.1 μM significantly decreased the expression of steroidogenic acute regulatory protein (*StAR*), CYP19 (aromatase), and 17β-hydroxysteroid dehydrogenase (*17βHSD4*) and a concentration of 3.4 μM decreased the expression of CY11A and 3β-hydroxysteroid dehydrogenase (*3βHSD2*) (Ma et al. 2011). Ma et al. (2011) also observed significant decreases in testosterone and estradiol concentrations at the highest exposure concentration (3.4 μM). Time-course experiments showed that decreases in cellular cAMP levels occurred at the same time as decreases in *StAR* mRNA and protein levels, suggesting that cAMP signaling was involved in the inhibition of steroidogenesis (Ma et al. 2011).

2.17 DEVELOPMENTAL

An epidemiological study investigated low birth weight of small-for-gestational-age (SGA) infants whose mothers were occupationally exposed to chlorophenols (Seidler et al. 1999). The cohort consisted of 3,946 German women recruited during weeks 15–28 of pregnancy. Occupational exposures to chlorophenols and other chemicals were estimated for each mother based on a job-exposure-matrix and used to assign chemical exposure categories (low, moderate, high) to each subject. The adjusted OR for infants classified as SGA was elevated for subjects with moderate exposure to chlorophenols (OR 7.0; 95% CI 1.2–43.0), which was the highest exposure category reported for chlorophenols (data for the high

exposure category for chlorophenols were not reported). The authors identified several potential limitations of the study, including potential exposure misclassification from the application of the job-exposure-matrix and recognized co-exposures to other chemicals (Seidler et al. 1999).

Other human studies used urinary chlorophenol concentrations to assess exposure. These studies are of uncertain utility for chlorophenol hazard identification, because chlorophenols in urine may result from metabolism after exposure to other compounds (e.g., chlorobenzenes or pesticides, such as lindane, 2,4-D, and 2,4,5-T) rather than exposure to chlorophenols themselves.

Philippat et al. (2012) evaluated relationships among birth outcomes (birth weight, length, and head circumference) and urinary phenols and phthalates in a nested case-control study of male genital malformations. The case-control was nested in two birth cohorts (the EDEN and PELAGIE cohorts in France), and cases consisted of male newborns with hypospadias or undescended testes at birth. For each case, 3 controls were matched by recruitment site and date and by gestational week at which maternal urine was collected, yielding 72 cases and 216 controls. Urine samples collected between 6 and 19 weeks of gestation (PELAGIE) or between 24 and 30 weeks of gestation (EDEN) were analyzed for phthalates and phenols including 2,4- and 2,5-DCP. Analyses of birth outcome data were adjusted for oversampling of malformation cases. Concentrations of 2,4- and 2,5-DCP in maternal urine were associated with decreased birth weight, and 2,4-DCP levels were also associated with decreased head circumference (Philippat et al. 2012). The authors noted that concentrations of the two dichlorophenols were highly correlated, so it is difficult to discern effects attributable each individual compound in this study.

A second study evaluating the association between maternal urinary chlorophenol concentrations (including 2,4-DCP, 2,5-DCP, 2,4,5-TCP, and 2,4,6-TCP) and birth outcomes in a cohort of 1,100 women reported associations between creatinine-adjusted 2,4,6-TCP concentration and birth weight and between head circumference in male newborns and between both dichlorophenols and head circumference in female newborns (Guo et al. 2016). However, in this study, urine samples were collected at parturition, so the temporal relationship between exposure and outcome is highly uncertain.

2-CP. Groups of 6–13 female Sprague-Dawley rats receiving a single gavage dose of 333, 667, or 1,000 mg/kg 4-CP on GD 11 showed no adverse changes in litter sizes, perinatal loss, pup weight, or litter biomass (Kavlock 1990). The only treatment-related effect was a transient decrease in maternal body weight at 1,000 mg/kg. No significant changes in offspring body or liver weights were observed in rats

treated with 2-CP in drinking water at doses up to 73 mg/kg/day throughout gestation and lactation and for an additional 15 weeks (Exon and Koller 1982, 1983b, 1985).

When neonatal (PND 4) Sprague-Dawley rats were given 500 mg/kg/day 2-CP by gavage in a dose range-finding study, all animals died within 9 days (Hasegawa et al. 2005). In the main study, rats survived doses of 300 mg/kg/day for 18 days (PNDs 4–21). Transient decreases in body weight were noted (data not reported) at 300 mg/kg/day, but not at lower doses. There were no effects on developmental milestones (surface righting, visual reflexes, fur appearance, tooth eruption, eye opening, preputial separation, vaginal opening, and estrous cycle) at any dose up to 300 mg/kg/day in the main study (Hasegawa et al. 2005). Histopathology examinations of the rats treated with 300 mg/kg/day showed increased incidences of basophilic renal tubules in males (4/6 compared with 0/6 controls) and females (5/6 compared with 0/6 controls). This finding was not observed in the 50 mg/kg/day dose group and was not assessed in the 20 or 100 mg/kg/day 2-CP exposed groups (Hasegawa et al. 2005). No changes in weights or histopathology of the brain, pituitary gland, thymus, thyroid, heart, lungs, liver, spleen, adrenals, or reproductive organs were observed.

4-CP. All male and three of four female Sprague-Dawley rats given 500 mg/kg/day 4-CP by gavage beginning on PND 4 died (timing of deaths not reported) in a dose range-finding study, while there were no deaths at 300 mg/kg/day for 18 days in the main study (Hasegawa et al. 2005). The main study showed no treatment-related changes in body weights, developmental milestones (surface righting, visual reflexes, fur appearance, tooth eruption, eye opening, preputial separation, vaginal opening, and estrous cycle), or weights or histology of the brain, pituitary gland, thymus, thyroid, heart, lungs, liver, spleen, adrenals, or reproductive organs (Hasegawa et al. 2005). No adverse treatment-related effects on offspring body weights, postnatal viability until PND 4, frequency of external anomalies, or necropsy findings were noted in a screening-level reproductive/developmental toxicity study of rats given gavage doses of 40 or 200 mg/kg/day before and during gestation; however, as discussed in Section 2.16, significantly fewer live offspring were delivered in the 200 mg/kg/day group (BSRC 2011).

2,4-DCP. Oral exposure of pregnant rats to 750 mg/kg/day 2,4-DCP for 10 gestation days induced a slight decrease in fetal weight and a statistically significant delayed ossification of sternal and vertebral arches and led to a slight insignificant increase in early embryonic deaths (0.8/average litter controls; 1.2/litter 750 mg/kg/day) (Rodwell et al. 1989). Maternal death occurred at this dose level, indicating that 2,4-DCP was not selectively toxic to embryos or fetuses. The authors indicated that, although the number of deaths and fetal weights differed from that of the concurrent controls, values were not different from

the historical control data from their laboratory. No evidence of malformations in the offspring was found in this study. At 375 mg/kg/day, maternal body weight was reduced, and at ≥200 mg/kg/day, there was a decrease in maternal body weight gain. No effect on birth or weaning weight or survival to weaning was observed when female Sprague-Dawley rats received 2,4-DCP in drinking water at doses up to 46 mg/kg/day from weaning through mating and parturition (~13 weeks total) (Exon and Koller 1985). The study examined few endpoints, and the fetus, not the litter, was the unit of statistical analysis.

In a two-generation reproductive and developmental toxicity study, Wistar-Hanover rats (24/sex/dose) were exposed to 2,4-DCP in the diet for 10 weeks prior to mating and through mating, gestation, and lactation. Dietary concentrations of 0, 400, 2,000, and 8,000 ppm were estimated to yield oral doses of 0, 33.4, 134, or 543 mg/kg/day for males and 0, 49.1, 194, or 768 mg/kg/day for females. The percentage of pups with eyes open on lactation day 14 was significantly decreased in high-dose F1 and F2 pups compared to their respective controls. In F1 male pups, age at preputial separation was significantly increased at the high dose, but the delay was attributed to reduced body weight in this group. In contrast, F1 female pup vaginal opening was accelerated at the high dose despite a significant decrease in body weight in this group. In addition, uterine weights were significantly elevated in high-dose F1 and F2 weanlings (42 and 20%, respectively, compared with controls). Body weight gain and feed consumption were significantly decreased in high-dose F1 generation males and females throughout exposure (Aoyama et al. 2005). A slight but statistically significant decrease in the number of implantation sites in F1 parental females was observed; a small, nonsignificant decrease in implantation sites was also noted in F0 parental females (Aoyama et al. 2005). In F2 weanling females, microscopic examination of the uteri showed increases in epithelial cell height in 7/10 females in the high-dose group (compared to 1/10 female controls).

2,4,5-TCP. Gavage administration of 650 mg/kg/day 2,4,5-TCP during organogenesis (GDs 6–15) produced no fetotoxicity, malformations, or structural terata in the offspring of Sprague-Dawley rats (Chernoff et al. 1990). Treatment resulted in maternal lethality (12 versus 0% in controls) and decrements in maternal weight gain (5–15 g less than controls) (Chernoff et al. 1990). In another developmental study, groups of mice received either a single gavage dose of 800–900 mg/kg 2,4,5-TCP on 1 day of gestation (any of GDs 8–15), or 250–300 mg/kg/day on any 3 days of gestation (GDs 7–9, 10–12, or 13–15) (Hood et al. 1979). A significant increase in the incidence of prenatal mortalities and resorptions was seen in dams dosed on day 14 with 800–900 mg/kg/day, but not in dams dosed on days 13–15 at 250–300 mg/kg/day. 2,4,5-TCP administered on other gestation days had no effect on

resorption incidence or pup survival. 2,4,5-TCP administration did not affect mean fetal weight or the incidence of gross malformations, skeletal malformations, or cleft palates (Hood et al. 1979).

2,4,6-TCP. In a study designed to examine reproductive effects, a 10–11% decrease in litter weights was observed in litters of female rats treated by gavage with 2,4,6-TCP at 500 mg/kg/day for 2 weeks before mating and throughout gestation (Blackburn et al. 1986). No effects on litter weights were observed at 100 mg/kg/day, and no effects on survival to PND 42 were observed. No effects on body weight were observed among offspring of male rats treated by gavage with 2,4,6-TCP at 1,000 mg/kg/day for 10 weeks before mating (Blackburn et al. 1986). Because comprehensive examinations of offspring were not completed, this study is not sufficient to conclude that developmental effects do not occur following exposure to 2,4,6-TCP.

Maternal exposure of rats to 500 mg/kg/day 2,4,6-TCP produced a transient reduction in the body weight of offspring (Blackburn et al. 1986). No developmental effects were noted in the offspring of female rats exposed to 2,4,6-TCP throughout gestation (Blackburn et al. 1986; Exon and Koller 1985). In addition, no developmental effects were noted in the offspring of male rats treated with 2,4,6-TCP and untreated females (Blackburn et al. 1986). These studies were limited by the lack of reporting on the number of animals from which group means were calculated (Blackburn et al. 1986) and by a lack of reporting on maternal toxicity (Exon and Koller 1985).

2,3,4,6-TeCP. In a developmental study in which female Sprague-Dawley rats orally received purified 2,3,4,6-TeCP throughout organogenesis, the only effect on the fetus was delayed ossification of the skull bones (Schwetz et al. 1974). The reported incidences were 14/173 (8%) and 18/104 (17%) at 0 and 30 mg/kg/day, respectively. When analyzed by litter, no statistical difference for delayed ossification was observed. Therefore, 30 mg/kg/day 2,3,4,6-TeCP is considered a NOAEL for developmental effects in rats. In a follow-up study, pregnant CD rats received 0,25, 100, or 200 mg/kg/day, in olive oil, every day during organogenesis (EPA 1987a, 1987b). Administration of the two highest doses resulted in decreases in corrected maternal body weight gain (dam body weight-gravid uterus weight) of 13 and 26%, respectively, with no effects at 25 mg/kg/day. Measurement of food intake indicated that these effects were not related to decreased food consumption. Minor variations between dose groups in fetal malformation and aberrations were not dose related. The investigators also noted a dose-related trend for 2,3,4,6-TeCP-mediated effects on implantation or postimplantation viability. No further evidence of maternal or fetotoxic effects were observed (EPA 1987a, 1987b). Based on maternal toxicity, this study identifies 100 mg/kg/day as a LOAEL and 25 mg/kg/day as a NOAEL for developmental effects.

2.18 OTHER NONCANCER

Two studies used NHANES data to examine the relationship between urinary levels of dichlorophenols and obesity among children (n=6,770, aged 6–19 years) from the 2003–2004 and 2005–2006 survey years (Twum and Wei 2011) or among adults (n=2,963, aged 20–85 years) from the 2005–2006 and 2007–2008 survey years (Wei et al. 2014). In both studies, urinary 2,5-DCP was associated with higher prevalence of obesity, while 2,4-DCP was not. Using later NHANES survey data (years 2007–2010), Wei and Zhu (2016a, 2016b) observed concentration-related associations between 2,5-DCP in urine and higher prevalences of diabetes and metabolic syndrome in adults; no associations were seen with urinary levels of 2,4-DCP in either study. In all four of these studies, urinary 2,5-DCP was assessed as a biomarker for exposure to *p*-dichlorobenzene.

Mechanisms of Toxicity. Chlorophenols have been shown to uncouple mitochondrial oxidative phosphorylation (Cascorbi and Ahlers 1989; Farquharson et al. 1958; Izushi et al. 1988; Mitsuda et al. 1963; Narasimhan et al. 1992; Ravanel et al. 1985, 1989; Shannon et al. 1991; Stockdale and Selwyn 1971; Weinbach and Garbus 1965). During the Krebs cycle, lipophilic weak acids uncouple oxidative phosphorylation from electron transport by picking up protons, diffusing across the inner mitochondrial membrane, deprotonating, and returning to pick up more protons, thereby dissipating the pH gradient and membrane electrochemical potential needed for the formation of ATP (Lou et al. 2007; Stryer 1988). During this uncoupling, electron transport from NADH to oxygen can increase several-fold, but the energy produced, which is normally stored as the chemical potential of ATP, is released as heat. Severe toxic manifestations of the uncoupling of oxidative phosphorylation may include central nervous system depression followed by increased respiration, hyperthermia, blood pressure rise, progressive neuromuscular weakness, convulsions, muscle rigidity, and death.

Most of the data on chlorophenol-induced uncoupling have been from *in vitro* mitochondrial preparations, but one study demonstrated the metabolic effects (such as increased body temperature and dyspnea) in male rats exposed *in vivo* (Farquharson et al. 1958). In this study, the manifestations of uncoupling increased with increasing chlorination and decreasing pK, as shown in the Table 2-11.

Table 2-11. Relationship Between Degree of Chlorination and Symptoms of Uncoupling in Rats Exposed by Intraperitoneal Injection

Compound	pK	LD_{50}	Convulsions	Change in rectal temperature
Phenol	9.98	250	+	-2.5
4-CP	9.37	281	+	-2.5
2-CP	8.65	230	+	-2.0
2,4-DCP	7.85	430	Twitching	-0.5
2,4,5-TCP[a]	7.07	355	–	+0.5
2,4,6-TCP[a]	6.62	276	+	+0.5
2,3,4,6-TeCP[a]	5.46	130	–	+4.0

[a]Rigor mortis within 5 minutes of death.

Source: Farquharson et al. 1958

The results of a number of *in vitro* studies (Cascorbi and Ahlers 1989; Izushi et al. 1988; Mitsuda et al. 1963; Narasimhan et al. 1992; Shannon et al. 1991; Stockdale and Selwyn 1971) indicate a concentration-dependent, triphasic effect of chlorophenols on phosphorylation and cellular respiration. At low concentrations, uncoupling produces stimulation of state 4 (resting state) respiration as a result of increased adenosine triphosphatase (ATPase) activity in the absence of a phosphate acceptor. Inhibition of state 3 (active) respiration is also observed. At moderate concentrations, resting respiration is neither stimulated nor inhibited. Significant inhibition of respiration, associated with a breakdown of the electron transport process and decreased ATPase activity, occurs at very high concentrations. These concentrations are also associated with mitochondrial swelling and disruption of the mitochondrial matrix structure. Investigators have cited two independent mechanisms to explain these effects on cellular metabolism. Uncoupling activity has been attributed to a protonophoric effect (a disruption of the energy gradient across the mitochondrial membrane resulting from distribution of chlorophenols in the phospholipid bilayer of the membrane), whereas inhibition of cellular respiration has been attributed to a direct action on intracellular proteins.

The results of these and other studies also illustrate that higher order chlorophenols have the greatest effects on cellular metabolism. In general, investigators have found that 2-CP and 4-CP are <7% as potent as tetrachlorophenol in uncoupling oxidative phosphorylation and inhibiting cellular respiration (Cascorbi and Ahlers 1989; Janik and Wolf 1992; Narasimhan et al. 1992; Weinbach and Garbus 1965). Within the chlorophenol series, two physicochemical parameters, the a-Hammett constant, a measure of electron withdrawing ability, and the octanol-water partition coefficient (log K_{ow}), accounted for 98% of the variability in the inhibition of ATPase activity (Cascorbi and Ahlers 1989).

In vitro, but not *in vivo*, data suggest that chlorophenols may induce oxidative stress through the formation of reactive metabolites (Bukowska et al. 2003, 2004, 2016; Truffin et al. 2003). In a study of 54 pregnant women (participants in the Puerto Rico Testsite for Exploring Contamination Threats, or PROTECT), urinary markers of oxidative stress (OHdG and isoprostane) were not correlated with urinary concentrations of 2,4-DCP or 2,5-DCP (Watkins et al. 2015). Results of an *in vitro* study in human hepatoma cells indicate that reactive metabolites of 4-CP may induce or contribute to conditions of oxidative stress (Truffin et al. 2003). Incubation of hepatoma cells (Hep G2 cell line) with 350 μM 4-CP for 24–48 hours significantly reduced the activities of cytochrome P-450 reductase, catalase, and glutathione peroxidase as well as levels of glutathione and ATP. In addition, mRNA expression of cytochrome P-450 isozymes, CYP3A7 and CYP2E1, was significantly increased, with more pronounced effects on CYP3A7. Incubation of human peripheral blood mononuclear cells with relatively high concentrations of 2,4-DCP resulted in significant increases in oxidative damage measured as 6-carboxy-2',7'-dichlorodihydrofluorescein diacetate (H2DCFDA) oxidation, lipid peroxidation, and protein carbonylation (Bukowska et al. 2016). *In vitro* exposure of human erythrocytes to 2,4-DCP (Bukowska et al. 2003) and 2,4,5-TCP (Bukowska et al. 2004) resulted in decreased levels of glutathione and antioxidant enzyme (SOD, catalase) activities, which are indicative of changes associated with oxidative stress. There were no changes observed for total glutathione levels (reduced plus oxidized glutathione) or glutathione reductase activity when cells were exposed to 100 ppm 2,4,5-TCP *in vitro*. Results of these studies are consistent with oxidative stress potentially induced by chlorophenol-derived free radicals.

Comparative cytotoxic effects and mediation of cell death through induction of apoptosis were evaluated for 4-CP, 2,4-DCP, 2,3,4-TCP, and pentachlorophenol in fibroblast L929 cells (mouse connective tissue fibroblast cell line) (Chen et al. 2004). Incubation of L929 cells with each of these compounds induced significant dose-and time-dependent reductions in cell growth. The results of deoxyribonucleic acid (DNA) fragmentation analysis (for 4-CP, 2,4-DCP, and 2,3,4-TCP), which is a distinctive feature of apoptosis, revealed dose-and time-dependent effects for these chlorophenol exposures. Observations are consistent with induction of cell death through apoptosis as the mechanism of action for exposure to 4-CP, 2,4-DCP, or 2,3,4-TCP, as opposed to cell necrosis for pentachlorophenol (Chen et al. 2004).

2.19 CANCER

Several case-control studies and an ecological study have suggested possible links between chlorophenol exposure and NHL, soft tissue sarcoma, and nasal cancers (Lampi et al. 2008). In the case-control studies

(Garabedian et al. 1999; Hoppin et al. 1998; Mirabelli et al. 2000; Richardson et al. 2008), exposure to individual chlorophenols was not evaluated; rather, exposure to chlorophenols as a class was assessed based on job history, and the subjects may have been exposed to pentachlorophenol. In addition, in the ecological study (Lampi et al. 2008), the water supply to which the community was exposed was contaminated with pentachlorophenol in addition to 2,4,6-TCP and 2,3,4,6-TeCP. As a result, it is not possible to determine whether the observed associations might be attributable to exposure to one or more of the chlorophenols addressed in this profile, or to pentachlorophenol exposure.

A retrospective cohort study was conducted by Demers et al. (2006) evaluating the association between pentachlorophenol and 2,3,4,6-TeCP, and cancer morbidity and mortality, in sawmill workers in British Columbia, Canada. The cohort consisted of 27,464 former male workers who were employed at 14 different sawmills during the period from 1950 to 1995. Cancers that occurred during the period from 1969 to 1995 were identified from records in cancer registries. No clear evidence was found to link 2,3,4,6-TeCP exposure to cancer mortality or incidence. The authors noted that the use of tetrachlorophenol at the sawmill was more recent than pentachlorophenol, and that the follow-up time for tetrachlorophenol may thus have been inadequate to evaluate its association with cancer.

A large population-based, case-control study yielded data on the association between occupational exposures to chlorophenols and three cancer types: soft tissue sarcoma (Hoppin et al. 1998), NHL (Garabedian et al. 1999), and nasal or nasopharyngeal cancers (Mirabelli et al. 2000). Cases consisted of men born between 1929 and 1953 whose cancers were reported to one of eight cancer registries in the United States between 1984 and 1988. The same group of 1,909 controls was used for all three cancers. Job history information was obtained via telephone interviews of cases and controls and each job was classified by chlorophenol exposure (unexposed, minimal exposure, moderate exposure, and substantial exposure) by an industrial hygienist based on exposure intensity and level of confidence with exposure intensity assignment. For NHL, adjusted ORs were based on 995 cases and 1,783 controls (Garabedian et al. 1999). The adjusted OR for “ever being occupationally exposed to low, medium, or high concentrations of chlorophenols with medium or high confidence levels” was 1.07 (95% CI 0.93–1.24; 255 cases, 399 controls), and when exposure durations were restricted to >8 years, the OR increased to 1.51 (95% CI 0.88 to 2.59; 18 cases, 8 controls).

For soft-tissue sarcoma, adjusted ORs were based on a total of 295 cases and 1,908 controls (Hoppin et al. 1998). The risk of soft tissue sarcoma increased with exposure duration, especially in those classified as having substantial exposure. The OR among those with at least 10 years of exposure to chlorophenols

was 7.8 (95% CI 2.46–24.65) (Hoppin et al. 1998). However, there was no increase in OR with exposure intensity or confidence in exposure intensity. For nasopharyngeal cancer, there were 43 nasal carcinoma cases, 92 nasopharyngeal carcinomas cases, and 1,909 controls. Mirabelli et al. (2000) found an increased risk of nasopharyngeal cancers for workers placed in the medium chlorophenols exposure group (adjusted OR 1.94; 95% CI 1.03–3.50; 18 exposed cases; 244 controls) and the high exposed group (OR 2.64; 95% CI 1.11–5.78). In addition, risk of nasopharyngeal cancer increased with increasing exposure duration (OR for exposure >10 years 9.07; 95% CI 1.41–42.9; 3 exposed cases; 7 controls) (Mirabelli et al. 2000). Several limitations preclude drawing definitive conclusions from these studies, including: (1) potential misclassification of exposure from use of a post-hoc categorical assignment of subjects to exposure categories, rather than specific measurements of exposure history (e.g., workplace or biomarker monitoring); (2) possibly previous or concurrent chemical exposures, which may have contributed to the outcomes that were not adjusted for in the study design or data analysis (e.g., solvents, formaldehyde, chromium, nickel, pentachlorophenol, and chlorinated dibenzo-*p*-dioxins and dibenzofurans); and (3) lack of evidence of dose-response relationships in some studies.

A potential association between chlorophenol exposure and NHL was reported in a case-control study of NHL in northern Germany (Richardson et al. 2008). A total of 858 incident cases of NHL diagnosed between 1986 and 1998 were compared with 1,821 age, sex, and region-matched population controls. Subjects were interviewed for detailed occupational histories and exposures were estimated with a job-exposure matrix. An increased risk for high malignancy NHL was reported (OR 1.95, 95% CI 1.32–2.87); however, there was no exposure-response trend when analyses were performed by tertile of cumulative chlorophenol exposure.

A study was conducted in Southern Finland to determine if drinking water contaminated with chlorophenols was associated with cancer morbidity (Lampi et al. 2008). At the end of 1987, environmental sampling of groundwater near a village where 2,000 residents lived revealed chlorophenols levels ranging from 70 to 140 μg/L. The residents used the groundwater as a source of drinking water. The village was located near a sawmill that used fungicides containing chlorophenols (primarily 2,3,4,6-TeCP); the fungicides also contained pentachlorophenol, 2,4,6-TCP, and polychlorinated dioxin and furan impurities. Polychlorinated dioxins and furans were not detected during groundwater monitoring. Environmental sampling of the deep aquifer in the vicinity of the sawmill revealed chlorophenols ranging from 56,000 to 190,000 μg/L; chlorophenols were also detected in the fish and water from a local lake. In 1987, the municipal drinking water intakes from groundwater near the area were closed. Evaluation of the cancer incidences in the village during three periods (1953–1971, prior to

exposure; 1972–1986, during exposure; and 1987–2006, after exposure ended) showed higher incidences of soft tissue cancers and NHL (compared with incidence rates for the region where the village was located) in the period during exposure. In that period, the standardized incidence ratios (SIRs) were 3.19 (95% CI 1.17–6.95) for soft tissue cancer and 2.08 (95% CI of 1.14–3.49) for NHL. No increase in the incidences of colon cancer, bladder cancer, Hodgkin's lymphoma, or leukemia was observed during the exposure period. The soft tissue cancer and NHL incidence rates did not differ from the reference rates during the periods before or after exposure, suggesting an association with the chlorophenol exposure.

Several other epidemiological studies (Eriksson et al. 1981, 1990; Hardell and Eriksson 1981, 1988; Hardell et al. 1995; Hooiveld et al. 1998; Kogevinas et al. 1997; Lynge 1985; Saracci et al. 1991; Zendehel et al. 2014) have examined potential associations between cancer and occupational exposure to chlorophenols during the manufacture or use of phenoxy herbicides (e.g., 2,4-D [2,4-dichlorophenoxy-acetic acid], 2,4,5-T [2,4,5-trichlorophenoxyacetic acid], Agent Orange [mixture of 2,4-D and 2,4,5-T], and related compounds). In these settings, workers may have been exposed to pentachlorophenol, phenoxy herbicide compounds, and polychlorinated dioxin and furan contaminants in addition to chlorophenols that are the subject of this profile. Although the studies suggest associations between some cancer types and these workplace exposures, most of the studies that focused narrowly on chlorophenol exposure (other than pentachlorophenol) have not shown any association.

IARC coordinated an international collaborative analysis of workers exposed to phenoxy herbicides and related chlorophenols and dioxin contaminants. The most recent publication on this effort included 21,863 male and female workers across 36 cohorts and 12 countries who were followed from 1939 to 1992 (Kogevinas et al. 1997). Among the workers who were exposed to phenoxy herbicides and/or chlorophenols but not exposed to TCDD or higher chlorinated dioxins, an elevated standardized mortality ratio (SMR) of 6.38 (95% CI 1.32–18.65) was reported for adrenal gland tumors. SMRs for NHL and lung cancer were close to unity. There was a slight increase in the SMR for soft tissue sarcoma (SMR 1.35), but this was based on only two deaths. Other tumor types for which some evidence of association was observed in this subgroup include sinonasal tumors (SMR 3.8) and thyroid tumors (SMR 2.17). None of the SMRs showed relationship with years since first exposure or duration of exposure.

In a cohort of 549 male Dutch chemical factory workers exposed to phenoxy herbicides, chlorophenols, and polychlorinated dioxins and furans between 1955 and 1991, increased SMRs were observed for

cancers of the bladder, kidney, and urinary organs (Hooiveld et al. 1998). When compared with an internal comparison group of 482 unexposed male workers, the relative risks (adjusted for age, calendar year at end of follow up, and time since first exposure) for cancers of the urinary organs and respiratory tract were elevated (relative risks [RRs] in the range of 4.2–7.5) but CIs included 1.0. The adjusted RR for NHL was 1.7 based on only one unexposed and three exposed deaths.

A number of case-control studies have reported associations between exposure to phenoxy herbicides, chlorophenols, and/or dioxins and NHL or soft tissue sarcomas in Sweden (Eriksson et al. 1981, 1990; Hardell and Eriksson 1988; Hardell et al. 1981). In a meta-analysis of soft tissue sarcomas in these studies, Hardell et al. (1995) reported an increased odds ratio for exposure specifically to chlorophenols. However, the authors indicated that pentachlorophenol was the primary chlorophenol used in Sweden at the time of the exposures, and indeed most of the subjects in the group exposed to chlorophenols were exposed to pentachlorophenol (27/34 cases and 30/34 controls).

Zendehel et al. (2014) conducted a meta-analysis of five studies evaluating lung cancer mortality among pesticide production workers exposed to phenoxyacetic acids and chlorophenols. In the three studies examining groups exposed only to chlorophenols (no TCDD or phenoxyacid exposures), there was no association with lung cancer. In a retrospective cohort study on Danish phenoxy herbicide workers, there were no cases of soft tissue sarcoma or malignant lymphoma among subjects (n=615) in the factory manufacturing only 2,4-DCP and 4-chloro-*o*-tolyloxy-acetic acid (MCPA) (Lynge 1985). Other factories evaluated by this author manufactured a wide range of phenoxy herbicides in addition to 2,4-DCP. Similarly, no deaths from soft tissue sarcoma or NHL were reported among workers producing or spraying exclusively chlorophenols in a cancer mortality study (2,377 deaths among a population of 18,910) of sprayers and production workers exposed to chlorophenoxy herbicides and chlorophenols (Saracci et al. 1991).

In well-conducted chronic cancer bioassays of chlorophenol compounds, 2,4-DCP did not induce an increase in cancer incidence in rats and mice treated with 2,4-DCP in the diet at doses up to 440 mg/kg/day (rats) and 1,300 mg/kg/day (mice) (NTP 1989), while rats and mice exposed to 2,4,6-TCP in the diet exhibited increased incidences of leukemia and liver cancer (respectively) (NCI 1979). Other chlorophenols discussed in this profile have not been adequately tested for potential carcinogenicity.

2-CP. In an oral carcinogenicity study located, groups of Sprague-Dawley rats received prenatal, postnatal, or both pre- and postnatal exposure to 2-CP (Exon and Koller 1985). The exposure

concentrations were 0, 5, 50, and 500 ppm in drinking water (0, 0.62, 6.2, or 62 mg/kg/day). Under all exposure conditions, 2-CP administration had no effect on the incidence, latency, or types of tumors relative to the untreated controls. Additional groups of gravid dams received ethylurea and nitrite, precursors of the carcinogenic initiator ethylnitrosourea (ENU), on GDs 14 and 21. No consistent effects on either tumor incidence or latency occurred in rats treated with ENU and then treated either prenatally or postnatally with 2-CP. The groups of males receiving ENU and both prenatal and postnatal 2-CP had increased tumor incidence and decreased tumor latency relative to a control group receiving ENU only. The investigators indicated that the combined changes were marginally statistically significant (p=0.10) in comparison to a group receiving the initiator ENU only. ENU-exposed female rats also exposed pre- and postnatally to 2-CP showed no consistent, concentration-related effects on either tumor incidence or latency (Exon and Koller 1985). Findings in the combined-exposure male treatment groups indicate that 2-CP may be either a cocarcinogen or a tumor promotor. However, an analysis of incidence and latency data suggests that the effects may not be concentration related. No effects on tumorigenicity were found in similar studies with 2,4-DCP given in drinking water at 0.62, 6.2, or 62 mg/kg/day. It is not clear whether a maximum tolerated dose was achieved in these studies (Exon and Koller 1985).

In 15-week mouse initiation-promotion studies, 2-CP showed tumor promoting activity (Boutwell and Bosch 1959); however, the significance of these results is limited by the lack of appropriate vehicle control groups, irritation, and the reporting of only gross pathological effects (EPA 1980). One application of the known tumor initiator, 9,10-dimethyl-1,2-benzanthracene (DMBA), to the middorsal region of mice was followed by twice weekly dermal applications of 25 μL of a 20% solution of 2-CP. Compared to DMBA treatment alone, 2-CP increased the number of skin tumors (Boutwell and Bosch 1959). In a study in which no initiator was used, 2-CP applied to the backs of mice twice per week for 12 weeks resulted in papillomas in 46% of the mice (Boutwell and Bosch 1959). No carcinomas were observed.

2,4-DCP. Chronic carcinogenicity bioassays in rats and mice treated with 2,4-DCP in the diet at doses up to 440 mg/kg/day for rats and 1,300 mg/kg/day for mice did not provide any evidence that 2,4-DCP is carcinogenic (NTP 1989).

2,4-DCP exhibited tumor promoting activity in a 15-week mouse dermal initiation-promotion study in which 2,4-DCP was applied twice weekly (25 μL of a 20% solution) after a single application of DMBA (Boutwell and Bosch 1959). An increase in the number of skin tumors was seen after promotion with 2,4-DCP compared with DMBA treatment alone.

2,4,6-TCP. Carcinogenicity bioassays with rats and mice have shown increased incidences of leukemia and liver cancer with chronic oral exposure to 2,4,6-TCP (NCI 1979). In male rats, chronic oral exposure to 2,4,6-TCP in the diet produced a significant dose-related increase in the incidence of monocytic leukemia (NCI 1979). The increase was statistically significant compared to both concurrent and historical control incidences. An increased incidence of leukemia also occurred in female rats; however, the increase was not significant compared to the controls. In addition, leukocytosis and monocytosis as well as hyperplasia of the bone marrow were induced in treated male and female rats that did not develop leukemia. In rats with leukemia, there were large numbers of circulating monocytes in the blood that ranged from well-differentiated monocytes to immature and blast forms. Monocytes were often observed in the liver, spleen, lymph tissue, and bone marrow and occasionally in the lungs, adrenals, and other organs.

In both male and female B6C3Fl mice treated chronically with 2,4,6-TCP in the diet, a significant dose-related increase in the incidence of hepatocellular adenomas and carcinomas was noted (NCI 1979). Statistically significant increases in liver tumor incidences were observed in both males and females when compared with both concurrent and historical control groups. Liver damage, including individual liver cell abnormalities, focal areas of cellular alteration, and focal and nodular areas of hyperplasia were commonly present in the treated mice. Significant limitations of this study included the failure to report the dioxin content of the 2,4,6-TCP formulation, changes in the dosing regimen of mice, and no testing of organ function.

A single oral dose of 2,4,6-TCP (200 mg/kg) did not significantly increase skin tumors in mice treated dermally with a tumor promoter (12-O-tetradecanoylphorbol-13-acetate [TPA]) relative to TPA alone, suggesting that 2,4,6-TCP does not act systemically as an initiator (Bull et al. 1986). Other studies also examined the possible carcinogenic effects of 2,4,6-TCP, but contained limitations that preclude a conclusion (Innes et al. 1969; NCI 1968; Stoner et al. 1986). The limitations included early termination of the experiment (24 weeks) (Stoner et al. 1986), only one treatment group (Innes et al. 1969; NCI 1968), a small number of treated animals (Innes et al. 1969; NCI 1968), and a change in dosing regimen and method of exposure (Innes et al. 1969; NCI 1968).

Skin tumor initiation and promotion assays using 2,4,6-TCP have not shown evidence of dermal tumor initiation or promotion activity. 2,4,6-TCP did not have initiating activity in another study in which mice were treated with a dermal dose of 200 mg/kg/day 2,4,6-TCP followed 2 weeks later by 20 weeks

(3 times/week) of dermal TPA treatment (Bull et al. 1986). In addition, 2,4,6-TCP did not increase the number of skin tumors when applied (25 µL of a 20% solution) twice weekly for 15 weeks to the skin of mice pretreated with a single dermal application of DMBA, when compared with the incidence in mice treated only with DMBA (Boutwell and Bosch 1959).

2.20 GENOTOXICITY

Available evidence indicates that the chlorophenols are not potent mutagens; however, there is evidence that they are capable of causing chromosomal aberrations and DNA damage. The lack of genotoxicity seen in most of the available *in vivo* studies may be attributable to rapid urinary excretion of chlorophenols in these single-dose studies (Borzelleca et al. 1985a; Kitchin and Brown 1988).

In a human study, Rocha et al. (2018) examined urinary concentrations of 2,4-DCP, 2,5-DCP, 2,4,5-TCP, and 2,4,6-TCP (and 36 other chemicals) in correlation with the oxidative DNA damage marker 8-hydroxy-2'-deoxyguanosine (8OHDG) in Brazilian children. Urinary levels of 2,4-DCP and 2,5-DCP (but not 2,4,5-TCP or 2,4,6-TCP) were correlated with higher levels of 8OHDG. No exposure information was reported; thus, it is not known whether the chlorophenols detected in the urine resulted from exposure to chlorophenols or metabolism of dichlorobenzene and/or other compounds.

Reactive intermediates produced by incubation of 2,4-DCP, 2,4,5-TCP, or 2,4,6-TCP with horseradish peroxidase formed covalent adducts with deoxyguanosine in isolated calf thymus DNA and in isolated deoxyguanosine (Dai et al. 2005).

Genotoxicity testing results for each chlorophenol are summarized below. Results of *in vitro* genetic testing are presented in Tables 2-12 (2-CP), 2-13 (4-CP), 2-14 (2,4-DCP), 2-15 (2,4-DCP), 2-16 (2,4,5-TCP), 2-17 (2,4,6-TCP), and 2-18 (other chlorophenols); *in vivo* genotoxicity test results are described in text for the corresponding chlorophenol.

2-CP. 2-CP has been tested in one *in vivo* and several *in vitro* genotoxicity assays (see Table 2-12). The results of prokaryotic mutagenicity (Ames) assays for 2-CP were negative with and without metabolic activation (Haworth et al. 1983; Rapson et al. 1980). Similarly, 2-CP did not induce DNA-repairing genes in an umu test system in *Salmonella typhimurium* (Ono et al. 1992), nor did it induce DNA damage in a prophage induction assay with *Escherichia coli* (DeMarini et al. 1990). In mammalian *in vitro* systems, 2-CP induced slight-to-moderate increases in c-mitosis (indicating disturbances of the spindle

function) and a significant increase in aneuploidy in cultured Chinese hamster lung cells (Onfelt 1987). In human lymphocytes, 2-CP induced concentration-related increases in the frequencies of micronuclei in a cytokinesis block micronucleus assay (Vlastos et al. 2016); however, cytotoxicity (measured as a significant change in the cytokinesis block proliferation index [CBPI]) was seen at the same doses. 2-CP also induced double-stranded DNA breaks (measured using the γ-H2AX focus assay) in human gingival fibroblasts (Shehata et al. 2012).

In an *in vivo* study in ICR mice, gavage administration of up to 69 mg/kg/day 2-CP in corn oil for 14 days did not increase sister chromatid exchange (SCE) rates in testicular or bone marrow cells (Borzelleca et al. 1985a). Details on the time between dosing and evaluation were not provided by the authors.

Table 2-12. Genotoxicity of 2-Chlorophenol *In Vitro*

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	Haworth et al. 1983
S. typhimurium TA100	Mutation	NA	–	Rapson et al. 1980
S. typhimurium TA1535/pSK1002 (umu test)	DNA damage/repair	–	–	Ono et al. 1992
Escherichia coli WP2s(λ) (prophage induction)	DNA damage/repair	–	–	DeMarini et al. 1990
Eukaryotic organisms:				
Chinese hamster V79 cells	Chromosomal aberrations	NA	+	Onfelt 1987
Human lymphocytes (CBMN)	Micronuclei	NA	+	Vlastos et al. 2016
Human gingival fibroblasts (γ-H2AX)	DNA damage	NA	+	Shehata et al. 2012

+ = positive results; – = negative results; DNA = deoxyribonucleic acid; NA = not applicable

4-CP. *In vitro* genotoxicity data are available for 4-CP; no *in vivo* studies of genotoxicity were identified for 4-CP. In *S. typhimurium* reverse mutation assays, treatment with 4-CP generally did not produce an increased number of revertants in the presence or absence of metabolic activation (DeMarini et al. 1990; Haworth et al. 1983; Kubo et al. 2002; Rapson et al. 1980) (see Table 2-13). In one study, 4-CP had a marginally positive response in strain TA1537 (Seuferer et al. 1979). In another study (Strobel and Grummt 1987), 4-CP induced increased numbers of revertants in *S. typhimurium* strains TA97, TA98, TA100, and TA104 with the most pronounced effects in strain TA97 in the presence of metabolic

activation; however, interpretation of these data is confounded by the absence of concentration-effect relationships. 4-CP was negative in assays for DNA damage in the umu test (Sakagami et al. 1988) and in a prophage induction assay with *E. coli* (DeMarini et al. 1990).

Table 2-13. Genotoxicity of 4-Chlorophenol *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	DeMarini et al. 1990
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	Mutation	–	–	Haworth et al. 1983
S. typhimurium TA98, TA100	Mutation	-	-	Kubo et al. 2002
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	Mutation	NA	+/–	Seuferer et al. 1979
S. typhimurium TA97, TA98, TA100, TA104	Mutation	+	+	Strobel and Grummt 1987
S. typhimurium TA1535/pSK1002	Mutation	NA	–	Rapson et al. 1980
S. typhimurium TA1535/pSK1002	Mutation	–	–	Sakagami et al. 1988
Escherichia coli WP2s(λ) (prophage induction)	DNA damage/repair	–	–	DeMarini et al. 1990
Eukaryotic organisms:				
Human primary peripheral lymphocytes (comet assay)	DNA damage	NA	–	Da Silva et al. 2007
Human primary skin fibroblasts (comet assay)	DNA damage	NA	–	Ribeiro et al. 2004
Human gingival fibroblasts (γ-H2AX assay)	DNA damage	NA	+	Shehata et al. 2012
Mouse lymphoma (L5178 cells) (comet assay)	DNA damage	NA	–	Ribeiro et al. 2004
CHO (K-1 cells) (comet assay)	DNA damage	NA	–	Ribeiro et al. 2005
SHE cells	Chromosome aberrations	+	–	Hagiwara et al. 2006
SHE cells	SCE	NA	+	Miyachi and Tsutsui 2005
SHE cells	Unscheduled DNA synthesis	–	–	Hamaguchi and Tsutsui 2000
SHE cells	Morphological transformation	–	–	Yamaguchi and Tsutsui 2003

+ = positive results; +/– = equivocal results; – = negative results; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NA = not applicable; SCE = sister chromatid exchange; SHE = Syrian hamster embryo

4-CP did not induce DNA damage in comet assays in human peripheral lymphocytes (Da Silva et al. 2007), human skin fibroblasts (Ribeiro et al. 2004), mouse lymphoma cells (Ribeiro et al. 2004), or Chinese hamster ovary (CHO) cells (Ribeiro et al. 2005). However, 4-CP induced double-stranded DNA breaks in human gingival fibroblasts as measured with the γ-H2AX focus assay (Shehata et al. 2012). The mixed results for DNA damage may stem from differences in cell type, exposure time (Shehata et al. 2012 exposed cells for 6 hours compared to 1 hour for the negative studies), or assay type (γ-H2AX versus comet assay). Both with and without metabolic activation, 4-CP failed to induce unscheduled DNA synthesis (Hamaguchi and Tsutsui 2000) or morphological transformation (Yamaguchi and Tsustui 2003) in Syrian hamster embryo (SHE) cells. However, 4-CP induced an increase in chromosomal aberrations in SHE cells in the presence (but not in the absence) of exogenous metabolic activation (Hagiwara et al. 2006). 4-CP also induced an increased frequency of SCEs in SHE cells in the absence of exogenous metabolic activation (this assay was not conducted in the presence of metabolic activation) (Miyachi and Tsutsui 2005).

2,4-DCP. Both *in vitro* (Table 2-14) and *in vivo* assays for genotoxicity of 2,4-DCP are available. In Ames assays, 2,4-DCP was negative for mutagenic activity (Haworth et al. 1983; Kubo et al. 2002; NTP 1989; Probst et al. 1981; Rapson et al. 1980; Rasanen et al. 1977; Simmon et al. 1977; Zeiger et al. 1990), but was positive with activation in a prophage induction assay (DeMarini et al. 1990) and positive without activation in a umu test system (Ono et al. 1992). 2,4-DCP was negative for mutation in a GreenScreen assay in *Saccharomyces cerevisiae* (Knight et al. 2007). In mammalian cells, 2,4-DCP yielded negative results for mutation in Chinese hamster V79 cells (Hattula and Knuutinen 1985; Jansson and Jansson 1986). However, 2,4-DCP produced chromosomal aberrations in Chinese hamster V79 cells (Onfelt 1987) and CHO cells (Hilliard et al. 1998); in addition, increased chromosomal aberrations were reported in human lymphoblast (TK6) cells after exposure to cytotoxic doses of 2,4-DCP (Hilliard et al. 1998). Positive results were obtained in a test for induced unscheduled DNA synthesis in rat hepatocytes (Probst et al. 1981).

Table 2-14. Genotoxicity of 2,4-Dichlorophenol *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	Haworth et al. 1983; NTP 1989; Zeiger et al. 1990
S. typhimurium TA98, TA100	Mutation	–	–	Kubo et al. 2002

Table 2-14. Genotoxicity of 2,4-Dichlorophenol *In Vitro*

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
S. typhimurium C3076, D3052, G46, TA98, TA100, TA1535, TA1537, TA1538	Mutation	–	–	Probst et al. 1981
S. typhimurium TA100	Mutation	–	–	Rapson et al. 1980
S. typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	Rasanen et al. 1977
S. typhimurium TA187, TA100, TA1535, TA1537, TA1538	Mutation	–	–	Simmon et al. 1977
S. typhimurium TA1535/pSK1002 (umu assay)	DNA damage/ repair	–	+	Ono et al. 1992
Escherichia coli WP2s(λ) (prophage induction assay)	DNA damage/ repair	+	–	DeMarini et al. 1990
Eukaryotic organisms:				
Chinese hamster V79 cells (with or without primary rat hepatocytes)	Mutation	–	–	Hattula and Knuutinen 1985
Chinese hamster V79 cells	Mutation	NA	–	Jansson and Jansson 1986
Human lymphoblast (TK6)	Chromosomal aberrations	NA	+/–	Hilliard et al. 1998
Chinese hamster V79 cells	Chromosomal aberrations	NA	+	Onfelt 1987
CHO cells	Chromosomal aberrations	+	+	Hilliard et al. 1998
Rat hepatocytes	Unscheduled DNA synthesis	NA	+	Probst et al. 1981
Saccharomyces cerevisiae GenC01, GenT01 (GreenScreen assay)	DNA damage/ repair	NA	–	Knight et al. 2007

+ = positive results; +/– = equivocal results; – = negative results; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NA = not applicable; SCE = sister chromatid exchange

Reactive intermediates produced by incubation of 2,4-DCP with horseradish peroxidase formed covalent adducts with deoxyguanosine in isolated calf thymus DNA and in isolated deoxyguanosine (Dai et al. 2005).

Galloway et al. (1998) tested whether 2,4-DCP induced chromosomal aberrations via an indirect mechanism involving inhibition of DNA synthesis. The authors used flow cytometry and BrdU uptake to assess DNA synthesis rates across the cell cycle. Following exposure to 2,4-DCP, BrdU uptake by CHO cells decreased with increasing dose, but then increased again at higher doses (Galloway et al. 1998).

This result was confirmed with a repeat experiment and despite efforts by the authors to test various hypotheses (e.g., precipitation and fluorescence signaling anomalies) to explain this unexpected result, the authors were not able to account for the U-shaped dose-response (Galloway et al. 1998).

In CD-1 ICR mice, oral administration of 2,4-DCP at doses of up to 638 mg/kg/day (in corn oil by gavage for 14 days) or up to 500 mg/kg/day (in drinking water for 90 days) yielded negative results for SCE induction in testicular and bone marrow cells (respectively) (Borzelleca et al. 1985a). After five daily intraperitoneal injections of 180 mg/kg 2,4-DCP, increased percentages of chromosomal aberrations (measured 35 days after the first injection) were observed in the bone marrow and spermatocytes of Swiss mice (Amer and Aly 2001).

2,5-DCP. The genotoxicity of 2,5-DCP has been tested in both *in vitro* and *in vivo* systems. 2,5-DCP was negative for mutagenic activity in Ames assays (*S. typhimurium*) in the presence or absence of metabolic activation (Haworth et al. 1983; Kubo et al. 2002; NTP 1989; Rasanen et al. 1977) (Table 2-15). In addition, 2,5-DCP was negative for gene mutation in a GreenScreen assay in yeast (Knight et al. 2007), and negative for hypoxanthine phosphoribosyl transferase (HPRT) mutation in CHO cells both in the absence and presence of exogenous metabolic activation (Tegethoff et al. 2000). In an *in vivo* assay, male NMRI mice received a single gavage dose of 1,500 mg/kg 2,5-DCP in corn oil. Bone marrow (femoral) micronucleus formation was assessed at 24, 48, and 72 hours post-administration, and no increase in the frequency of micronuclei was observed (Tegethoff et al. 2000).

Table 2-15. Genotoxicity of 2,5- Dichlorophenol *In Vitro*

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	Haworth et al. 1983; NTP 1989
S. typhimurium TA98, TA100	Mutation	–	–	Kubo et al. 2002
S. typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	Rasanen et al. 1977
Eukaryotic organisms:				
CHO (K-1-BH4 cell line)	Mutation (HPRT locus)	–	–	Tegethoff et al. 2000

– = negative results; CHO = Chinese hamster ovary; HPRT = hypoxanthine phosphoribosyl transferase

2,4,5-TCP. Available genotoxicity data for 2,4,5-TCP include both *in vitro* and *in vivo* studies. 2,4,5-TCP was negative in most *S. typhimurium* reverse mutation assays (George et al. 1992; Kubo et al. 2002; Rasanen et al. 1977) (Table 2-16). One study (Strobel and Grummt 1987) reported increased numbers of revertants in strains TA97, TA98, and TA100, both with and without S9 fraction; however, the results lacked evidence of concentration-response relationships. Evidence of DNA damage induced by 2,4,5-TCP was reported for λ-prophage induction assays with activation (DeMarini et al. 1990), without activation (George et al. 1992), and in a umu test system both with and without activation (Ono et al. 1992). No increase in mutations was observed when 2,4,5-TCP was tested in Chinese hamster V79 cells without exogenous activation (Jansson and Jansson 1986). However, 2,4,5-TCP increased the frequency of chromosome aberrations in CHO cells both with and without metabolic activation (Armstrong et al. 1993) and induced DNA damage in human peripheral blood mononuclear cells (PBMCs) (Michalowicz and Majsterek 2010).

Table 2-16. Genotoxicity of 2,4,5-Trichlorophenol *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA98, TA100, TA102, TA104	Mutation	–	–	George et al. 1992
S. typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	Haworth et al. 1983
S. typhimurium TA98, TA100	Mutation	–	–	Kubo et al. 2002
S. typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	Rasanen et al. 1977
S. typhimurium TA98, TA100, TA97, TA104	Mutation	+	+	Strobel and Grummt 1987
S. typhimurium TA1535/psK1002 (umu assay)	DNA damage/ repair	+	+	Ono et al. 1992
Escherichia coli WP2s(λ) (prophage induction)	DNA damage/ repair	+	+	DeMarini et al. 1990; George et al. 1992
Eukaryotic organisms:				
Human PBMCs	DNA damage	NA	+	Michalowicz and Majsterek 2010
Chinese hamster V79 cells	Mutation	NA	–	Jansson and Jansson 1986
CHO cells	Chromosomal aberrations	+	+	Armstrong et al. 1993

+ = positive results; – = negative results; CHO = Chinese hamster ovary; NA = not applicable; PBMC = peripheral blood mononuclear cell

Covalent adducts with deoxyguanosine in isolated calf thymus DNA and in isolated deoxyguanosine were formed by reactive intermediates produced by incubation of 2,4,5-DCP with horseradish peroxidase (Dai et al. 2005).

In *in vivo* testing, a single gavage dose of 2,4,5-TCP (164 mg/kg) given to rats did not damage DNA as measured by the fraction of DNA eluted from white blood cells or livers (Kitchin and Brown 1988). Human peripheral blood lymphocytes from an occupational cohort of 19 herbicide production workers exposed to 2,4,5 TCP and 2,4-D showed higher frequencies (2-fold increase) of chromosomal aberrations compared with 36 control workers without chemical contact and 21 controls from the vicinity of the plant (Kaioumova and Khabutdinova 1998).

2,4,6-TCP. 2,4,6-TCP was tested for genotoxicity in both *in vitro* and *in vivo* assays. 2,4,6-TCP did not induce mutations in *S. typhimurium* (Ames) assays in the presence or absence of metabolic activation in the preponderance of available studies (Haworth et al. 1983; Kinae et al. 1981; Kubo et al. 2002; Rapson et al. 1980; Rasanen et al. 1977) (Table 2-17). Strobel and Grummt (1987) reported increased mutations in *S. typhimurium* TA97, TA98, and TA104 with exogenous metabolic activation; however, the results lacked evidence of concentration-response relationships. In umu assay testing, 2,4,6-TCP did not induce DNA damage with activation but did induce damage without activation (Ono et al. 1992). Positive results were also reported for DNA damage in a prophage induction assay both with and without activation (DeMarini et al. 1990) and in a bacterial (*Bacillus subtilis*) assay of DNA damage (Kinae et al. 1981).

Table 2-17. Genotoxicity of 2,4,6-Trichlorophenol *In Vitro*

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA100, TA1535, TA1537	Mutation	–	–	Haworth et al. 1983
S. typhimurium TA98, TA100, TA1537	Mutation	–	–	Kinae et al. 1981
S. typhimurium TA98, TA100	Mutation	–	–	Kubo et al. 2002
S. typhimurium TA100	Mutation	NA	–	Rapson et al. 1980
S. typhimurium TA98, TA100, TA97, TA104	Mutation	+	–	Strobel and Grummt 1987
S. typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	Rasanen et al. 1977

Table 2-17. Genotoxicity of 2,4,6-Trichlorophenol *In Vitro*

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
S. typhimurium TA1535/pSK1002 (umu test)	DNA damage/repair	–	+	Ono et al. 1992
Escherichia coli WP2(λ) (prophage induction)	DNA damage/repair	+	+	DeMarini et al. 1990
Bacillus subtilis H-17, M-45	DNA damage	NA	+	Kinae et al. 1981
Eukaryotic organisms:				
Mouse (L5178Y TK+/- cells)	Mutation	NA	+	McGregor et al. 1988
Chinese hamster V79 cells	Mutation	NA	–	Jansson and Jansson 1992, 1986
Chinese hamster V79 cells (with or without primary rat hepatocytes)	Mutation	–	+	Hattula and Knuutinen 1985
Saccharomyces cerevisiae MP-1	Mutation	–	+	Fahrig et al. 1978
CHO cells	Chromosomal aberrations	+	+	Armstrong et al. 1993
CHO cells	SCEs and chromosomal aberrations	NA	–	Galloway et al. 1987
Chinese hamster V79 cells	Chromosomal aberrations	NA	+	Jansson and Jansson 1992
Chinese hamster CHL/IU cells	Chromosomal aberrations	+	–	Matsuoka et al. 1998
Mouse embryonic fibroblasts (C3H10T1/2)	DNA damage	+/–	–	Wang and Lin 1995
S. cerevisiae MP-1	Mitotic crossing over or gene conversion	NA	–	Fahrig et al. 1978

+ = positive results; +/– = borderline mutagen; – = negative results; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NA = not applicable; SCE = sister chromatid exchange

In testing in yeast cells (*S. cerevisiae*), 2,4,6-TCP induced mutations in the absence (but not in the presence) of activation but showed no evidence for increased mitotic gene conversion or mitotic crossing over (Fahrig et al. 1978). *In vitro* evaluations of mutation yielded positive results in the absence of metabolic activation in Chinese hamster V-79 cells (Hattula and Knuutinen 1985) and mouse lymphoma L5178Y TK +/- cells (McGregor et al. 1988), and negative results in the presence of metabolic activation in Chinese hamster V-79 cells (Hattula and Knuutinen 1985; Jansson and Jansson 1992).

2,4,6-TCP treatment resulted in increased frequencies of chromosomal aberrations in Chinese hamster V79 cells without metabolic activation (Jansson and Jansson 1992). Mixed results were obtained with

CHO cells; Armstrong et al. (1993) reported increased chromosomal aberrations both with and without metabolic activation, while Galloway et al. (1987) reported negative results in assays for both chromosomal aberrations and SCEs in the absence of metabolic activation. No increase in chromosomal aberrations was observed in Chinese hamster CHL/IU cells exposed to 2,4,6-TCP in the absence of activation, but positive results were seen with activation (Matsuoka et al. 1998). Equivocal or negative results were reported in testing for DNA damage in mouse embryonic fibroblasts (Wang and Lin 1995).

As was seen with 2,4-DCP and 2,4,5-TCP, incubation of 2,4,6-TCP with horseradish peroxidase resulted in the formation of reactive intermediates that formed covalent adducts with deoxyguanosine in isolated calf thymus DNA and in isolated deoxyguanosine (Dai et al. 2005).

In vivo, 2,4,6-TCP demonstrated genotoxic activity in somatic cells of mice in the spot test (Fahrig et al. 1978). A single gavage dose of 2,4,6-TCP (164 mg/kg) to rats did not damage DNA as measured by alkaline elution of DNA from white blood cells or livers (Kitchin and Brown 1988). *In vivo* tests of 2,4,6-TCP using insect systems (*Drosophila melanogaster*) were also negative (Valencia et al. 1985).

2,3,4,6-TeCP. Both *in vitro* and *in vivo* genotoxicity data are available for 2,3,4,6-TeCP. 2,3,4,6 TeCP tested negative for mutation in Ames assays (Rasanen et al. 1977; Zeiger et al. 1988) and tested negative in a prophage induction assay (DeMarini et al. 1990). However, 2,3,4,6-TeCP was positive both with and without activation in a umu test system (Ono et al. 1992). 2,3,4,6-TeCP did test positive for mutation in Chinese hamster V79 cells (Hattula and Knuutinen 1985). When tested with hydrogen peroxide, 2,3,4,6-TeCP induced DNA damage in human fibroblast GM5757 cells (Lueken et al. 2004). A single gavage dose of 2,3,4,6-TeCP (28 or 193 mg/kg) given to rats did not damage DNA in white blood cells or livers as measured by the alkaline elution assay (Kitchin and Brown 1988).

Other Chlorophenols. In tests using the umu assay, 2,3-DCP was negative both with and without S9 fraction, while both 3,4- and 3,5-TCP were negative with activation and positive without activation (Ono et al. 1992) (Table 2-18). In the same study, positive results both with and without metabolic activation were reported for 2,3,4-TCP (Ono et al. 1992). 2,3,4-TCP did not induce reverse mutations in Ames assays (Zeiger et al. 1992). In Chinese hamster lung cells treated with 2,3,4-TCP, there was no treatment-related increase in chromosomal aberrations in the presence or absence of metabolic activation; however, chromosomal aberrations were increased in CHO cells by treatment with 2,3,4-TCP in the presence of metabolic activation (Sofuni et al. 1990).

Table 2-18. Genotoxicity of Other Chlorophenols *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference	Compound (purity)
Prokaryotic organisms:					
Salmonella typhimurium TA1535/psK1002 (umu test)	DNA damage/ repair	–	–	Ono et al. 1992	2,3-DCP
S. typhimurium TA1535/psK1002 (umu test)	DNA damage/ repair	–	+	Ono et al. 1992	3,4-DCP
S. typhimurium TA1535/psK1002 (umu test)	DNA damage/ repair	–	+	Ono et al. 1992	3,5-DCP
S. typhimurium TA98, TA100, TA1535, and TA97 or TA1537	Mutation	–	–	Zeiger et al. 1992	2,3,4-TCP
S. typhimurium TA1535/psK1002 (umu test)	DNA damage/ repair	+	+	Ono et al. 1992	2,3,4-TCP
S. typhimurium TA97, TA98, TA100, TA1535	Mutation	–	–	Zeiger et al. 1988	2,3,4,5-TeCP
Escherichia coli WP2s(λ) (prophage induction)	DNA damage/ repair	+	–	DeMarini et al. 1990	2,3,4,5-TeCP
S. typhimurium Ta97, TA98, TA100, TA1535	Mutation	–	–	Zeiger et al. 1988	2,3,5,6-TeCP
E. coli WP2s(λ) (prophage induction)	DNA damage/ repair	–	–	DeMarini et al. 1990	2,3,5,6-TeCP
Eukaryotic organisms:					
Chinese hamster lung cells	Chromosomal aberrations	–	–	Sofuni et al. 1990	2,3,4-TCP
CHO cells	Chromosomal aberrations	+	–	Sofuni et al. 1990	2,3,4-TCP
Chinese hamster lung cells	Chromosomal aberrations	+	–	Sofuni et al. 1990	2,3,4,5-TeCP
CHO cells	Chromosomal aberrations	–	–	Sofuni et al. 1990	2,3,4,5-TeCP
Chinese hamster lung cells	Chromosomal aberrations	+	–	Sofuni et al. 1990	2,3,5,6-TeCP
CHO cells	Chromosomal aberrations	+	–	Sofuni et al. 1990	2,3,5,6-TeCP

+ = positive results;– = negative results; CHO = Chinese hamster ovary; CP = chlorophenol; DCP = dichlorophenol; DNA = deoxyribonucleic acid; TCP = trichlorophenol; TeCP = tetrachlorophenol

Both 2,3,4,5- and 2,3,5,6-TeCP were negative for mutation in *S. typhimurium* with and without activation (Zeiger et al. 1988). In λ-prophage induction assays, results for 2,3,4,5- and 2,3,5,6-TeCP were negative in the absence and presence of metabolic activation (DeMarini et al. 1990). 2,3,4,5-TeCP induced an increase in chromosomal aberrations in Chinese hamster lung cells with (but not without) exogenous

metabolic activation, but not in CHO cells (Sofuni et al. 1990). In contrast, 2,4,5,6-TeCP increased chromosomal aberrations in both cell types when tested with metabolic activation (Sofuni et al. 1990).

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

3.1 TOXICOKINETICS

Toxicokinetic data on the chlorophenols discussed in this profile are available primarily from studies in animals exposed orally or by intraperitoneal injection. There are few human data on the toxicokinetics of chlorophenols. In addition, no toxicokinetic information was located for 2,5-DCP, 3,4-DCP, 3,6-DCP, 2,4,5-TCP, 2,3,4,5-TeCP, or 2,3,5,6-TeCP. Inferences that can be drawn from the available data are briefly summarized below.

- Absorption of the subject chlorophenols after oral, dermal, or inhalation exposure is rapid and virtually complete. Quantitative estimates of fractional absorption based on radioactivity in urine after oral administration of radiolabeled chlorophenols in animals range between 69 and 100%. Estimates of fractional dermal absorption in humans vary widely between 30 and 100%. No quantitative estimates of the fractional absorption of chlorophenols following inhalation were identified.

- Chlorophenols are widely distributed in the body, with the highest concentrations in the liver, kidney, and spleen. The extent of plasma protein binding, which is a major determinant of both the body burden and elimination kinetics, increases with increasing chlorination.

- Rapid metabolism to glucuronide and sulfate conjugates appears to be the predominant route of chlorophenol metabolism. The relative proportions of these conjugates may vary by species, dose, and exposure route. Metabolism of chlorophenols via cytochrome P-450 isozymes can also produce reactive quinone and semiquinone intermediates. Finally, there is evidence that 2,4,6-TCP is isomerized in rats to other trichlorophenols.

- Chlorophenols are rapidly excreted in the urine after oral, dermal, or intraperitoneal injection exposure. Half-lives in the range of hours to a few days have been estimated. Elimination rates tend to decrease with increasing chlorination, likely due to increased plasma protein binding with increased chlorination. No information pertaining to excretion after inhalation exposure was located.

- No physiologically based pharmacokinetic (PBPK) models of any of the subject chlorophenols were identified in the literature reviewed.

3.1.1 Absorption

Inhalation Exposure. Information pertaining to the absorption of inhaled chlorophenols is limited to indirect evidence. The identification of 2,4,6-TCP and 2,3,4,6-TeCP in the serum and urine of workers exposed while treating lumber indicates that 2,4,6-TCP and 2,3,4,6-TeCP are absorbed through inhalation and/or dermal routes (Pekari et al. 1991).

Oral Exposure. The animal data indicating rapid and complete absorption of chlorophenols are from studies reporting recovery of all or most of the orally administered chlorophenols in the urine. Spencer and Williams (1950) recovered 100% of a single oral dose of 2- or 4-CP (emulsified in water) given to rabbits. Approximately 69% of an oral dose of radiolabelled 2,4-DCP (in deionized water) was recovered in the urine of rats within 48 hours of exposure (Pascal-Lorber et al. 2012). Five days after three daily gavage treatments of rats with radiolabelled 2,4,6-TCP (vehicle not reported), 82.3% of the administered radioactivity was recovered in the urine (Korte et al. 1978). In a 15-day study in rats exposed to 25 µg/day radiolabelled 2,4,6-TCP, 92% of the administered radioactivity was recovered in the urine collected during exposure (Bahig et al. 1981).

Dermal Exposure. *In vivo* and *in vitro* data indicate that the chlorophenols are readily absorbed following dermal exposure. In an industrial accident, 20 minutes after a worker was splashed with a pure solution of 2,4-DCP on <10% of his body (arm and leg), he collapsed and shortly thereafter died (Kintz et al. 1992). Postmortem blood and urine concentrations of 2,4-DCP were 24.3 and 5.3 mg/L, respectively. Using a fluorescent tracer, and measures of urinary excretion of TeCP in lumber mill workers exposed to a wood preservative (20% TeCP, 3% pentachlorophenol, <0.4% other CPs), Fenske et al. (1987) estimated that 30–100% of the 2,3,4,6-TeCP deposited on the skin is absorbed. Absorption occurred through the hands and forearms despite the use of chemical-resistant gloves. Fenske et al. (1987) also indicated that the skin regions with greatest exposure, the hands and forearms, were in frequent contact with wood so that abrasion may have reduced the barrier properties of the stratum corneum.

Dermal absorption can be inferred from *in vivo* animal studies resulting in death and/or adverse systemic effects following dermal exposure to 2-CP (Monsanto 1975) and 2,4-DCP (Carreon et al. 1980a, 1980b; Hencke and Lockwood 1978; Monsanto 1976).

The results of diffusion experiments using hydrated human cadaver epidermis also indicate that the chlorophenols readily cross the skin at low concentrations. The permeability coefficients determined in excised human abdominal epidermis were 5.5, 6.1, 10.0, and 9.9 cm/minute x $1x10^{4}$, respectively, for 2-CP, 4-CP, 2,4-DCP, and 2,4,6-TCP (Roberts et al. 1977). Xiao et al. (2012) reported an *in vitro* permeability rate of 0.021 cm/hour for 2,4-DCP in an experiment with fresh human skin. 2-CP and 4-CP were reported to damage the skin, determined by an increase in the permeability coefficient at aqueous concentrations of 0.8 and 0.75% (w/v), respectively, while no damage was observed with 2,4-DCP and 2,4,6-TCP at concentrations up to saturation. In a study using abdominal skin exposed to air, absorption

of 2,3,4,6-TeCP over 24 hours was 33% from an aqueous medium (1.54% 2,3,4,6-TeCP) and 63% from a diesel-oil-based medium (0.96 2,3,4,6-TeCP) (Horstman et al. 1989). These values were determined by assuming that the amount of the applied dose that was not recovered from the skin's surface was the amount absorbed. The actual amounts recovered in the skin and receiving solutions were 9.5 and 3.9% for the aqueous- and oil-based medium, respectively. The authors attribute low recovery to difficulties in extracting 2,3,4,6-TeCP from the skin.

Chlorophenols are also readily permeable in rodent skin *in vitro* preparations. At solution pHs between 5.0 and 5.74, the apparent permeability constants for 2-CP, 2,4-DCP, and 2,4,6-TCP in a hairless mouse skin preparation over a concentration range of 0.05–0.5% varied from 0.14 to 0.36 cm/hour in whole skin and from 0.136 to 0.276 cm/hour in skin stripped of the stratum corneum (Huq et al. 1986). The investigators proposed that permeability is probably greater in the more highly vascularized human tissue because the extensive network of surface capillaries in humans reduces the thickness of the diffusional barrier. In another *in vitro* diffusion study of 4-CP, 87.4–90.5% of the applied dose crossed rat epidermal preparations in 72 hours, indicating extensive absorption (Hughes et al. 1993). Those phenols (both chlorophenols and other substituted phenols) with log K_{ow}, values between 1.4 and 3.5 showed the greatest amount of permeability through the dermal membrane. Although specific data were not identified, dermal absorption of chlorophenols should also be greater for the neutral acid form than for the phenolate anion as ions do not readily cross cell membranes.

An experiment with rabbits showed that 2,4,6-TCP is absorbed through the cornea to a minor degree following ocular application (Ismail et al. 1977).

3.1.2 Distribution

Distribution in Blood. The concentration of 2,4-DCP in blood was 24.3 mg/L in a worker who collapsed and died shortly after being splashed with pure 2,4-DCP on his right arm and leg (Kintz et al. 1992). Peak concentrations of 2,4,6-TCP were observed in blood 30 minutes after rats were given a single intraperitoneal injection of 25 mg/kg 2,4,6-TCP (Pekari et al. 1986).

The results of in vitro binding studies using human serum proteins indicate that both 2,4-DCP and 2,4,6-TCP strongly bind to serum proteins, including albumin and globulin (Judis 1982). The percentage of compound bound to albumin was slightly greater for 2,4,6-TCP (94.1%) than for 2,6-DCP (87.7%).

Distribution to Extravascular Tissues. Liver 2-CP concentrations were 2.2, 3.2, and 0.8 ppm, and kidney 2-CP concentrations were 2.6, 2.4, and 2.2 ppm in female rats exposed to 2-CP in the drinking water for 16 weeks at 5, 50, and 500 ppm, respectively (Exon and Koller 1982). The investigators did not provide an explanation for the low value (0.8 ppm) found in the livers of rats receiving the high dose, and did not indicate whether these values were wet or dry weight concentrations. Radioactivity was not recovered in the liver, lung, or subcutaneous fat of rats after three daily gavage doses of radiolabelled 2,4,6-TCP (Korte et al. 1978) or in unspecified tissues of rats at the end of 15 days of exposure to radiolabelled 2,4,6-TCP by gavage (Bahig et al. 1981).

The highest concentrations of 2,3,4,6-TeCP were found in the spleen, followed by the kidneys and liver, 24 hours after a single oral dose was given to rats (Hattula et al. 1981). In a 55-day study in which rats were treated by gavage with 2,3,4,6-TeCP at 10, 50, or 100 mg/kg/day, tissue levels, measured 24 hours after the last dose, increased with dose. For all doses, the concentrations of 2,3,4,6-TeCP in the brain and muscle were lower than those found in the kidney, liver, and spleen. At the 100 mg/kg/day dose, the kidney had the highest 2,3,4,6-TeCP concentrations (5.1 ppm) followed by the spleen (3.2 ppm), liver (2.2 ppm), brain (1.2 ppm), and muscle (0.46 ppm) (Hattula et al. 1981). At the 10 mg/kg/day dose, 2,3,4,6-TeCP was not detected in the brain or muscle (detection limit not stated), while low levels were found in the spleen (0.04 ppm), kidney (0.03 ppm), and liver (0.01 ppm).

Intravenously-administered 2,4-DCP rapidly distributed to the kidney, liver, fat, and brain in rats, with the highest concentrations in the kidney and liver (Somani and Khalique 1982). Similarly, in rats given a single intraperitoneal injection of 25 mg/kg 2,4,6-TCP, the kidneys exhibited the highest concentration (329±117 nmol/g tissue), followed by blood, liver, fat, muscle, and brain (Pekari et al. 1986). Concentrations of 2,4,6-TCP in the tissues peaked 30 minutes after exposure.

In rabbits, following ocular exposure, radiolabelled 2,4,6-TCP was distributed to various compartments of the eye (Ismail et al. 1977). At 30 minutes post exposure, the applied radioactivity was detected in the cornea (4%), aqueous humor (0.37%), lens (0.037%), iris (0.18%), choroid (0.04%), vitreous (0.01%), conjunctiva (2.14%), limbus (0.96%), and sclera (0.35%).

3.1.3 Metabolism

Both human and animal studies indicate that sulfation and glucuronidation are the main metabolic pathways of chlorophenols. Gulcan et al. (2008) showed that all of the subject chlorophenols were

substrates for human hydroxysteroid sulfotransferase 2A1 (hSULT2A1) when expressed in E. coli and tested *in vitro*. The highest rates of sulfation were observed with the tri- and tetrachlorophenols, with lower rates for mono- and dichlorophenols, indicating that hSULT2A1 likely contributes little to the sulfation of the mono- and dichlorophenols.

Monochlorophenols. A number of rabbit studies (Azouz et al. 1953; Bray et al. 1952a, 1952b; Spencer and Williams 1950) have shown that metabolism of the monochlorophenols occurs principally via conjugation. In the study by Spencer and Williams (1950), groups of six rabbits were treated by gavage with 171.3 mg/kg of 2-CP or 4-CP emulsified in water as a single dose. For both isomers, the 24-hour urine analysis indicated that between 78.1 and 88.3% of the administered dose was excreted as the glucuronide, and between 12.8 and 20.6% of the administered dose was excreted as the sulfate. A total of 101.7 and 101.1% of the administered 2-CP or 4-CP doses, respectively, was accounted for as urinary glucuronide and sulfate conjugates. Metabolism was further investigated in four rabbits, each treated by gavage with an average dose of 395 mg/kg/day of 4-CP. After 36 hours, 54.1% of the administered dose appeared in the urine as the glucuronide conjugate, and 10.4% of the administered dose appeared in the sulfate fraction. Only 0.1% of the administered dose was excreted as 4-chlorocatechol. The low total recovery (64.5%) in the latter experiment limits conclusions. Other rabbit studies indicated that chlorocatechols constituted only 1.5–4.5% of the administered doses of 300 mg/kg 2-CP or 500 mg/kg 4-CP (Azouz et al. 1953).

In a limited study in dogs (Coombs and Hele 1926), about half of an oral dose of 2- or 4-CP was excreted in the urine as the sulfate. No evidence for metabolism to mercapturic acid was found. In contrast to the study in dogs, Phornchirasilp et al. (1989a) proposed that 4-CP could be metabolized in mice by cytochrome P-450 enzymes to intermediates that react with glutathione to form glutathionyl adducts, based on the observation that 4-CP treatment of mice depleted liver thiol stores. The depletion of liver thiol stores was prevented by a P-450 inhibitor (SKP 525-A), suggesting that P-450 activity was required for this effect.

Dichlorophenols. A study in rats found that glucuronides and other unspecified conjugates were formed following a single intravenous dose of 2,4-DCP (10 mg/kg) (Somani and Khalique 1982). Although other unspecified conjugates were found in the fat, glucuronide conjugates were not found in the fat at any time interval.

Two minor metabolites of 2,4-DCP, both dichloromethoxy phenols, have been identified in studies using isolated perfused rat livers (Somani et al. 1984). In microsomal fractions and whole cells of yeast *S. cerevisiae* expressing human cytochrome P-450 3A4, 2,4-DCP has been shown to be metabolized to two major metabolites identified as 2-chloro-1,4-hydroxyquinone and 2-chloro-1,4-benzoquinone (Mehmood et al. 1997). Another metabolite, 1,2,4-hydroxybenzene, was also detected during biotransformation by whole cells, but was not observed in microsomal fractions. Thus, human CYP3A4 can remove either or both chlorine atoms from the aromatic ring of 2,4-DCP molecule, forming 2-chloro-1,4-hydroxyquinone and 1,2,4-hydroxybenzene, respectively. 2-Chloro-1,4-hydroxyquinone was probably acted on by dehydrogenase from yeast microsomes, forming 2-chloro-1,4-benzoquinone (Mehmood et al. 1997).

Trichlorophenols. Among sawmill workers exposed to tri-, tetra-, and penta-chlorophenols, virtually all the absorbed chlorophenols were excreted in the urine as conjugated metabolites, predominantly sulfate conjugates (Pekari et al. 1991). In rats, 2,4,6-TCP undergoes biotic isomerization to other trichlorophenol isomers and conjugation with glucuronic acid (Bahig et al. 1981). Male rats eliminated 63% of a gavage dose of 2,4,6-TCP in the urine as four trichlorophenol isomers, and 28% as conjugates. Three of the trichlorophenol isomers were identified as 2,4,6-TCP (parent compound), 2,3,6-TCP, and 2,4,5-TCP; the fourth isomer was not identified. Glucuronic acid accounted for approximately 80% of the conjugates detected in urine (Bahig et al. 1981). A majority (70%) of intraperitoneally administered 2,4,6-TCP detected in the blood of rats was in conjugated form (not further identified) 30 minutes after dosing. The authors speculated that the chemical was conjugated with glucuronic acid (Pekari et al. 1986). The average percentage of the metabolites of 2,4,6-TCP conjugated in the blood over the course of the study was 83±11%. Metabolism of 2,4,6-TCP by the skin was not detected in a study of hairless mouse skin tested *in vitro* (Huq et al. 1986).

In vitro studies using rat liver microsomes have shown that 2,4,5-TCP can be metabolized to 3,4,6-trichlorocatechol, 2,5-dichlorohydroquinone, and a dihydroxydichlorobenzene (not further characterized) (Butte et al. 1988; Juhl et al. 1991). Metabolites were also dimerized to a dihydroxy-hexachlorobiphenyl, a dihydroxypentachlorodiphenyl ether, two hydroxypentachlorodiphenyl ethers, a hydroxyhexachlorodiphenyl ether, and a hydroxyhexachlorodioxin or hydroxyhexachlorodiphenoquinone (Butte et al. 1988). Metabolites generated following incubation of 2,4,6-TCP with rat liver S-9 fraction were 2,6-dichloro-1,4-hydroquinone and two isomers of hydroxypentachlorodiphenyl ether (Juhl et al. 1989). The 2,6-dichloro-1,4-semiquinone free radical was also identified. Although *in vivo*, the latter

metabolite may be minor, reactive oxygen species produced during formation of the semiquinone was judged to be responsible for DNA damage in *in vitro* testing (Juhl et al. 1989).

Tetrachlorophenols. As noted earlier, virtually all of the absorbed tri- and tetrachlorophenols were excreted as conjugated metabolites (predominantly sulfate conjugates) in the urine of sawmill workers (Pekari et al. 1991). In rats exposed to TeCP isomers via intraperitoneal injection, much of the dose is excreted in the urine unchanged (Ahlborg and Larrson 1978). Following treatment with 2,3,4,5- and 2,3,4,6-TeCP, a trichlorohydroquinone was identified in the urine as a minor metabolite. Following treatment with 2,3,5,6-TeCP, about 35% of the recovered dose (total recovery 98.7%) was tetrachloro-*p*-hydroquinone, while the remaining was unchanged parent compound (Ahlborg and Larrson 1978).

3.1.4 Excretion

Routes of Excretion. Excretion of chlorophenols occurs primarily via urinary elimination of conjugated forms (glucuronide and sulfate) in both humans and animals. After occupational exposure by combined dermal and inhalation routes to a chlorophenol dipping solution, maximal urinary concentrations were 1–11.8, 3.4–17.3, and 0.2–0.9 µmol/L for tri-, tetra-, and pentachlorophenol, respectively (Pekari et al. 1991).

Limited data indicate that orally-administered monochlorophenols are rapidly excreted in the urine, primarily as glucuronide and sulfate conjugates, in rats, rabbits, and dogs (Bray et al. 1952a, 1952b; Coombs and Hele 1926; Spencer and Williams 1950). Most of the administered dose is excreted in the urine within 24 hours.

Male rats administered radiolabelled 2,4,6-TCP by gavage for 3 days and observed for 5 days after dosing eliminated a total of 82.3% of the total dose in the urine and 22.2% in the feces (Korte et al. 1978). In a second study using male rats, radiolabelled 2,4,6-TCP was administered by gavage for 15 days, with sacrifice 3 days after administration ended. A total of 92.5% of the administered dose was excreted in the urine, and 6.4% was excreted unchanged in the feces (Bahig et al. 1981). In rats administered 2,4,6-TCP by intraperitoneal injection, approximately 90% of the administered dose was eliminated in the urine within 4–6 hours (Pekari et al. 1986).

Ahlborg and Larrson (1978) studied the urinary excretion of TeCP isomers in rats following intraperitoneal injection of a single dose. During the 72 hours after dosing, about 60% of the

2,3,4,5-TeCP dose was recovered in the urine. In contrast, following treatment with 2,3,4,6-TeCP, 95.9% of the dose was excreted in the urine within 48 hours, and 98.7% of the administered 2,3,5,6-TeCP was excreted in the urine within 24 hours after dosing. The investigators (Ahlborg and Larsson 1978) did not provide an explanation regarding the slower excretion of 2,3,4,5-TeCP compared to the excretion of 2,3,4,6-TeCP and 2,3,5,6-TeCP.

Limited information suggests that 2,4-DCP may be excreted in bile. 2,4-DCP was measured at concentrations of 5.3, 18.7, and 1.2 mg/L, respectively, in the urine, bile, and stomach contents of a worker who collapsed (within 20 minutes) and died shortly after being splashed with pure 2,4-DCP on his right arm and leg (Kintz et al. 1992).

Rates of Elimination. Little data on rates of chlorophenol elimination in humans were available. After occupational exposure by combined dermal and inhalation routes to a chlorophenol dipping solution, elimination half-lives were 18 hours, 4.2 days, and 16 days for tri-, tetra-, and pentachlorophenol, respectively. The renal clearance rate of 2,3,4,6-TeCP was approximately 5 times faster than the clearance rate of pentachlorophenol, reflecting the increased plasma protein binding of the higher chlorinated compound (Pekari et al. 1991). The clearance rate of 2,4,6-TCP could not be calculated because of highly variable serum concentrations (Pekari et al. 1991).

Studies in rats, rabbits, and dogs (Bray et al. 1952a, 1952b; Coombs and Hele 1926; Spencer and Williams 1950) demonstrate rapid elimination of monochlorophenols after oral exposure; in these studies, most of the administered dose was excreted in the urine within 24 hours. At oral doses of 150–450 mg/kg in rabbits, excretion of the glucuronide conjugate of 4-CP followed first-order kinetics (Bray et al. 1952a). The rate of glucuronide excretion relative to remaining body burden was 0.41/hour.

A study in rats showed rapid clearance from the kidney, liver, fat, brain, and plasma of both the parent compound and metabolites after intravenous administration of 10 mg/kg/day 2,4-DCP in an aqueous solution (Somani and Khalique 1982). Half-lives for 2,4-DCP and its conjugates ranged from 4 to 30 minutes in these tissues, with the highest values in kidney, followed by the liver, fat, plasma, and brain (Somani and Khalique 1982). The elimination half-time for plasma was approximately 10 minutes. No detectable amounts were found in the brain at 60 minutes.

In male rats administered radiolabeled 2,4,6-TCP by gavage for 15 days, the excretion of radioactivity declined rapidly after dosing ended; by the third day postexposure, only 4.3% of the radioactivity in a

daily dose was detected in the urine, and 1.9% in the feces (Bahig et al. 1981). When rats were exposed to 2,4,6-TCP by intraperitoneal injection, about 90% of the administered dose had been eliminated via the urine within 4–6 hours of exposure, and only trace amounts of trichlorophenol were detected in tissues 10 hours after dosing (Pekari et al. 1986). The authors estimated the biological half-life of conjugated 2,4,6-TCP (the predominant form found in blood) as 1.4 hours in blood and from 1.4 to 1.8 hours in other tissues (Pekari et al. 1986).

Ahlborg and Larrson (1978) observed slower excretion of 2,3,4,5-TeCP compared to 2,3,4,6-TeCP and 2,3,5,6-TeCP in rats following intraperitoneal injection of a single dose; only 51% of the dose of 2,3,4,5-TeCP was excreted in the urine within 24 hours, while ≥93.7% of the doses of other isomers was excreted in that time period.

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 models for chlorophenols were identified.

3.1.6 Animal-to-Human Extrapolations

Studies of health effects in humans exposed to chlorophenols are limited by coexposures to other compounds; thus, there are few data to inform a comparison between humans and animals. Extrapolating animal toxicity data to predict human risk from chlorophenol exposure appears to be reasonable based on similarities in metabolic pathways. It is possible that humans may be more sensitive than animals to the toxic effects of 2,4-dichlorophenol, based on the human deaths following dermal and/or inhalation exposures.

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

Susceptibility of Infants and Children. No direct information is available regarding the health effects of chlorophenols observed in children. However, health effects observed in adults are also expected to be of potential concern in children. The available studies of developmental effects in animals exposed to chlorophenols examined limited endpoints, but have generally shown effects only at doses inducing maternal toxicity (Chernoff et al. 1990; Exon and Koller 1982, 1983a, 1983b, 1985; Exon et al. 1984; Hood et al. 1979; Rodwell et al. 1989). The one exception is a study in which maternal exposure of rats to 500 mg/kg/day 2,4,6-TCP produced a transient reduction in the body weight of offspring (Blackburn et al. 1986).

However, one study (Hasegawa et al. 2005) clearly showed that neonatal rats exposed from PNDs 4 to 21 were more susceptible to the toxic effects of 2- and 4-CP than young (5–6 weeks old) rats exposed for 28 days. In this study, a dose of 500 mg/kg/day 4-CP was lethal to nearly all (7/8) neonatal rats, while all 24 young rats survived 4 weeks at this dose. In experiments with 2-CP, tremors were seen in neonatal rats exposed to 300 mg/kg/day, while young rats did not exhibit tremors at 500 mg/kg/day; tremors were seen in young rats at 1,000 mg/kg/day (Hasegawa et al. 2005).

Maternal exposure to chlorophenols prior to pregnancy is unlikely to lead to exposure of the fetus or a nursing neonate due to the relatively rapid metabolism and excretion of chlorophenols (Keith et al. 1980) and evidence for limited to no accumulation in animals after oral exposure (Bahig et al. 1981; Korte et al. 1978). More lipophilic chlorophenols may accumulate in the body; 2,3,4,6-TeCP was detected in adipose tissues from Finnish people not occupationally exposed to chlorophenols (Mussalo-Rauhamaa et al. 1989). Chlorophenols and/or their metabolites might cross the placenta, based on evidence for embryo- and/or fetotoxicity (decreased litter sizes or increased stillborn pups) in rats exposed to 2-CP, 2,4-DCP, or 2,4,6-TCP (Exon and Koller 1982, 1983a, 1983b, 1985; Exon et al. 1984), but these could be indirect effects on the fetus.

Metabolism of chlorophenols has not been studied in infants or children. However, sulfation and glucuronidation are the main metabolic pathways for chlorophenols in both human and animal studies. The conjugated metabolites are then eliminated in urine. In humans, activity of some hepatic UDP-glucuronosyltransferase (responsible for glucuronide conjugates) isoforms does not reach adult levels until adolescence, although others reach adult levels within a month (Badée et al. 2019). Activity of sulfotransferases (responsible for sulfate conjugates) seems to develop earlier, although again, it is isoform-specific (Coughtrie 2015). The activity of some human hepatic sulfotransferase isoforms may be greater than that of adults during infancy and early childhood (Ladumor et al. 2019). It is possible that chlorophenols might be eliminated at a slower rate in infants or children, resulting in increased susceptibility of children to their toxicity.

Potential Susceptibility of Other Subpopulations. No specific population with particular susceptibility to chlorophenol intoxication has been identified; however, toxicokinetic and target organ information suggest some possibilities. For example, Huq et al. (1986) suggested that 2,4,6-TCP absorbed through the skin could be more toxic than a similar ingested dose because the ingested compound is partially converted to glucuronide conjugates; thus, persons with dermal exposure could be more susceptible than those with oral exposure. Because of the extensive hepatic conjugation and renal clearance of these compounds, individuals with liver or kidney dysfunction may be more sensitive than healthy persons. In particular, individuals with Gilbert's disease or Crigler-Najjar syndrome, inherited deficiencies of bilirubin UDP-glucuronyl transferase, may have increased sensitivity due to their impaired ability to conjugate chlorophenols (de Morais and Wells 1988; de Morais et al. 1992). Finally, evidence from rat studies (Exon and Koller 1985; Exon et al. 1984) suggests that the cell-mediated and humoral immune systems are sensitive to 2,4-DCP. Thus, persons with immune system deficiencies may be more susceptible to the adverse effects of 2,4-DCP exposure.

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 chlorophenols 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 chlorophenols 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 chlorophenols 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

No specific, reliable biomarkers of chlorophenol exposure have been identified. Urinary concentrations of the parent compounds and dechlorinated derivatives have been used as biomarkers of chlorophenol exposure; however, these extracts are not unique to chlorophenol exposure. For example, conjugated forms of higher chlorophenols have been observed after laboratory administration of hexachlorocyclohexanes (Engst et al. 1976; Koransky et al. 1975), indicating that urinary chlorophenol levels are not specific to chlorophenol exposure. Similarly, the presence of chlorophenols or their metabolites in urine is not necessarily diagnostic for chlorophenol exposure because these compounds are also detectable in urine after exposure to certain other compounds, such as lindane (Karapally et al. 1973), VC-13 (Shafik et al. 1973), 2,4-D, and 2,4,5-T (Hill et al. 1989). Importantly, 2,5-DCP in urine is considered to be a reliable biomarker for exposure to *p*-dichlorobenzene (Yoshida et al. 2002) rather than a marker for exposure to 2,5-DCP. Finally, metabolic dechlorination of higher chlorophenols to lower chlorophenols occurs under some conditions (Renner and Mucke 1986). Consequently, urinary chlorophenol concentrations cannot be considered specific, reliable measures of potential exposure in the absence of measured concentrations in exposure media (air, water, soil).

3.3.2 Biomarkers of Effect

Specific biomarkers of effects induced by chlorophenols have not been identified.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Only one study of the interaction of chlorophenols with other chemical substances, or among different chlorophenols, was located. Using an *in vitro* rat liver microsomal preparation, Arrhenius et al. (1977) noted that 2,4-DCP, 2,4,6-TCP, and 2,3,4,6-TeCP in the concentration range of 0.03–3 mM shifted the metabolism of aromatic amines from C-oxygenation to N-oxygenation. The carcinogenic metabolites of aromatic amines can be formed by N-oxygenation. Therefore, Arrhenius et al. (1977) suggested that the chlorophenols could act synergistically to enhance the carcinogenicity of aromatic amines.

Because Phase II conjugation is involved in the detoxification of chlorophenols, it is plausible that compounds capable of inhibiting sulfation or glucuronidation reactions could potentiate the toxicity of chlorophenols, while compounds that stimulate these reactions could mitigate toxicity. Similarly, compounds that induce effects on identified target organs of chlorophenols (e.g., liver, central nervous

system, reproductive system, and immune system) or exert effects through a similar mechanism may interact with chlorophenols. For example, several chlorophenols have been shown to uncouple oxidative phosphorylation; thus, exposure to chlorophenols with other compounds that operate via this mechanism (e.g., dinitrophenol) may result in additive or synergistic effects.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

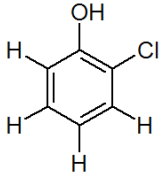
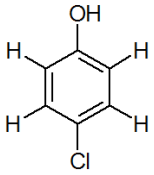
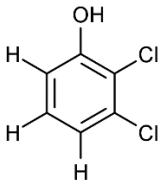
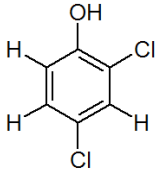
4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of the chlorophenols is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of the chlorophenols is located in Table 4-2. Except for 2-CP, which is a liquid at room temperature, all of the chlorophenols discussed in this profile are solids at room temperature.

Table 4-1. Chemical Identity of Chlorophenol Compounds

Characteristic	Information			
Chemical name	2-Chlorophenol	4-Chlorophenol	2,3-Dichlorophenol	2,4-Dichlorophenol
Synonym(s) and registered trade name(s)	2-CP, 2-chloro-1-hydroxy-benzene, 2-hydroxy-chlorobenzene, *o*-chlorophenol	4-CP, 4-chloro-1-hydroxy-benzene, 4-hydroxy-chlorobenzene, *p*-chlorophenol	2,3-DCP	2,4-DCP, 2,4-dichlorohydroxybenzene
Chemical formula	C_6H_5ClO	C_6H_5ClO	$C_6H_4Cl_2O$	$C_6H_4Cl_2O$
Chemical structure				
CAS Registry Number	95-57-8	106-48-9	576-24-9	120-83-2

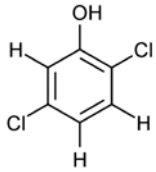
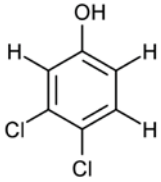
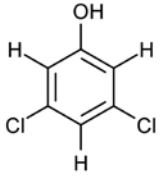
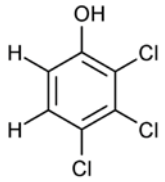
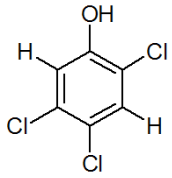
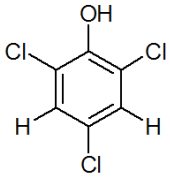
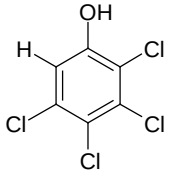
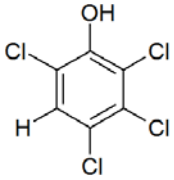
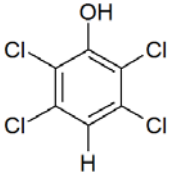
Characteristic	Information		
Chemical name	2,5-Dichlorophenol	3,4-Dichlorophenol	3,5-Dichlorophenol
Synonym(s) and registered trade name(s)	2,5-DCP, 2,5-dichloro-1-hydroxy-benzene, 1-Hydroxy-2,5-dichlorobenzene	3,4-DCP, 4,5-dichlorophenol	3,5-DCP, 1-Hydroxy-3,5-dichlorobenzene
Chemical formula	$C_6H_4Cl_2O$	$C_6H_4Cl_2O$	$C_6H_4Cl_2O$
Chemical structure			
CAS Registry Number	583-78-8	95-77-2	591-35-5

Table 4-1. Chemical Identity of Chlorophenol Compounds

Characteristic	Information		
Chemical name	2,3,4-Trichlorophenol	2,4,5-Trichlorophenol	2,4,6-Trichlorophenol
Synonym(s) and registered trade name(s)	2,3,4-TCP	2,4,5-TCP	2,4,6-TCP, Omal, Phenachlor
Chemical formula	$C_6H_3Cl_3O$	$C_6H_3Cl_3O$	$C_6H_3Cl_3O$
Chemical structure			
CAS Registry Number	15950-66-0	95-95-4	88-06-2

Characteristic	Information		
Chemical name	2,3,4,5-Tetrachlorophenol	2,3,4,6-Tetrachlorophenol	2,3,5,6-Tetrachlorophenol
Synonym(s) and registered trade name(s)	2,3,4,5-TeCP	2,3,4,6-TeCP	2,3,5,6-TeCP
Chemical formula	$C_6H_2Cl_4O$	$C_6H_2Cl_4O$	$C_6H_2Cl_4O$
Chemical structure			
CAS Registry Number	4901-51-3	58-90-2	935-95-5

CAS = Chemical Abstracts Service

Sources: NLM (2003a, 2003b, 2003c, 2009a, 2009b, 2009c, 2015, 2019, 2020a, 2020b, 2020c, 2020d, 2020e)

Table 4-2. Physical and Chemical Properties of Chlorophenol Compounds[a]

Characteristic	2-Chlorophenol	4-Chlorophenol	2,3-Dichlorophenol	2,4-Dichlorophenol
Molecular weight	128.56	128.56	163.00	163.00
Color	Light amber	White to pink crystals	Brown	White
Physical state	Liquid	Solid	Solid	Solid
Melting point	9.3°C	43.2–43.7°C	58°C	45°C
Boiling point	174.9°C	220°C	206°C	210°C
Density at 20°C	1.2634	1.2238 at 78°C/4°C	No data	1.383 at 60°C/25°C
Odor	Unpleasant, medicinal odor	Medicinal odor	No data	Strong medicinal odor
Odor threshold:				
Water at 30°C[b]	0.33 µg/L	33 µg/L	No data	0.65 µg/L
Air[c]	0.0189 mg/m^3	0.0189 mg/m^3	No data	1.40 mg/m^3
Solubility:				
Water at 25°C[d]	20,000 ppm	27,000 ppm at pH 5.1	8,215 ppm at pH 4.9	4,500 ppm
Organic solvents	Acetone, alcohol, benzene	Alcohol, glycerol, ether, chloroform, fixed and volatile oils, benzene	Alcohol, ethyl ether, benzene, ligroin	Alcohol, carbon tetrachloride, ethyl ether, benzene, chloroform
Partition coefficients:				
Log K_{ow}	2.17[d]	2.4[d]	2.84	3.06
Log K_{oc}[d]	1.25–3.7	1.2–2.7	2.63	2.42–3.98
Vapor pressure at 25°C[d]	0.99 mmHg at 25°C	0.23 mmHg at 25°C	0.058 mmHg at 25°C[a]	0.14 mmHg at 25°C
Henry's law constant at 25°C[d]	6.8x10^{-6} atm-m^3/mol	9.2x10^{-7} atm-m^3/mol	1.6x10^{-6} atm-m^3/mol (calculated)	4.3x10^{-6} atm-m^3/mol
pKa[f]	8.52	9.37	7.71	7.90
Autoignition temperature	No data	No data	No data	No data
Flashpoint	64°C	121°C	No data	114°C
Flammability limits	No data	No data	No data	No data
Conversion factors	1 ppm=5.3 mg/m^3 at 25°C, 1 atm	1 ppm=5.3 mg/m^3 at 25°C, 1 atm	1 ppm=6.7 mg/m^3 at 25°C, 1 atm	1 ppm=6.7 mg/m^3 at 25°C, 1 atm
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Chlorophenol Compounds[a]

Characteristic	2,5-Dichlorophenol	3,4-Dichlorophenol	3,5-Dichlorophenol
Molecular weight	163.00	163.00	163.00
Color	White	Brown or yellow	Pink
Physical state	Solid	Solid	Solid
Melting point	59°C	68°C	68°C
Boiling point	211°C	253°C	233°C
Density at 20°C	No data	No data	No data
Odor	No data	No data	No data
Odor threshold:			
Water at 30°C[b]	3.3 µg/L	No data	No data
Air[c]	No data	No data	No data
Solubility:			
Water at 25°C[d]	2,000 ppm at unknown pH[a]	9,256 ppm at pH 5.1	7,394 ppm at pH 4.7
Organic solvents	Alcohol, ethyl ether, benzene, petroleum ether	Alcohol, ethyl ether, benzene, petroleum ether	Alcohol, ethyl ether, petroleum ether
Partition coefficients:			
Log K_{ow}	3.06	3.33	3.62
Log K_{oc}	2.78 (estimated)[e]	2.93 (estimated)[e]	3.1 (estimated)[e]
Vapor pressure at 25°C	0.0562 mmHg at 25°C	0.00173 mmHg at 25°C (estimated)[e]	0.00842 mmHg at 25°C[d]
Henry's law constant at 25°C	6.0×10^{-6} atm-m^3/mol (calculated)[d]	3.1×10^{-7} atm-m^3/mol (estimated)[e]	2.4×10^{-7} atm-m^3/mol (calculated)[d]
pKa[f]	7.51	8.62	8.25
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	1 ppm=6.7 mg/m^3 at 25°C, 1 atm	1 ppm=6.7 mg/m^3 at 25°C, 1 atm	1 ppm=6.7 mg/m^3 at 25°C, 1 atm
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Chorophenol Compounds[a]

Characteristic	2,3,4-Trichlorophenol	2,4,5-Trichlorophenol	2,4,6-Trichlorophenol
Molecular weight	197.45	197.46	197.45
Color	Peach	Gray	Yellow
Physical state	Solid	Solid	Solid
Melting point	83.5°C	67°C	69°C
Boiling point	252°C	235°C	246°C
Density at 20°C	No data	1.678 at 25°C/4°C	1.4901
Odor	Strong disinfectant odor	Strong phenolic odor	Strong phenolic odor
Odor threshold:			
Water at 30°C[b]	No data	11 µg/L	100 µg/L
Air[c]	No data	No data	No data
Solubility:			
Water at 25°C[d]	915 ppm at pH 5.1	948 ppm at pH 5.1	434 ppm at pH 5.1
Organic solvents	No data	Acetone, benzene, carbon tetrachloride, ether, denatured alcohol, methanol, liquid petroleum, toluene	Acetone, benzene, carbon tetrachloride, diacetone alcohol, methanol, Stoddard solvent, toluene, turpentine, ether
Partition coefficients:			
Log K_{ow}[d]	3.80	3.72	3.69
Log K_{oc}[d]	No data	2.55–3.98	1.94–3.34
Vapor pressure at 25°C[d]	0.0027 mmHg at 25°C (estimated)	0.05 mmHg at 25°C	0.03 mmHg at 25°C
Henry's law constant at 25°C	3.9×10^{-6} atm-m^3/mol[d]	2.21×10^{-6} atm-m^3/mol (estimated)[e]	6.8×10^{-6} atm-m^3/mol[d]
pKa[f]	6.97	6.72	5.99
Autoignition temperature	No data	No data	No data
Flashpoint	62°C	No data	64°C
Flammability limits	No data	No data	No data
Conversion factors	1 ppm=8.1 mg/m^3 at 25°C, 1 atm	1 ppm=8.1 mg/m^3 at 25°C, 1 atm	1 ppm=8.1 mg/m^3 at 25°C, 1 atm
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Chorophenol Compounds[a]

Characteristic	2,3,4,5-Tetrachlorophenol	2,3,4,6-Tetrachlorophenol	2,3,5,6-Tetrachlorophenol
Molecular weight	231.89	231.89	231.89
Color	No data	Light brown	No data
Physical state	Solid	Solid	Solid
Melting point	116–117°C	70°C	115°C
Boiling point	Sublimes	64°C	No data
Density at 20°C	No data	1.83 at 25°C/4°C	No data
Odor	No data	Strong odor	No data
Odor threshold:			
Water at 30°C[b]	No data	915 µg/L	No data
Air[c]	No data	No data	No data
Solubility:			
Water at 25°C[d]	166 ppm at pH 4.9	183 ppm at pH 5.3	100 ppm at pH 5.0
Organic solvents	Alcohol	Acetone, alcohol, benzene, chloroform, ligroin	Benzene
Partition coefficients:			
Log K_{ow}[d]	4.8	4.45	4.9
Log K_{oc}[d]	2.9–4.14	3.2–4.21	No data
Vapor pressure at 25°C[d]	0.0059 mmHg at 25°C	0.0059 mmHg at 25°C	0.0059 mmHg at 25°C
Henry's law constant at 25°C	$3.5x10^{-7}$ atm-m^3/mol (estimated)[e]	$4.3x10^{-6}$ atm-m^3/mol[d]	$5.1x10^{-6}$ atm-m^3/mol[d]
pKa[f]	5.64	5.22	5.03
Autoignition temperature	No data	No data	No data
Flashpoint	121°C	114°C	No data
Flammability limits	No data	No data	No data
Conversion factors	1 ppm=9.5 mg/m^3 at 25°C, 1 atm	1 ppm=9.5 mg/m^3 at 25°C, 1 atm	1 ppm=9.5 mg/m^3 at 25°C, 1 atm

Table 4-2. Physical and Chemical Properties of Chorophenol Compounds[a]

Characteristic	2,3,4,5-Tetrachlorophenol	2,3,4,6-Tetrachlorophenol	2,3,5,6-Tetrachlorophenol
Explosive limits	No data	No data	No data

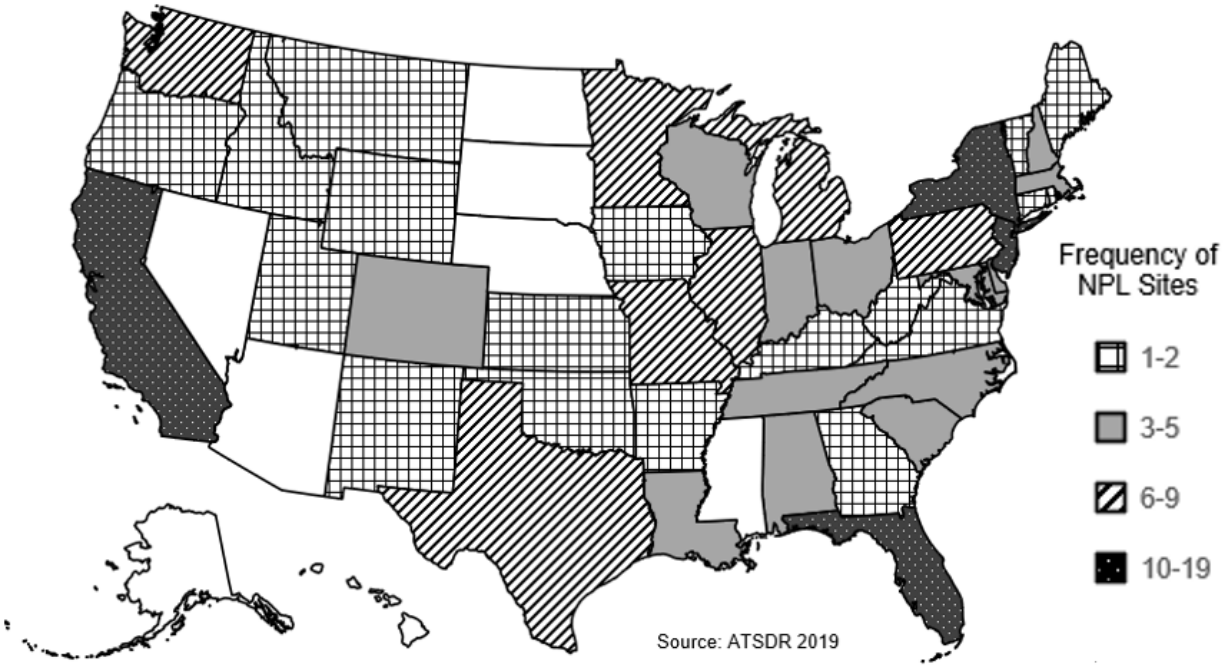
[a]Data from NLM (2003a, 2003b, 2003c, 2009a, 2009b, 2009c, 2015, 2019, 2020a, 2020b, 2020c, 2020d, 2020e) except where noted.
[b]Hoak 1957.
[c]Ruth 1986.
[d]Shiu et al. 1994.
[e]EPA 2012.
[f]Muller and Caillard 2011.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Chlorophenols have been identified in at least 191 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 chlorophenols have been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 190 are located within the United States, 1 is located in Puerto Rico (not shown).

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



- The general population can be exposed to chlorophenols from ingestion of drinking water and inhalation of ambient air.
- The chlorophenols in this profile have rarely been detected in food items, but have been shown to migrate from packaging materials used in some food containers.
- Most chlorophenols are used to produce other chemicals and exposure through their presence in consumer products is expected to be low.
- Chlorophenols have been detected in ambient air, surface water, groundwater, and soil.

- The environmental fate and transport of chlorophenols are pH-dependent since they can exist as the fully protonated phenol or its conjugate base (phenolate anion).

- Under acidic conditions, chlorophenols have greater tendency to volatilize and adsorb to soil surfaces. Under neutral to alkaline conditions, volatilization from water and moist soils decreases and mobility in soils increases.

- The chlorophenols in this profile are considered to possess low to moderate bioconcentration potential.

- Chlorophenols are considered moderately persistent, and resistance to biodegradation increases with increasing chlorine content and the location of the chlorine atoms on the aromatic ring.

The majority of known environmental releases of chlorophenols were to surface water (EPA 1982). The principal point source of water pollution by chlorophenols is industrial waste discharge; another point discharge is the leaching of chlorophenols from landfills. Chlorophenols enter the atmosphere through volatilization, with mono- and dichlorophenols being the most volatile. The primary nonpoint source pollution of chlorophenols comes from the application of pesticides that are made from chlorophenols and the chlorination of wastewater containing phenol.

Once released to the environment, chlorophenols are subject to a series of physical, chemical, and biological transformations. Sorption, volatilization, degradation, and leaching are the primary processes governing their fate and transport. The pH in water, soil, and sediment is a major factor affecting the fate and transport of chlorophenols in these media, since the degree to which the compounds ionize increases with increasing pH. In addition, physiochemical properties of chlorophenols such as water solubility, Henry's law constant, organic carbon sorption coefficient, volatilization rate, and photolysis rate determine transport processes. Important environmental parameters influencing these processes include organic matter content and clay content in soil, sediment, and water, as chlorophenols are, in general, preferentially adsorbed to these soil constituents. In general, as the number of chlorine molecules increase, there is a reduction in vapor pressure, an increase in boiling point, and a reduction in water solubility of the chlorophenols (Solomon et al. 1994). Therefore, increasing chlorination increases the tendency of these compounds to partition into sediments and lipids and to bioconcentrate. Chlorophenols are subject to abiotic and biotic degradation and transformations. However, compounds containing chlorine in the meta positions show greater resistance to microbial attack.

The general population may be exposed to chlorophenols through ingestion of chlorinated drinking water and food contaminated with the compounds and inhalation of contaminated air. Exposure to 4-CP could also occur through its use as a root canal packing. Populations with potentially unusually high exposure

to chlorophenols generally include employees of facilities that manufacture or use chlorophenols and their derivatives and those who live in the vicinity of chlorophenol-containing waste disposal sites and waste incinerators.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

The chlorinated phenols are manufactured by chlorination of phenol, or for the higher chlorinated phenols, the chlorination of lower chlorinated phenols at high temperatures (WHO 1989). Lower chlorinated phenols (mono-, di-, and trichlorophenols) are synthesized via chlorination of phenol with chlorine gas in a melt in cast-iron reactors (Muller and Caillard 2011). The distribution of isomers can be controlled by the level of chlorination and by recycling various intermediates that are formed. The manufacture of the tetrachlorinated phenols requires a catalyst. They are produced batchwise in nickel reactors by the chlorination of lower halogenated chlorophenols using aluminum trichloride or iron trichloride (Muller and Caillard 2011). 2,4,5-TCP, 2,3,4,5-TeCP, and 2,3,5,6-TeCP have also been produced by the alkaline hydrolysis of hexachlorobenzene (WHO 1989). Chlorophenol production can result in the formation of impurities. The main impurities of the lower mono, di-, and tri-chlorophenols are other isomers of the chlorophenol or chlorophenols with more or fewer chlorine atoms than desired. The major impurity of the higher chlorophenols (tetrachlorophenols and pentachlorophenol) are polychlorophenoxyphenols (up to several percent) (Muller and Caillard 2011). Trace quantities of chlorobenzoparadioxins and chlorobenzofuran are also found. Thermal or chemical degradation of chlorophenols can also result in the formation of polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans, polychlorinated phenoxyphenols, polychlorinated diphenyl ethers, polychlorinated benzenes, and polychlorinated biphenyls (Muller and Caillard 2011; WHO 1989). Muller and Caillard (2011) have noted that the highly toxic substance, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, has never been detected in products made by chlorination reaction.

Worldwide production of chlorophenols was reported as >10,000 metric tons annually in 2009, with the majority being used for the production of agricultural chemicals (Muller and Caillard 2011).

Table 5-1 summarizes information on U.S. companies that reported the manufacture or processing of chlorophenols in 2018 to the Toxic Release Inventory (TRI) (TRI18 2019). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	1	10,000	99,999	12
MI	1	100	999	14
OH	1	1,000	9,999	12
TX	3	100	999,999	1, 5, 6, 12, 13
UT	1	10,000	99,999	12
WI	2	10,000	99,999	7
Total	9	100	999,999	1, 5, 6, 7, 12, 13, 14

[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: TRI18 2019 (Data are from 2018)

5.2.2 Import/Export

No recent data were located regarding the import or export volumes of chlorophenols in the United States.

5.2.3 Use

Chlorophenols are used in the production of agricultural chemicals, pharmaceuticals, biocides, and dyes, with approximately 80–90% being used for agricultural purposes (Muller and Caillard 2011). The monochlorophenols have been used as antiseptics, although they have largely been replaced in this role by other chemicals (WHO 1989). Specifically, 4-CP has been used as a disinfectant for home, hospital, and farm uses (WHO 1989) and as an antiseptic in root canal treatment (Gurney and Lantenschlager 1982). 2,4-DCP has been used for mothproofing and as a miticide (WHO 1989), while the higher chlorophenols have been used as germicides, algicides, and fungicides.

The principal use of the monochlorophenols has been as intermediates for the production of higher chlorinated phenols (WHO 1989). The largest uses for 2,4-DCP and 2,4,5-TCP have also been used as an

intermediate, especially in the production of the herbicides, 2,4-D and 2,4,5-T (WHO 1989). In the United States, 2,4-D is still in use, while 2,4,5-T was taken off the market in 1985. 2,4,6-TCP has been used as an intermediate in the production of higher chlorinated phenols, especially 2,3,4,6-TeCP and pentachlorophenol (WHO 1989).

5.2.4 Disposal

Chlorophenols are listed as toxic substances under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Super-fund Amendments and Reauthorization Act (SARA)(EPA 1995). Disposal of wastes containing chlorophenols is controlled by a number of federal regulations (see Chapter 7).

Chlorophenols are often disposed of via incineration and precautions include the assurance of complete combustion in order to prevent the formation of toxic phosgene gas and the use of an acid scrubber to remove any halo-acids produced upon combustion (Sittig 1985). However, even after incineration, various isomers have been detected in the fly ash from municipal waste incinerators (Karasek et al. 1987; Paasivirta et al. 1985).

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 4,008 pounds (~1.8 metric tons) of chlorophenols to the atmosphere from nine domestic manufacturing and processing facilities in 2018, accounted for about 17% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2019). These releases are summarized in Table 5-2.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Chlorophenols[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
AK	1	0	0	0	14	0	0	14	14
MI	1	490	160	0	0	0	650	0	650
OH	1	0	0	0	0	0	0	0	0
TX	3	2,018	0	19,592	0	0	21,610	0	21,610
UT	1	0	0	0	0	0	0	0	0
WI	2	1,500	0	0	30	0	1,500	30	1,530
Total	9	4,008	160	19,592	44	0	23,760	44	23,804

[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 II0V 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: TRI18 2019 (Data are from 2018)

Only a small fraction (approximately 5%) of chlorophenols (based on 2-CP, 2,4-DCP, and 2,4,6- TCP) are emitted to the atmosphere (EPA 1982). These releases are primarily in vapor form and are principally associated with chlorophenol production and its use in the manufacture of end-use products (EPA 1982).

Releases of chlorophenols to the atmosphere may also occur through the incineration of chlorinated wastes. 2,4-DCP has been detected in atmospheric emissions from the combustion of municipal solid waste, hazardous waste, coal, wood, and 2,4-DCP-based herbicides (Gomez et al. 1988; Junk et al. 1986; Oberg et al. 1989; Paasivirta et al. 1985). Trichlorophenols have been detected in flue gas condensates and fly ash from municipal incinerators (Viau et al. 1984). Di-, tri-, and tetrachlorophenols have also been detected in fly ash from wood, oil, and coal-fired power plants at concentrations in the ng/g level (Paasivirta et al. 1985).

5.3.2 Water

Estimated releases of 160 pounds (~0.07metric tons) of chlorophenols to surface water from nine domestic manufacturing and processing facilities in 2018, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2019). These releases are summarized in Table 5-2.

The majority (85%) of known environmental releases of three chlorophenols (2-CP, 2,4-DCP, and 2,4,6-TCP) were to surface water (EPA 1982). The estimated 1977 water emissions of 2,4-DCP were 741,000 pounds from U.S. production facilities (EPA 1982). Industrial waste discharge is a major point source of water pollution by mono- and dichlorophenols (Krijgsheld and van der Gen 1986). Monochlorophenol concentrations of between 10 and 20 µg/L have been released in wastewater produced during the manufacture of specialty chemicals (Buikema et al. 1979; Hites et al. 1979), and 5.3 µg/L of 4-CP was detected in a bleaching effluent released to surface water from a straw mill (Folke and Lindgaard-Jorgensen 1985). 2,4-DCP or 2,4,6-TCP were also detected in effluents discharged from industries that manufacture iron and steel, electrical components, photographic equipment/supplies, pharmaceuticals, and organic chemicals/plastics and from paper pulp and paperboard mills (EPA 1979; Paasivirta et al. 1985). Oikari et al. (1985) reported that concentrations of 2,4,6-TCP and 2,3,4,6-TeCP were higher downstream from a pulp and paper mill than upstream from the facility. Free chlorophenols were still present in water 11 km downstream from the mill. However, the release of chlorophenols to water from pulp bleaching mills is being reduced as the use of elemental chlorine for bleaching is being phased out in favor of the use of chlorine dioxide (Solomon et al. 1994). Compared to chlorine, chlorine dioxide bleaching results in the production of fewer chlorophenols, and the chlorophenols that are produced contain fewer chlorine molecules.

Other sources of discharge of chlorophenols into aquatic systems include sewage treatment plants and drinking water treatment, which can result in the chlorination of phenol. In a study of 40 Canadian potable water treatment facilities, 4-CP, 2,4-DCP, and 2,4,6-TCP are the three halogenated phenols found most frequently in samples taken from chlorinated water supplies (Sithole and Williams 1986). The frequency of detection ranged from 1 to 12 out of 40 samples. Mean values were <7 ng/L and the maximum values were <130 ng/L. 2-CP has also been detected in treated drinking water in the Netherlands (1 µg/L) (Buikema et al. 1979). The maximum monochlorophenol concentrations measured in river water range from 2 to 6 µg/L (Krijgsheld and van der Gen 1986).

Chlorophenols may enter groundwater systems via leaching from landfills or underground injection disposal. 2-CP has been detected in the leachate from a municipal landfill, while 2,4-DCP was found in the leachate from an industrial landfill (Brown and Donnelly 1988). 2-CP was detected in the runoff from 1 of 15 cities, while neither 2,4-DCP nor 2,4,6-TCP were detected in the runoff from 3 cities (Cole et al. 1984). Analysis of groundwater taken from 479 waste disposal sites found that 2,4-DCP was detected at 19 sites, 2-CP at 14 sites, and 2,4,5-TCP at 2 sites, while 2,3,4,6-TeCP was not detected at any of the sites (Plumb 1991).

The detection of 2,4,6-TCP in industrially unpolluted surface water in Sweden at concentrations up to 10 ng/L suggests that this compound can be formed by natural chlorination of humic substances (Grimvall et al. 1991). A laboratory investigation (Hodin et al. 1991) reported that the addition of chloroperoxidase from the fungus, *Culduriomyces fumugo*, hydrogen peroxide, and potassium chloride to bog water (pH adjusted to 3 with 100 mM phosphate) did result in the production of 2,4,6-TCP. Chloroperoxidase could also chlorinate added phenol to form 2-CP and 4-CP. These results suggest that chloroperoxidase-mediated chlorination of natural organic matter does contribute to the levels of chlorophenols (especially 2,4,6-TCP) that are found in surface water.

5.3.3 Soil

Estimated releases of 44 pounds (~0.02 metric tons) of chlorophenols to soil from nine domestic manufacturing and processing facilities in 2018, accounted for about <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2019). An additional 19,592 pounds (~8.9 metric tons), accounted for about 82% of the total environmental emissions, were released via underground injection (TRI18 2019). These releases are summarized in Table 5-2.

Releases of chlorophenols to soils may occur through several processes such as disposal of manmade wastes (e.g., landfills), atmospheric deposition, and accidental releases (e.g., spills) (EPA 1982). Smith (1985) found that the herbicide 2,4-D can be degraded to 2,4-DCP following soil application. Unspecified trichloro- and tetrachlorophenols have been identified at sites composting yard waste and municipal solid waste (Malloy et al. 1993). The investigators suggested that the source was pentachlorophenol on treated wood in chipped form that had been added as a bulking agent. The use of chlorophenols as a wood preservative (predominantly 2,3,4,6-TeCP) has also resulted in the contamination of soil around sawmills where these compounds were used (Kitunen et al. 1985, 1987; Vale et al. 1984).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

The environmental fate and transport of chlorophenols are highly influenced by their physical and chemical properties and environmental conditions. Chlorophenols are weak acids and will exist as a combination of the free acid and its conjugate base depending upon the pH of the environmental media. The pKa of mono- and dichlorophenols is higher than the more chlorinated tri- and tetrachlorophenols (Table 4-2) and as a consequence, mono- and dichlorophenols will exist primarily as the protonated species in water and soil at typical environmental pH, whereas tri- and tetrachlorophenols will exist primarily as the conjugate base (anion).

Air. The higher vapor pressures of the monochlorophenols suggest that among the chlorophenols, these compounds are most likely to be found in air. The vapor pressures of the chlorophenols suggest that the compounds will not partition from the vapor phase to the particulate phase (Eisenreich et al. 1981). That 2,4-DCP and other chlorophenols do not partition into the particulate phase is supported by the identification of 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP in rain but not on rain filters (Leuenberger et al. 1985). This study indicates that gas scavenging rather than particle scavenging is the more important process for removing chlorophenols from the air (Leuenberger et al. 1985). Estimated rain/air partition coefficients at 8°C are 2.2×10^4 for 2,4-DCP and 1.8×10^4 for 2,4,5-TCP and 2,4,6-TCP combined (Leuenberger et al. 1985).

Water. The Henry's Law constants suggests that volatilization from water surfaces may be an important environmental fate parameter for the protonated chlorophenols; however, depending upon the

pH of the water, a substantial fraction of the substance may exist as the conjugate base (anion), which will not volatilize. Among the chlorophenols discussed in this profile, 2-CP has the highest vapor pressure and Henry's Law constant and is therefore most likely to evaporate from water (Krijgsheld and van der Gen 1986). In laboratory studies, evaporation half-lives of 2-CP and 4-CP from water 0.38 cm deep were 1.35–1.6 and 12.8–17.4 hours, respectively (Chiou et al. 1980). Since the evaporation rate is inversely related to the depth of water, extrapolation of these data indicates that-2-CP evaporation in still water 1 m deep would require approximately 15 days; evaporation would occur more rapidly in turbulent waters. The amount of volatilization of 2-CP from fine sandy soil (0.087% organic carbon), applied in spiked municipal wastewater, was too small to be directly measured (Piwoni et al. 1986).

The amount of tri- and tetrachlorophenols evaporating from water is expected to be significantly lower than the amount of monochlorophenols evaporating, since the pKa values of tri- and tetrachlorophenols are orders of magnitude lower, indicating that a much higher percentage will exist as anions in the water column. In 2-hour laboratory studies, the volatilization rates of 2,4,6-TCP from water and three soil types were determined by Kilzer et al. (1979). These rates, expressed as the percentage of applied compound per mL of water evaporated from humus, loam, sand, and water, were 0.15,0.73, 1.05, and 1.4%, respectively, in the first hour after the addition of 50 ppb 2,4,6-TCP. Similar rates were reported during the second hour. In wind tunnel experiments, Sugiura et al. (1984) estimated a half-life of 48 hours for loss of 2,4,6-TCP from water through volatilization. An estimated 58%of 2,4,6-TCP in a nutrient solution in which tomatoes were grown was lost to the air (from photolysis and/or volatilization) over a period of 30 days (Fragiadakis et al. 1981).

Sediment and Soil. Given the range of K_{oc} values in Table 4-1, chlorophenols tend to have low to moderate mobility in soils; however, mobility is also pH-dependent. Under neutral or alkaline conditions, a greater fraction will exist in the ionic form, which has greater solubility and more mobility in soil and a greater tendency to partition into the water column rather than sediment (Shiu et al. 1994). Under acidic conditions, more of the chlorinated phenols are expected to exist in the protonated form, which tends to adsorb to soil and sediment.

The adsorption potential of 2,4-DCP, 2,4,6-TCP, and 2,3,4,5-TeCP with an aquatic humic sorbent was examined as single and mixed solutions at different acidities (pH 3, 5.5, and 7) (Peuravouri et al. 2002). Adsorption increased with increasing chlorine content of the chlorophenols and decreasing pH of the solution. Log K_{oc} values ranged from 2.1 for 2,4-DCP at pH 7 to 3.30 for 2,3,4,5-TeCP at pH 3 for the single solution experiments and from 1.99 for 2,4-DCP at pH 7 to 3.09 for 2,3,4,5-TeCP at pH 3 for the

mixed solution experiments. A slightly larger log K_{oc} (2.89) for 2,4-DCP was measured using sediment samples of varying organic carbon content obtained from the Thermaikos Gulf, Greece (Fytianos et al. 2000).

Hyun and Lee (2004) studied the sorption behavior of 2,3,4,6-TeCP, 2,4,6-TCP, 2,4,5-TCP, and 2,4-DCP in two variable charged surface soils. The first soil, A1, was characterized as a Petroferric hapludox (41% clay, 1.38% organic carbon) and the second soil, DRC, was characterized as Typic hapludox (81% clay, 1.34% organic carbon). Both soils were acidic, with the DRC soil being the more acidic of the two. Adsorption experiments using calcium chloride solutions resulted in a soil pH of 5.8 and 4.2 for the A1 and DRC soils, respectively. In each case, significantly more adsorption was observed for each chlorophenol on the DRC soil where a greater fraction of the compound was expected to exist as the free acid rather than the anion. Log K_{oc} values for 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP were 1.93, 2.52, 2.06, and 2.38, respectively, on the A1 soil (pH 5.8). These values increased to 2.42, 2.85, 2.59, and 3.31 for 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP, respectively, on the DRC soil (pH 4.2). The authors calculated the fraction expected to exist as an anion based on their pKa values and the pH of the soils. In the less acidic A1 soil, the percentage of 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP present as an anion was 0.88, 6.8, 31, and 72%, respectively. In the more acidic DRC soil, the percent present as an anion was 0.002, 0.18, 1.1, and 5.9% for 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP, respectively.

Chlorophenol groundwater contamination will occur if sufficient quantities of the chemical are present to exceed the sorption capacity of the vadose zone saturated soils (EPA 1982). Contamination is most likely in soils with low organic carbon content or high pH. Once in groundwater, sorption of chlorophenols by the solid aquifer matrix may be estimated based on log K_{ow} and organic carbon content, provided that the organic carbon content exceeds 0.1% and the aquifer pH is not sufficiently high for significant dissociation to occur (Schellenberg et al. 1984; Schwarzenbach and Westall 1985). In a natural gradient tracer test conducted within an unconsolidated aquifer, sorption was not an important factor, compared to dispersion and degradation, in the attenuation of 4-CP concentrations (Sutton and Barker 1985). The authors attributed this finding to the low organic carbon content of the aquifer sand unit, which prevented significant hydrophobic sorption.

Other Media. The bioconcentration of chlorophenols is also likely pH-dependent as greater bioconcentration is expected under acidic conditions when a higher fraction is present in the protonated species as opposed to the anion. Under environmental pH, chlorophenols tend to have low to moderate

bioconcentration potential. The bioconcentration factors (BCFs) of 2-CP, 2,4-DCP, and 2,3,4,6-TeCP were measured at two concentrations in carp over 6–8-week incubation periods in a flow-through system (CITI 2019). The BCF ranges for 2-CP were 14–24 at an initial concentration of 40 µg/L and 16–29 at a starting level of 4 µg/L over a 6-week exposure period. The BCF ranges of 2,4-DCP were 7.1–69 at 30 µg/L and 10–55 at an initial concentration of 3 µg/L over an 8-week incubation period. The ranges of BCF values for 2,3,4,6-TeCP were 25–62 at an initial concentration of 10 µg/L and 36–95 at an initial concentration of 1 µg/L over an 8-week exposure period. BCFs for 2,4-DCP in Japanese medaka (*Oryzias latipes*) were determined at five different concentrations (Kondo et al. 2005). The BCF values of 2,4-DCP ranged from 340±300 at 0.235±0.060 µg/L to 92±27 at 27.3±1.6 µg/L. Generally, BCF values increased as the aqueous concentrations of the chlorophenols decreased.

Research on biomagnification of chemical residues within the aquatic food chain indicates that the potential for residue accumulation by fish through food chains is relatively insignificant (<10%) for most compounds when compared to the tissue residues resulting from the bioconcentration process (i.e., direct uptake from water) (Barrows et al. 1980). These data suggest that only those chemicals that are relatively persistent in fish tissues appear to have any potential for significant transfer through food chains (Barrows et al. 1980). A very short tissue half-life of <1 day was measured after exposure of bluegill sunfish to 2-CP was terminated (Veith et al. 1980). Therefore, due to their relatively low BCFs (<1,000) and short biological half-lives (<7 days), monochlorophenols will probably not biomagnify within aquatic food chains (Barrows et al. 1980). Data regarding the biomagnification of the higher chlorophenols were not located.

Isensee and Jones (1971) studied the uptake of 2,4-DCP from solution and soil by oats and soybeans. The compound was taken up by the plants, with the concentrations decreasing as the plants matured. At maturity, 2,4-DCP was below detection (<0.001 µg/g) in oat seeds and 0.003 µg/g in soybeans. Data regarding the uptake of other chlorophenols by plants were not located.

The bioaccumulation of 2,3,4,6-TeCP was examined in earthworms (*Lumbricus rubellus* and *Aporrectodea caliginosa tuberculata*) at a sawmill that had been closed for 28 years before sampling (Haimi et al. 1992). At a distance of 5 m from the dipping basin, 2,3,4,6-TeCP concentrations were 430 and 1,980 µg/g fat in *Lumbricus* and *Aporrectodea*, respectively, while the soil concentration was 336 µg/g dry soil. The difference between the two genera was attributed to greater ingestion of contaminated soil by *Aporrectodea*. Additional data regarding bioaccumulation of chlorophenols in terrestrial organisms were not identified. It is not known whether 2,3,4,6-TeCP biomagnifies up the

terrestrial food chain. Based on physical properties (i.e., log K_{ow}), the tetrachlorophenols, rather than lower chlorinated phenols, would have the greatest potential to biomagnify.

5.4.2 Transformation and Degradation

Air. Chlorinated phenols are expected to be degraded via reaction with photochemically generated hydroxyl radicals. Using the method of Meylan and Howard (1993), a range of atmospheric half-lives of approximately 0.54 days (2-CP) to 19.3 days (2,3,4,6-TeCP) has been estimated for the vapor-phase reaction using an average hydroxyl radical concentration of $1.5x10^6$ molecule/cm^3.

Water. Both direct photolysis and the reaction of chlorophenols with hydroxyl radicals and singlet oxygen produced by ultraviolet radiation may be important processes of chlorophenol degradation near the water surface. Photolysis of monochlorophenols in water results in dechlorination, with the position of the chlorine on the ring strongly influencing the transformation (Boule 1982). In the molecular form, 2-CP is converted into pyrocatechol. However, in the anionic form, it is reduced in a cyclopentadienic acid and dimerizes. For 3-CP, the photochemical product is resorcinol regardless of the pH. For 4-CP, hydroquinone is formed along with polyphenolic oligomers (Boule 1982). The photolysis rates of 2-CP in natural waters depends on pH, season, and dissolved organic material (Kawaguchi 1992a, 1992b). In all cases, the reaction rate is first-order. Based on empirical data, the study authors proposed that direct photolysis of 2-CP may only occur in natural waters at pH between 7 and 9. Indirect photolysis in lake waters was only significant in summer months; in sea waters, indirect photolysis has a more significant role in the spring and fall. Kawaguchi et al. (1992a, 1992b) also found that the dissolved organic matter in pond water does not contribute to indirect photolysis as significantly as a humic acid solution.

The photocatalytic degradation process with titanium dioxide particles has been shown to be feasible for achieving a high degree of removal of 2-CP in water (Ku et al. 1996), with almost complete disappearance in only a few hours of illumination time. However, the demineralization of reaction intermediates requires a longer time, and was found to be more effective for acidic solutions. Increasing the light intensity would significantly increase the decomposition rate of 2-CP at pH 3, but not pH 11. The higher removals at acidic conditions may be due to the increased amounts of undissociated 2-CP species adsorbed on the TiO_2 surface, with the TiO_2 acting as a catalyst in the photochemical degradation.

The reaction of hydroxyl radicals with mono- and dichlorophenols was studied by Kochany and Bolton (1991) using spin trapping with electron paramagnetic resonance detection of spin adducts. The reaction

rate of 4-CP ($3.2/10^{10}$ $M^{-1}second^{-1}$) and 2,4-DCP ($3.8/10^{10}$ $M^{-1}second^{-1}$) with hydroxyl radicals was greater than the reaction rate of 2-CP ($1.92/10^{10}$ $M^{-1}second^{-1}$). The observation that chlorophenols with *meta*-substitution have even slower reaction rates ($1.04/10^{10}$ $M^{-1}second^{-1}$ for 3-CP, $0.9/10^{10}$ $M^{-1}second^{-1}$ for 3,5-DCP) indicates that for the mono- and dichlorophenols, the location of chlorine rather than the number of chlorines is more important in determining the reaction rate. Higher chlorinated phenols were not examined in this study. Chlorophenols may also be removed via reaction with photochemically produced singlet oxygen in natural waters. The estimated half-life for the reaction of 2,4-DCP at pH 7 and 2,4,6-TCP with singlet oxygen at pH 5.5 under midday sun (assuming a singlet oxygen concentration of $4x10^{-14}$) using experimentally determined rate constants is 62 hours (Scully and Hoigne 1987). The rate of reaction of singlet oxygen with 2,4-DCP and 2,4,6-TCP increased significantly as the solution pH was raised from 5.5 to 9 (Scully and Hoigne 1987). This observation is consistent with a study by Tratnyek and Hoigne (1991),which found that the reaction of phenolate ions with singlet oxygen was about 1 order of magnitude greater than the reaction of the undissociated chlorophenol. The compounds examined in this study were 2-CP, 4-CP, 2,4-DCP, and 2,4,6-TCP. Although tetrachlorophenols are most likely to exist as ions in natural waters, it is not known whether the ions react more readily with singlet oxygen than the undissociated tetrachlorophenol compounds.

Hwang et al. (1986) studied the photolysis and microbial degradation of 4-CP, 2,4-DCP, and 2,4,5-TCP in both estuarine and distilled water. Photolysis was the primary transformation process for 2,4-DCP and 2,4,5-TCP, with the rate of photolysis decreased in the order 2,4,5-TCP, 2,4-DCP, and 4-CP. The rate of photolysis of 2,4-DCP was greater in estuarine water compared to distilled water, suggesting a photosensitized reaction. The type of water had no effect on the photolysis of 4-CP and 2,4,5-TCP. Unlike the polychlorinated phenols, microbial degradation was the primary transformation process for 4-CP (Hwang et al. 1986). 2-CP, 2,4-DCP, and 2,3,4,6-TeCP were all shown to be not readily biodegradable following a 4-week incubation period in an activated sludge inoculum and the Japanese MITI test (Organisation for Economic Cooperation and Development [OECD] 301C guideline) (CITI 2019).

There are numerous studies regarding the microbial degradation of chlorophenols in water and sediments (Abrahamsson and Klick 1991; Aly and Faust 1964; Banerjee et al. 1984; Genther et al. 1989; Hwang et al. 1986; Vaishnav and Korthals 1988), as well as numerous studies concerning the degradation of these compounds by sludge (Armenante et al. 1992; Battersby and Wilson 1989; Boyd and Shelton 1984; Liu and Pacepavicius 1990; Tabak et al. 1981). Although as a group, chlorophenols are poorly biodegradable and persistent in the environment, several studies have shown that aerobic degradation of chlorophenol

congeners is possible (Armenante et al. 1992; Steiert et al. 1988). The aerobic degradation of chlorophenols by microorganisms requires the participation of the oxygenase enzymes to incorporate atmospheric oxygen into their substrates. For fission of the benzene nucleus, the ring is usually first dihydroxylated by an oxygenase such that two hydroxyl groups are situated either *ortho* or *para* to one another on the ring (Steiert and Crawford 1985). Subsequent ring fission occurs through another oxygenase-catalyzed reaction involving the insertion of dioxygen into the aromatic nucleus. The crucial step in the biodegradation of chlorophenols is the removal of the chlorine substituents. For the catabolism of the lesser substituted phenols (mono- and dichlorophenols), dioxygenase from chlorophenol-degrading bacteria usually opens the dehydroxylated aromatic ring before dechlorination takes place (Steiert and Crawford 1985). With more highly substituted phenols, some of the chlorosubstituents must be removed before ring cleavage since the halogen atoms deactivate the aromatic nucleus to electrophilic attack by dioxygenases.

It has been reported that 4-CP can be partially or completely degraded by several aerobic bacteria such as *Pseudomonas* sp. B13 (Knackmuss 1978) and *Azobactirium* sp. GPl (Wieser 1997). The catabolic degradation routes for mono- or dichlorophenols are known to be *meta*- and modified *ortho*- pathways (Bae et al. 1996). In these pathways, 4-CP is hydroxylated to 4-chlorocatechol, which then undergoes intradiol cleavage before the chloro-substituent is removed. In addition, 4-CP degradation by *Azobactirium ureufaciens* CPR706 was reported via a pathway in which the chloro-substituent of 4-CP was replaced with an incoming hydroxyl group to form hydroquinone (Bae et al. 1996). After 4-CP degradation was completed, the accumulated hydroquinone disappeared from the medium via ring fission forming the 4-hydroxymuconic semialdehyde intermediate. The general observation of these studies is that compounds with a chlorine in the *meta*- and/or *para*- position are the most resistant to degradation (Abrahamsson and Klick 1991). In addition, if the bacteria have not been cultured in the presence of a chlorophenol, they require an adaption period before the compounds can be degraded. For example, degradation of 2,4-DCP was observed in natural water collected from a river following lag times of 2.5 and 8.3 days for two separate collections (Banerjee et al. 1984). The rates of degradation of 4-CP, 2,4-DCP, and 2,3,4,5-TeCP in river water were $6.5x10^{-6}$, $2.3x10^{-6}$, and $1.4x10^{-7}$ moles/hour, respectively (Banerjee et al. 1984). A study by Liu and Pacepavicius (1990) indicates that the position, rather than the number of chlorine atoms, is more important in determining the biodegradation of chlorophenols. The biodegradation of chlorophenols was studied in both aerobic and anaerobic systems using a pentachlorophenol-degrading bacterial culture. The results, shown in Table 5-3, indicate lag time to degradation, and half-life tended to be shorter for compounds with a chlorine in the 4 position and longer for compounds

with a chlorine at the 5 position. Anaerobic degradation of the chlorophenols required a longer lag time and the half-lives were longer.

Table 5-3. Degradation of Chlorophenols by Bacteria Adapted to Pentachlorophenol Under Different Oxygen Conditions

	Lag period hours		Degradation half-life (hours)	
Substance	Aerobic conditions	Anaerobic conditions	Aerobic conditions	Anaerobic conditions
2-Chlorophenol	25	250	140	75
4-Chlorophenol	25	51	88	84
2,4-Dichlorophenol	0	310	125	430
2,4,5-Trichlorophenol	300	Undegraded	380	Undegraded
2,4,6-Trichlorophenol	0	300	120	470
2,3,4,5-Tetrachlorophenol	50	500	165	510
2,3,5,6-Tetrachlorophenol	Undegraded	Undegraded	Undegraded	Undegraded

Liu and Pacepavicius (1990)

Reductive dehalogenation of chlorinated aromatic compounds whereby chlorines are being replaced by hydrogens occurs extensively under anaerobic conditions (Steiert and Crawford 1985). Anaerobic dehalogenation of 2-CP, a common intermediate of polychlorophenol degradation, by mixed cultures was reported (Themel et al. 1996). Acetate was found to be the major end product, with phenol and benzoate as intermediate products, but CO_2 was not found to be an end product.

A study of anaerobic degradation of chlorophenols in wastewater in an upflow anaerobic sludge blanket reactor indicated that the higher chlorophenols were converted to lower chlorinated compounds via reductive dechlorination reactions (Woods et al. 1989). The rate of these reactions was dependent on the position of the chlorine; chlorines adjacent to the hydroxyl group were preferentially removed, and *meta* chlorines were removed following acclimation, with no evidence for the removal of *para* chlorines. Woods et al. (1989) also found no evidence for the dechlorination of monochlorophenols in this system.

4-CP was demonstrated to be quickly removed from formulated wastewater catalyzed by horseradish peroxidase (Zhang et al. 1997) to form radicals or quinones, which might be subsequently polymerized to form less-soluble large molecules and precipitated from aqueous phase. The flocculant might increase the removal percentage of the pollutant through enhancing the sedimentation of the reaction products. The

optimum pH for the removal efficiency of chlorophenol was 9.0. The analytical method would, thus, have to quantify both salt and acid forms of the chlorophenol.

Sediment and Soil. Chlorophenol isomers undergo biodegradation in soils under aerobic conditions. Aerobic microorganisms that can degrade chlorophenols have been isolated from soil bacterial cultures. *Pseudomonas picketti* DTP0602, which used 2,4,6-TCP as the sole source of carbon and energy, was isolated from mixed cultures of soil bacterial populations that had been acclimatized to 2,4,6-TCP (Kiyohara et al. 1992). This bacterial species dechlorinates the phenol at position 4 of various chlorophenols to yield their corresponding hydroquinones and may involve oxygenation. Two different enzyme systems for hydroxylation at the *ortho* and *para* positions of the phenol ring may be present in this bacterial species. The *para*-hydroxylation system, which may use a monooxygenase, possibly involves the dechlorination of a 4-position chlorine atom of chlorophenols. 2,4,6-Trichlorophenol-4-monooxygenase, a dehalogenating enzyme, was also isolated from trichlorophenol-degrading soil bacterium *Azotobacter* sp., strain GPl (Wieser et al. 1997). NADH, flavin adenine dinucleotide, and O_2 are required as cofactors. 2,6-Dichlorohydroquinone and Cl^- ions were identified as reaction products. Trichlorophenol was the best substrate for this enzyme. However, the majority of other chlorophenols converted by the enzyme bear a chloro-substituent in the 4-position. 2,6-DCP, also accepted as a substrate, was hydroxylated in the 4-position to 2,6-dichlorohydroquinone in a nondehalogenating reaction. It was also reported that the addition to the culture medium of a vitamin solution containing biotin, folic acid, pyridoxine hydrochloride, riboflavin, thiamine hydrochloride, niacin, pantothenic acid, cyanocobalamin, *p*-aminobenzoic acid, and thioctic acid can increase the aerobic degradation and dechlorination of 2-CP and 4-CP by *Pseudomonas picketti* strain LDl culture by 11–16% (Kafkewitz et al. 1996).

The extent and rate of biodegradation depend on numerous factors, including soil pH, organic carbon content, biomass, and the chlorophenol isomer and its concentration. In neutral clay-loam soil at 20°C under aerobic conditions, 2-CP was degraded the fastest (Baker and Mayfield 1980). Decomposition rates were as follows: 100% of the 2-CP in 1.5 days, 95% of the 2,4,6-TCP in 3 days, 83% of the 4-CP in 20 days, 81% of the 2,4-DCP in 40 days, and 72 and 31% of the 2,4,5-TCP and 2,3,4,5-TeCP, respectively, in 160 days (Baker and Mayfield 1980). Dasappa and Loehr (1991) examined the loss of 2-CP, 4-CP, 2,4-DCP, and 2,4,6-TCP from a laboratory soil microcosm. The loss from soil and the water-soluble fraction were examined at two concentrations for each compound. The loss of chlorophenols from the water-soluble fraction was about 1.5 times greater than the loss from soil, and chemical loss was slower at higher initial concentrations. Mineralization of 2,4,5-TCP in soil not

previously exposed to chloroorganics has been reported (Matus et al. 1996). The observation of 2,3,4,6-TeCP in soil (157–338 µg/g dry soil) at a sawmill 28 years after it closed provides evidence that this compound can persist in soil. Soil concentrations of 2,3,4,6-TeCP when the mill was closed were not stated. In general, degradation or complete mineralization to carbon dioxide (CO_2) is greater in soils with low organic carbon content (Kjeldsen et al. 1990), slightly alkaline pH (Balfanz and Rehm 1991), increased temperatures (Baker and Mayfield 1980; Baker et al. 1980; Balfanz and Rehm 1991), and increased inoculum concentrations (Balfanz and Rehm 1991).

Microbial degradation of chlorophenols in soil under anaerobic conditions has not been observed consistently. For 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,5-TeCP, no statistically significant differences in degradation rates between nonsterile and sterile clay loam soils occurred when both soil samples were incubated under anaerobic conditions (Baker and Mayfield 1980).

In a study of the degradation of halogenated phenols in anoxic marine sediments, the main degradation pathway was progressive dehalogenation with ortho > para > meta. Sediments that had been exposed to effluent water from a paper and pulp mill showed a higher dehalogenation potential (Abrahamsson and Klick 1991).

Another study demonstrated that anaerobic degradation of chlorophenols with an estuarine sediment inoculum was coupled to sulfate reduction, which was the electron sink. The relative rates of degradation were 4-CP > 3-CP > 2-CP, 2,4-DCP (Haggblom and Young 1990).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to chlorophenols depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of chlorophenols 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 chlorophenols levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-4 shows the lowest limits of detections that are achieved by analytical analysis in environmental media. Morias et al. (2012) reviewed extraction and chromatographic techniques for the detection of chlorophenols in environmental media (water, sludge, soil, and sediment), biological samples, and food.

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[b] (ppbv)	$2x10^{-5}$	Leuenberger et al. 1985
Drinking water (ppb)	0.02	EPA 2000
Surface water and groundwater (ppb)	$1x10^{-4}$	Grimvall et al. 1991
Soil (ppb)	0.007	de Morais et al. 2012
Sediment (ppb)	1	de Morais et al. 2012
Urine (ppb)	0.2	CDC 2019

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

Table 5-5. Summary of Environmental Levels of Chlorophenols

Media	Low	High	For more information
Outdoor air (ppbv)	<LOD	190	Section 5.5.1
Surface water (ppb)	<LOD	17	Section 5.5.2
Ground water (ppb)	<LOD	80	Section 5.5.2
Drinking water (ppb)	<LOD	0.15	Section 5.5.2
Soil	<LOD	1,776,000	Section 5.5.3

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

Table 5-6. Chlorophenols 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
2-Chlorophenol					
Water (ppb)	73	73.0	11.7	9	8
Soil (ppb)	38,200	32,200	32.3	15	9
Air (ppbv)	No data	No data	No data	No data	No data
4-Chlorophenol					
Water (ppb)	39	66.9	3.04	3	2
Soil (ppb)	No data	No data	No data	No data	No data

Table 5-6. Chlorophenols 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
Air (ppbv)	No data	No data	No data	No data	No data
2,4-Dichlorophenol					
Water (ppb)	1,250	622	26.8	10	7
Soil (ppb)	160,000	36,800	45.0	21	14
Air (ppbv)	No data	No data	No data	No data	No data
2,4,5-Trichlorophenol					
Water (ppb)	5,210	3,280	2.23	3	2
Soil (ppb)	253	341	6.56	5	5
Air (ppbv)	No data	No data	No data	No data	No data
2,4,6-Trichlorophenol					
Water (ppb)	240	245	22.0	11	9
Soil (ppb)	108,000	26,100	33.8	16	12
Air (ppbv)	No data	No data	No data	No data	No data
Tetrachlorophenol					
Water (ppb)	23.5	13.9	62.0	6	4
Soil (ppb)	263,000	87,500	12.1	2	2
Air (ppbv)	No data	No data	No data	No data	No data

[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

During seven rain events in Portland, Oregon, in 1984, 2,4-DCP was detected in the air in all seven events at an average concentration of 1.5 ng/m^3 (0.23 pptv), combined 2,4,5-TCP and 2,4,6-TCP were detected in 6/7 events at an average concentration of 0.15 ng/m^3 (0.02 pptv), and 2,3,4,6-TeCP was detected in 5/7 events at an average concentration of 0.27 ng/m^3 (0.03 pptv) (Leuenberger et al. 1985). Average concentrations in rain for the seven events were 5.9, 1.1, 1.4, and 20 ng/m^3 (0.89, 0.14, 0.17, and 2.1 pptv) for 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP, which were detected in 7/7, 4/7, 5/7, and 7/7 of the events, respectively. Additional data regarding ambient levels of chlorophenols in indoor or outdoor air were not identified. However, data on 2-CP levels after the accidental derailment and rupture of a train tanker are available. On the day of the accident, air concentrations ranging from 0.02 to 0.7 mg/m^3

(0.04–0.19 ppmv) were detected in the immediate vicinity of the spill (EPA 1982). Eighteen days after the spill, air levels were <2 µg/m^3 (<0.5 ppbv). No additional data are available regarding air emissions following accidental releases.

5.5.2 Water

Grimvall et al. (1991) measured 2,4,6-TCP in unpolluted surface waters in remote areas of southern Sweden and in pulp bleaching plant receiving waters, Lake Vattern and the Baltic Sea. Concentrations up to 10 ng 2,4,6-TCP/L were found in unpolluted waters, with concentrations of 2,4,6-TCP in Lake Vattern decreasing from 12 to 1 ng/L with increasing distance from the bleaching plant. 2,4,6-TCP concentrations in the Baltic Sea were <1 ng/L. This study suggests that 2,4,6-TCP can be formed by both industrial and natural chlorination of humic substances, an observation that was confirmed in the laboratory (Haimi et al. 1992).

Analysis of chlorophenol concentrations downstream of paper mills along the Rainy River in Canada and northern Minnesota did not identify 2-CP, 4-CP, 2,4,5-TCP, 2,3,5,6-TeCP, or 2,3,4,5-TeCP using methods with detection limits as low as 50 ng/L (Merriman 1988). In water samples from northern Alberta, Canada, 2-CP was not detected (detection limit 0.005 µg/L), while 2,4-DCP concentrations were <0.002–7.1 µg/L, and 2,4,6-TCP concentrations were <0.002–17 µg/L (Morales et al. 1992). 2,4-DCP, 2,4,6-TCP, and 2,3,4,6-TeCP were identified in water samples from at least one of the three sampling stations. A summary of STORET data of priority pollutants in ambient water (Staples 1985) indicated that 2-CP was detected in 0.2% of 814 samples, 2,4-DCP was detected in 0.4% of 876 samples, and unspecified trichlorophenols were detected in 0.1% of 880 samples. Analysis of runoff from 15 U.S. cities for 2-CP, 2,4-DCP, and 2,4,6-TCP identified only 2-CP, which was found in samples from only one city (Cole et al. 1984).

Chlorophenols are produced during the chlorination of organic material present in industrial and municipal waste waters. Several investigators have detected these chemicals downstream of wastewater discharge points. Maximum surface water concentrations measured in 13 samples downstream from a chlorinated waste water discharge in the Netherlands were (in µg/L) 0.6 for 2-CP, 2.1 for 4-CP, 0.33 for 2,4-DCP, 0.32 for 2,4,5-TCP, 0.74 for 2,4,6-TCP, 0.02 for 2,3,4,5-TeCP, 0.2 for 2,3,4,6-TeCP, and 0.08 for 2,3,5,6-TeCP (Wegman and van de Broek 1983). Maximum monochlorophenol concentrations of between 2 and 6 µg/L have been measured in European rivers (Krijgsheld and van der Gen 1986).

Chlorophenols have been detected in groundwater from waste disposal sites, indicating that these compounds can leach through soil (Plumb 1991). 2,4-DCP was detected most frequently, followed by 2,4,6-TCP, 2-CP, and 2,4,5-TCP. 2,3,4,6-TeCP was not detected at any of the 479 sites. It was not reported how much of each chlorophenol was disposed at each site, and soil concentrations at the sites were not reported. 2,4-DCP in the concentration range of 3.2–79.7 µg/L, as well as other organic compounds, has been found in groundwater samples taken near an abandoned creosote waste site in Conroe, Texas (Bedient et al. 1984).

Chlorination of drinking water at treatment plants can result in detectable levels of chlorophenols if the required precursors are available in the raw water (Krijgsheld and van der Gen 1986). In a study of Canadian potable water treatment facilities conducted in the summer, maximum concentrations of 65, 127, 72, and 148 ng/L of 2-CP, 4-CP, 2,4-DCP, and 2,4,6-TCP, respectively, were measured, while 2,3,4,5-TeCP was not detected in the water (Sithole and Williams 1986). 2,4-DCP and 2,4,6-TCP were monitored for in 304 public water systems (PWS) between 2001 and 2005 as part of the EPA Unregulated Contaminant Monitoring Rule (UCMR). The UCMR was developed to collect data for contaminants that could be present in drinking water but do not have health-based standards set under the Safe Drinking Water Act (SDWA). Neither 2,4-DCP nor 2,4,6-TCP were detected in 2,308 samples that were tested in the 304 PWS (EPA 2005).

5.5.3 Sediment and Soil

Kitunen et al. (1985) reported soil concentrations (in mg/kg wet weight) of 2.7–47.4, 2,4-DCP; 0.8–15.7, 2,4,5-TCP; 7.3–1,258.3, 2,4,6-TCP; 231–1,776.4, 2,3,4,6-TeCP; and 0.9–2.2, 2,3,4,5-TeCP in soil at an operating sawmill in Finland where chlorophenols (predominantly 2,3,4,6-TeCP) were being used as a wood preservative. The highest concentrations of chlorophenols were found at depths of 5–40 cm. Soil concentrations of 157–338 mg 2,3,4,6-TeCP/kg dry soil were found at a sawmill in Finland 28 years after it had closed, indicating that this compound can persist for long periods (Haimi et al. 1992). Soil concentrations of 2,3,4,6-TeCP when the sawmill was in operation were not reported, and soil concentrations of other chlorophenols discussed in this profile were not measured.

A limited amount of data concerning chlorophenol sediment concentrations in areas of known surface water contamination are available. 2-CP and 4-CP were not detected in sediments, while the maximum concentrations of 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, 2,3,4,5-TeCP, 2,3,4,6-TeCP, and 2,3,5,6-TeCP were 10, 15, 3.7, 9.8, 4.9, and 2.8 pg/kg, respectively (Wegman and van de Broek 1983). In the same study,

none of the isomers appeared in sediment samples collected from six locations in the vicinity of chemical and industrial wastewater effluent discharge points. These findings may be misleading because of the poor sensitivity (detection limit of 10 µg/kg) of the gas chromatography/electron capture detector (GC/ECD) analytical procedure. No 2-CP, 2,4-DCP, or 2,4,6-TCP were detected in sediment samples from northern Alberta, Canada, where water concentrations of these chlorophenols were low or not detectable (Morales et al. 1992). The limits of detection in sediments were 0.02 µg/g for 2-CP and 0.01 µg/g for 2,4-DCP and 2,4,6-TCP.

5.5.4 Other Media

The use of the chlorophenoxy herbicides may result in contamination with 2,4-DCP and 2,4,5-TCP. For example, Cook et al. (1983) analyzed the free and acid hydrolyzable residues of 2,4-DCP in millet resulting from treatment with 2,4-D. The total residues of 2,4-DCP ranged from not detected (<0.02 ppm detection limit) to 0.031 ppm for postemergence and preharvest treatment. Only 15–19% of the 2,4-DCP residues were in the free unaltered form, while the remaining residues were conjugated to sugars and amino acids and converted to the free form by acid hydrolysis.

Few data were found on the levels of chlorophenols in U.S. foods. Most of the data or estimates are for concentrations in fish or shellfish; 2-CP, 2,4-DCP, and 2,4,6-TCP were not detected in 22 composite samples of fish collected from harbors and tributaries of the Great Lakes (DeVault 1985). 4-CP, 2,4-DCP, and 2,4,6-TCP were not detected (detection limit 0.02 mg/kg) in fish from 13 Lake Michigan tributaries (Camanzo et al. 1987) or in fish from northern Alberta, Canada, (detection limit 0.01 µg/g) (Morales et al. 1992). Fish in the Fraser River estuary downstream from a lumber mill were found to contain chlorophenols including 2,4,5-TCP, 2,4,6-TCP, 2,3,5,6-TeCP, 2,3,4,6-TeCP, and 2,3,4,5-TeCP (Carey et al. 1988). Among the chlorophenols discussed in this profile, 2,3,4,6-TeCP was the most predominant compound, and the highest concentrations (49 ng/g) were found in sculpin, which had concentrations of about 400 times the concentration found in water in the estuary. Trichlorophenol (combined 2,4,5- and 2,4,6- isomers) concentrations of 29–629 ppb (wet weight) were measured in fish livers collected from the Pacific Ocean 6 km northwest of the discharge zone for the Los Angeles County wastewater treatment plant by Gossett et al. (1983). Concentrations in edible tissues were not measured. De Morais et al. (2012) reported that levels of chlorophenols the Slovak Republic total diet were on the order of ng/g and they have been identified in wine, milk, clams, and honey.

A potential source for chlorophenol contamination of food is migration from packaging materials. Shang-Zhi and Stanley (1983) reported levels of 0.1–0.68 ppm 2,4,6-TCP and 0.14–0.55 ppm 2,3,4,6-TeCP in cardboard food containers. Analysis for other chlorophenols was not completed. Shang-Zhi and Stanley (1983) indicated that the source of chlorophenol contamination was polyvinyl acetate and starch adhesives used in carton manufacture.

5.6 GENERAL POPULATION EXPOSURE

Oral exposure to chlorophenol-contaminated water or inhalation of air are the main routes of exposure to the general population. Water contaminated through chlorination is most likely to contain lower chlorinated phenols, while higher chlorinated phenols are more likely to be found in fish. Although food monitoring data are lacking, exposure to chlorophenols through the ingestion of food is expected to be relatively minor. Estimates of total chlorophenol intake reviewed by WHO (1989) ranged from 2.2 µg/person/day, assuming that contaminated water and fish were the main sources of exposure, to about 10–40 µg/person/day, assuming that indoor rooms were treated with a chlorophenol preservative.

The identification of chlorophenols in urine and fat of persons not occupationally exposed to chlorophenols confirms general population exposure to these compounds. Analysis of urine from 197 children living near a herbicide manufacturing plant in Arkansas for 2,4-DCP, 2,4,5-TCP, and 2,4,6-TCP, identified these compounds in 27, 54, and 11% of the samples, respectively (Hill et al. 1989). The 95th percentile concentrations (in ppb) were 7 for 2,4-DCP, 7 for 2,4,5-TCP, and 4 for 2,4,6-TCP. In the NHANES II, 2,4,5-TCP was detected (detection limit 5 ppb) in 3.4% of about 6,000 urine samples taken from a representative sample of nonoccupationally exposed persons from 64 communities in the United States during 1976–1980 (Kutz et al. 1992; Murphy et al. 1983). The maximum concentration detected was 56 ppb (Kutz et al. 1992). The investigators warn that because of the considerable variability among the recovery rates over time and between laboratories, the level for 2,4,5-TCP may be underestimated. The average fat concentrations of combined 2,3,4,6-TeCP and 2,3,5,6-TeCP and of 2,3,4,5-TeCP in autopsy specimens were 22 and 6 ng/g respectively in Kingston, Ontario, which is on Lake Ontario, relative to 7 ng/g for 2,3,4,6-TeCP, 2,3,5,6-TeCP, and 2,3,4,5-TeCP in tissue from persons living in Ottawa (Williams et al. 1984). 2,3,4,6-TeCP was detected in 29/46 adipose samples from persons in Finland not occupationally exposed to chlorophenols, while 2,4,6-TCP was detected in only one adipose sample (Mussalo-Rauhamaa et al. 1989). The concentration of 2,3,4,6-TeCP in adipose tissue ranged from <0.001 (the detection limit) to 0.031 µg/g. 2,3,4,6,-TeCP was also found in 2/13 liver samples, while 2,4,6-TCP was not detected (0.001 µg/g detection limit) in any liver samples.

The most recent data for urinary levels from the fourth NHANES report are presented in Tables 5-7 and 5-8 (2,4-DCP), Tables 5-9 and 5-10 (2,5-DCP), Tables 5-11 and 5-12 (2,4,5-TCP), and Tables 5-13 and 5-14 (2,4,6-TCP) (CDC 2009, 2019).

Occupational exposure to chlorophenol isomers may occur during chemical production and during subsequent use as intermediates in the synthesis of higher chlorinated phenols, phenolic resins, dyes, and drugs (Exon et al. 1984; Krijgsheld and van der Gen 1986). Exposures result from inhalation and/or dermal contact and are most likely associated with process, storage, or fugitive emissions at chemical manufacturing plants. No estimates of the number of workers exposed to the chlorophenols discussed in this profile were available.

Occupational exposure to chlorophenols may also occur during the incineration of wastes containing chlorinated chemicals (Angerer et al. 1992, 1993) and through indirect exposure following worker inhalation and subsequent metabolism of chlorobenzene (Kusters and Lauwerys 1990; Yoshida et al. 1986). In a study of 53 municipal waste incinerator workers' urine, concentrations of 2,4-DCP and 2,4,5-TCP were small but significantly ($p=0.05$; nonparametric U-test of Wilcoxon, Mann, and Whitney) greater than the urinary concentrations of these chlorophenols in 248 persons with no known occupational exposure to organic chemicals (Angerer et al. 1992, 1993). However, 4-CP and combined 2,3,4,6-TeCP and 2,3,5,6-TeCP urine concentrations were small but significantly higher in the control group, which included 88 people from urban communities, than in the incinerator workers. The investigators suggested that the higher 4-CP urine concentrations in the urban population were a result of atmospheric exposure to chlorobenzene, but they did not have an explanation for the higher tetrachlorophenol concentrations (Angerer et al. 1992).

An industrial hygiene investigation of workers exposed to chlorophenols at a sawmill indicated that dermal exposure was the most important route (Lindroos et al. 1987). The workers were exposed to a wood preservative that contained 80% 2,3,4,6-TeCP, 10–20% 2,4,6-TCP, and 5% pentachlorophenol.

Median urinary concentrations of total chlorophenols were 7.8 µmol/L in workers with the skin as the main route of exposure, 1.4 µmol/L in workers with combined inhalation and skin exposure, and 0.9 µmol/L in workers with inhalation as the principal route of exposure.

Table 5-7. Geometric Mean and Selected Percentiles of Urinary 2,4-Dichlorophenol Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2014

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total population	2003–2004	1.04 (0.895–1.21)	0.900 (0.800–1.10)	2.70 (2.30–3.10)	8.80 (6.60–11.9)	21.3 (14.1–29.5)	2,525
	2005–2006	0.945 (0.791–1.13)	0.800 (0.700–1.00)	2.00 (1.60–2.40)	4.90 (3.90–6.30)	11.9 (7.00–20.4)	2,548
	2007–2008	0.970 (0.852–1.11)	0.800 (0.700–.900)	1.80 (1.50–2.30)	5.10 (3.80–7.60)	12.6 (9.00–18.1)	2,604
	2009–2010	0.803 (0.729–.885)	0.700 (0.700–.800)	1.50 (1.40–1.70)	4.00 (3.30–5.00)	8.80 (6.40–15.7)	2,749
	2011–2012	0.695 (0.619–0.781)	0.600 (0.600–0.700)	1.30 (1.10–1.60)	3.50 (2.80–4.40)	9.00 (5.60–13.0)	2,489
	2013–2014	0.669 (0.603–0.743)	0.600 (0.500–0.700)	1.30 (1.20–1.40)	3.00 (2.70–3.50)	6.40 (4.80–11.5)	2,686
Age group							
Age 6–11 years	2003–2004	1.01 (0.796–1.28)	0.800 (0.600–1.20)	2.30 (1.70–3.20)	7.70 (3.80–20.1)	23.5 (9.40–31.0)	314
	2005–2006	1.01 (0.879–1.15)	0.800 (0.800–1.10)	2.00 (1.60–2.30)	4.90 (3.30–6.60)	9.80 (6.30–17.6)	356
	2007–2008	1.04 (0.778–1.39)	0.900 (0.700–1.20)	1.80 (1.20–2.80)	5.90 (2.90–10.1)	11.4 (6.60–20.7)	389
	2009–2010	0.975 (0.768–1.24)	0.700 (0.600–0.900)	1.80 (1.40–2.30)	5.00 (3.20–8.40)	14.2 (4.40–90.9)	415
	2011–2012	0.672 (0.558–0.810)	0.600 (0.400–0.700)	1.10 (1.00–1.40)	3.60 (1.90–5.50)	11.3 (4.10–23.2)	396
	2013–2014	0.773 (0.646–0.925)	0.700 (0.600–0.900)	1.20 (1.10–1.60)	2.90 (2.10–4.80)	8.90 (3.30–21.8)	409
Age 12–19 years	2003–2004	1.27 (0.971–1.67)	1.10 (0.800–1.50)	3.40 (2.50–5.00)	13.6 (6.10–25.5)	31.5 (14.5–85.0)	722
	2005–2006	1.18 (0.997–1.39)	1.00 (0.900–1.20)	2.50 (2.00–3.10)	5.50 (4.00–8.30)	13.9 (7.10–33.6)	702
	2007–2008	1.19 (0.989–1.44)	1.10 (0.800–1.40)	2.60 (2.00–3.00)	5.60 (3.10–10.8)	11.6 (5.70–36.5)	401
	2009–2010	0.967 (0.794–1.18)	0.800 (0.700–0.900)	1.60 (1.40–2.70)	5.80 (3.70–10.1)	14.4 (7.10–24.8)	420
	2011–2012	0.711 (0.591–0.857)	0.600 (0.500–0.800)	1.30 (1.00–1.50)	3.30 (2.10–5.80)	9.00 (4.10–13.0)	388
	2013–2014	0.668 (0.576–0.775)	0.600 (0.500–0.700)	1.10 (0.900–1.40)	2.40 (1.70–4.40)	7.30 (3.10–13.8)	462
Age 20+ years	2003–2004	1.01 (0.874–1.17)	0.900 (0.700–1.10)	2.60 (2.20–3.00)	8.50 (6.60–10.4)	19.4 (12.2–27.0)	1,489
	2005–2006	0.907 (0.737–1.12)	0.800 (0.600–1.00)	2.00 (1.50–2.40)	4.90 (3.70–6.40)	11.1 (6.50–20.9)	1,490
	2007–2008	0.932 (0.820–1.06)	0.800 (0.700–0.900)	1.70 (1.40–2.20)	5.00 (3.80–7.60)	13.2 (9.20–18.1)	1,814
	2009–2010	0.764 (0.699–0.836)	0.700 (0.600–0.700)	1.40 (1.30–1.60)	3.60 (3.10–4.50)	8.00 (5.60–13.9)	1,914
	2011–2012	0.695 (0.613–0.789)	0.600 (0.500–0.700)	10.30 (10.10–1.60)	3.50 (2.80–4.60)	9.00 (5.20–13.1)	1,705
	2013–2014	0.659 (0.593–0.732)	0.600 (0.500–0.700)	1.30 (1.20–1.40)	3.10 (2.70–3.50)	6.20 (4.90–10.8)	1,815

Table 5-7. Geometric Mean and Selected Percentiles of Urinary 2,4-Dichlorophenol Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2014

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2003–2004	1.22 (1.02–1.45)	1.10 (0.800–1.50)	3.00 (2.50–3.50)	9.40 (6.80–13.9)	22.7 (13.6–40.9)	1,231
	2005–2006	1.16 (0.973–1.37)	1.00 (0.900–1.20)	2.40 (2.00–2.80)	5.50 (4.40–7.90)	12.9 (7.30–25.3)	1,270
	2007–2008	1.06 (0.943–1.19)	0.900 (0.800–1.00)	1.90 (1.60–2.20)	5.40 (3.90–8.20)	13.6 (10.1–18.1)	1,294
	2009–2010	0.879 (0.789–0.979)	0.800 (0.700–0.800)	1.60 (1.40–1.80)	4.00 (3.20–5.70)	10.4 (5.20–18.4)	1,399
	2011–2012	0.717 (0.641–0.802)	0.600 (0.600–0.700)	1.30 (1.10–1.60)	3.20 (2.20–4.40)	7.10 (4.60–10.6)	1,259
	2013–2014	0.708 (0.637–0.786)	0.600 (0.600–0.700)	1.30 (1.10–1.60)	2.90 (2.60–3.30)	6.20 (4.10–11.3)	1,285
Females	2003–2004	0.896 (0.754–1.07)	0.800 (0.600–0.900)	2.30 (2.00–2.70)	8.10 (5.70–11.1)	19.8 (12.0–27.5)	1,294
	2005–2006	0.779 (0.637–0.954)	0.700 (0.500–0.800)	1.50 (1.30–2.10)	4.30 (2.80–6.20)	9.40 (5.40–19.6)	1,278
	2007–2008	0.893 (0.750–1.06)	0.700 (0.600–0.800)	1.80 (1.20–2.50)	4.70 (3.10–8.00)	11.9 (7.60–18.6)	1,310
	2009–2010	0.737 (0.659–0.824)	0.600 (0.600–0.700)	1.40 (1.30–1.70)	4.00 (3.00–5.50)	7.80 (5.80–15.8)	1,350
	2011–2012	0.675 (0.581–0.784)	0.600 (0.500–0.700)	1.20 (1.00–1.60)	3.80 (2.80–6.00)	11.1 (4.90–24.3)	1,230
	2013–2014	0.635 (0.553–0.729)	0.600 (0.500–0.700)	1.20 (1.10–1.40)	3.10 (2.50–4.10)	7.60 (4.40–12.3)	1,401
Race/ethnicity							
Mexican Americans	2003–2004	1.94 (1.46–2.56)	1.70 (1.20–2.10)	4.50 (2.80–9.30)	26.9 (12.7–52.1)	66.0 (47.5–84.2)	617
	2005–2006	1.97 (1.49–2.59)	1.60 (1.20–2.10)	5.00 (3.30–6.60)	20.9 (8.80–39.7)	46.5 (21.9–79.5)	637
	2007–2008	1.59 (0.969–2.60)	1.20 (0.600–2.60)	4.20 (2.10–9.50)	13.4 (7.90–29.6)	38.0 (16.4–74.0)	531
	2009–2010	1.25 (0.860–1.81)	0.900 (0.700–1.30)	2.70 (1.60–4.30)	11.3 (4.30–26.3)	29.1 (7.60–76.3)	566
	2011–2012	0.895 (0.720–10.11)	0.800 (0.600–10.00)	1.80 (1.30–2.60)	6.60 (3.50–10.5)	14.5 (7.40–27.0)	316
	2013–2014	0.807 (0.609–10.07)	0.600 (0.400–10.00)	1.70 (1.10–2.90)	4.00 (3.00–12.2)	14.6 (3.90–49.9)	438
Non–Hispanic blacks	2003–2004	2.42 (1.92–3.06)	2.20 (1.70–2.70)	7.40 (4.00–9.60)	20.8 (11.2–38.3)	49.2 (24.0–69.7)	636
	2005–2006	2.45 (1.93–3.12)	2.10 (1.70–2.40)	5.20 (3.90–7.40)	20.3 (10.6–36.9)	42.6 (21.3–129)	678
	2007–2008	1.73 (1.49–2.01)	1.40 (1.10–1.60)	3.70 (2.90–4.90)	17.8 (9.70–25.8)	37.7 (24.6–56.8)	597
	2009–2010	1.54 (1.06–2.23)	1.20 (0.800–2.00)	3.10 (2.10–4.80)	12.4 (4.30–46.4)	35.2 (7.80–107)	516
	2011–2012	10.23 (0.965–10.57)	0.900 (0.800–10.20)	2.20 (1.60–3.30)	6.90 (4.20–14.8)	25.0 (8.40–53.6)	665
	2013–2014	10.11 (0.791–10.54)	0.800 (0.700–10.10)	2.00 (1.40–3.30)	8.20 (3.00–28.2)	23.5 (6.50–81.9)	609

Table 5-7. Geometric Mean and Selected Percentiles of Urinary 2,4-Dichlorophenol Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2014

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non–Hispanic whites	2003–2004	0.837 (0.698–1.00)	0.700 (0.600–0.900)	2.10 (1.70–2.60)	6.20 (4.00–8.80)	13.4 (8.60–22.0)	1,077
	2005–2006	0.734 (0.610–0.883)	0.700 (0.500–0.900)	1.40 (1.20–1.80)	3.10 (2.70–3.90)	5.30 (4.30–7.90)	1,038
	2007–2008	0.817 (0.732–0.911)	0.700 (0.600–0.800)	1.50 (1.20–1.80)	3.10 (2.60–4.40)	6.40 (4.60–8.80)	1,077
	2009–2010	0.651 (0.594–0.712)	0.600 (0.500–0.700)	1.30 (1.10–1.40)	2.80 (2.20–3.50)	5.60 (3.80–7.40)	1,206
	2011–2012	0.577 (0.514–0.647)	0.500 (0.500–0.600)	1.00 (0.900–1.20)	2.50 (1.70–3.70)	4.90 (3.30–9.40)	813
	2013–2014	0.588 (0.525–0.659)	0.500 (0.500–0.600)	1.10 (1.00–1.30)	2.60 (2.30–2.90)	4.60 (3.10–5.50)	988
All Hispanics	2011–2012	0.981 (0.760–10.27)	0.800 (0.600–10.00)	2.10 (1.30–3.10)	6.10 (3.90–13.0)	15.9 (7.00–42.0)	571
	2013–2014	0.786 (0.641–0.965)	0.600 (0.500–0.800)	1.60 (1.20–2.10)	3.50 (3.10–7.80)	12.4 (4.20–26.1)	690
Asians	2011–2012	0.621 (0.478–0.807)	0.500 (0.400–0.700)	1.10 (0.800–1.60)	3.60 (1.70–7.10)	11.1 (3.50–17.7)	352
	2013–2014	0.567 (0.435–0.738)	0.500 (0.300–0.700)	1.20 (0.800–1.60)	2.70 (1.70–5.80)	7.30 (2.50–58.9)	289

[a]The LODs for survey years 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2104 are 0.17, 0.2, 0.2, 0.2, 0.2, and 0.1, respectively.

CI = confidence interval; LOD = limit of detection

Source: CDC 2019

Table 5-8. Geometric Mean and Selected Percentiles of Urinary 2,4-Dichlorophenol Concentrations (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2014

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total population	2003–2004	1.02 (0.873–1.18)	0.880 (0.770–1.00)	2.19 (1.84–2.73)	7.39 (5.00–9.83)	15.4 (11.1–20.9)	2,522
	2005–2006	0.922 (0.798–1.06)	0.750 (0.660–0.880)	1.58 (1.33–1.86)	4.00 (3.00–5.71)	8.90 (5.98–16.6)	2,548
	2007–2008	0.978 (0.867–1.10)	0.790 (0.700–0.880)	1.63 (1.36–1.89)	4.00 (3.14–5.63)	11.7 (6.82–18.9)	2,604
	2009–2010	0.838 (0.757–0.929)	0.680 (0.630–0.740)	1.33 (1.18–1.58)	3.48 (2.77–4.55)	8.17 (5.44–14.3)	2,749
	2011–2012	0.791 (0.706–0.886)	0.614 (0.560–0.690)	1.29 (1.08–1.48)	3.33 (2.67–4.57)	8.10 (5.65–11.2)	2,487
	2013–2014	0.668 (0.611–0.730)	0.556 (0.510–0.595)	1.13 (1.03–1.29)	2.73 (2.26–3.33)	5.96 (4.41–8.38)	2,684

Table 5-8. Geometric Mean and Selected Percentiles of Urinary 2,4-Dichlorophenol Concentrations (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2014

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Age group							
Age 6–11 years	2003–2004	1.23 (0.965–1.56)	1.03 (0.750–1.45)	2.39 (1.82–3.36)	9.29 (3.98–16.5)	20.9 (12.9–38.1)	314
	2005–2006	1.11 (0.950–1.29)	0.970 (0.800–1.08)	1.74 (1.38–2.19)	4.38 (3.33–7.80)	10.9 (5.12–23.3)	356
	2007–2008	1.28 (1.00–1.63)	1.06 (0.750–1.40)	2.06 (1.44–3.21)	4.49 (3.13–9.27)	11.2 (5.70–24.4)	389
	2009–2010	1.27 (0.986–1.64)	0.930 (0.820–1.20)	2.03 (1.54–2.94)	5.89 (3.50–11.0)	15.9 (5.71–121)	415
	2011–2012	0.964 (0.807–1.15)	0.741 (0.620–0.851)	1.38 (1.07–1.61)	3.51 (2.22–7.36)	12.4 (5.13–34.9)	395
	2013–2014	0.977 (0.833–1.14)	0.800 (0.698–0.909)	1.52 (1.20–1.94)	3.41 (2.22–6.60)	9.68 (4.48–23.7)	409
Age 12–19 years	2003–2004	0.954 (0.725–1.26)	0.790 (0.660–1.00)	2.08 (1.44–3.75)	8.02 (4.72–12.5)	14.8 (8.02–40.0)	720
	2005–2006	0.878 (0.765–1.01)	0.700 (0.600–0.800)	1.65 (1.22–1.93)	3.92 (2.90–4.82)	8.28 (4.82–15.9)	702
	2007–2008	0.927 (0.776–1.11)	0.790 (0.640–1.00)	1.51 (1.14–2.22)	3.81 (2.38–5.92)	10.3 (4.28–21.8)	401
	2009–2010	0.778 (0.656–0.921)	0.580 (0.510–0.690)	1.18 (0.970–1.40)	3.38 (2.11–6.27)	7.38 (3.39–19.4)	420
	2011–2012	0.693 (0.582–0.825)	0.545 (0.465–0.678)	1.15 (0.875–1.50)	2.73 (1.96–4.00)	4.82 (3.06–9.75)	388
	2013–2014	0.542 (0.472–0.623)	0.439 (0.385–0.519)	0.833 (0.678–1.13)	1.72 (1.31–3.08)	4.10 (2.45–5.27)	462
Age 20+ years	2003–2004	1.00 (0.863–1.16)	0.870 (0.770–1.00)	2.17 (1.80–2.69)	7.16 (4.88–9.01)	15.0 (10.6–20.8)	1,488
	2005–2006	0.909 (0.774–1.07)	0.740 (0.650–0.870)	1.55 (1.25–1.89)	4.00 (2.84–6.19)	8.80 (5.71–16.8)	1,490
	2007–2008	0.958 (0.847–1.08)	0.770 (0.670–0.880)	1.60 (1.32–1.85)	3.98 (3.14–5.59)	12.1 (8.15–18.9)	1,814
	2009–2010	0.810 (0.735–0.892)	0.670 (0.620–0.730)	1.27 (1.11–1.56)	3.33 (2.65–4.23)	7.64 (5.16–12.3)	1,914
	2011–2012	0.790 (0.694–0.898)	0.610 (0.556–0.675)	1.30 (1.07–1.54)	3.33 (2.55–4.77)	8.33 (5.75–11.3)	1,704
	2013–2014	0.661 (0.600–0.728)	0.538 (0.495–0.588)	1.14 (0.991–1.31)	2.77 (2.22–3.47)	5.96 (4.39–8.53)	1,813
Gender							
Males	2003–2004	0.995 (0.850–1.17)	0.900 (0.730–1.06)	2.23 (1.82–2.82)	6.84 (4.54–9.01)	13.7 (9.29–21.8)	1,230
	2005–2006	0.927 (0.814–1.06)	0.770 (0.670–0.880)	1.60 (1.36–1.86)	4.12 (3.08–5.45)	8.90 (5.19–16.6)	1,270
	2007–2008	0.891 (0.808–0.984)	0.720 (0.660–0.790)	1.44 (1.29–1.67)	4.00 (2.97–5.30)	9.96 (6.82–13.4)	1,294
	2009–2010	0.788 (0.706–0.879)	0.620 (0.580–0.660)	1.25 (1.06–1.48)	3.66 (2.52–5.47)	7.69 (4.84–16.9)	1,399
	2011–2012	0.670 (0.594–0.756)	0.538 (0.462–0.609)	1.08 (0.903–1.27)	2.89 (2.10–3.46)	5.65 (4.26–7.63)	1,258
	2013–2014	0.595 (0.550–0.642)	0.496 (0.455–0.538)	1.03 (0.906–1.12)	2.41 (2.11–2.77)	4.39 (3.06–7.65)	1,284

Table 5-8. Geometric Mean and Selected Percentiles of Urinary 2,4-Dichlorophenol Concentrations (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2014

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Females	2003–2004	1.03 (0.845–1.27)	0.870 (0.770–1.00)	2.17 (1.73–2.73)	8.00 (4.57–12.1)	17.2 (11.1–23.7)	1,292
	2005–2006	0.916 (0.770–1.09)	0.740 (0.640–0.880)	1.56 (1.19–1.96)	3.91 (2.66–6.50)	8.93 (5.53–23.7)	1,278
	2007–2008	1.07 (0.910–1.26)	0.850 (0.720–1.00)	1.75 (1.43–2.29)	4.07 (3.13–7.65)	14.4 (6.50–26.8)	1,310
	2009–2010	0.890 (0.789–1.00)	0.740 (0.660–0.850)	1.41 (1.24–1.67)	3.39 (2.76–4.52)	8.79 (5.16–14.8)	1,350
	2011–2012	0.928 (0.816–1.06)	0.714 (0.634–0.833)	1.45 (1.27–1.76)	4.02 (3.06–6.37)	11.2 (6.37–18.1)	1,229
	2013–2014	0.747 (0.667–0.836)	0.616 (0.560–0.676)	1.29 (1.11–1.43)	3.29 (2.37–4.15)	7.69 (4.69–12.6)	1,400
Race/ethnicity							
Mexican Americans	2003–2004	1.76 (1.30–2.38)	1.33 (1.04–1.74)	3.85 (2.29–8.81)	23.8 (10.6–51.6)	71.4 (30.8–88.8)	616
	2005–2006	1.77 (1.38–2.27)	1.25 (0.990–1.73)	3.79 (2.70–5.35)	16.6 (6.75–31.8)	38.1 (23.8–55.3)	637
	2007–2008	1.55 (0.925–2.60)	1.18 (0.630–2.28)	3.33 (1.93–6.50)	14.2 (5.65–30.6)	33.1 (16.6–60.0)	531
	2009–2010	1.24 (0.860–1.78)	0.910 (0.630–1.28)	2.03 (1.43–3.90)	11.0 (3.54–26.4)	26.4 (10.2–93.5)	566
	2011–2012	1.01 (0.856–1.19)	0.788 (0.620–1.04)	1.67 (1.50–2.14)	5.94 (3.50–9.36)	14.7 (6.16–33.3)	316
	2013–2014	0.823 (0.614–1.10)	0.632 (0.452–0.864)	1.43 (0.938–2.29)	6.25 (2.45–12.0)	13.5 (6.32–37.3)	438
Non-Hispanic blacks	2003–2004	1.66 (1.28–2.16)	1.47 (1.06–1.96)	4.14 (2.46–7.31)	14.9 (7.93–20.1)	22.9 (16.7–45.0)	635
	2005–2006	1.72 (1.39–2.14)	1.32 (1.11–1.56)	3.28 (2.33–5.35)	14.9 (7.40–28.1)	37.0 (15.0–83.4)	678
	2007–2008	1.34 (1.14–1.59)	0.990 (0.800–1.17)	2.36 (1.85–3.12)	13.1 (5.70–23.3)	33.8 (22.7–41.1)	597
	2009–2010	1.11 (0.739–1.67)	0.890 (0.630–1.19)	2.07 (1.25–3.87)	8.37 (2.99–22.0)	22.0 (7.05–83.1)	516
	2011–2012	0.959 (0.766–1.20)	0.737 (0.588–0.851)	1.56 (1.18–2.34)	5.26 (3.00–15.0)	19.9 (6.61–40.7)	665
	2013–2014	0.815 (0.617–1.08)	0.576 (0.500–0.704)	1.40 (0.952–2.30)	5.32 (2.37–14.7)	15.4 (4.69–51.3)	609
Non-Hispanic whites	2003–2004	0.864 (0.721–1.03)	0.780 (0.690–0.890)	1.86 (1.54–2.23)	5.08 (3.58–8.00)	10.8 (6.84–18.2)	1,076
	2005–2006	0.772 (0.660–0.904)	0.670 (0.580–0.790)	1.25 (1.07–1.56)	2.78 (2.11–3.52)	4.82 (3.33–8.62)	1,038
	2007–2008	0.853 (0.765–0.950)	0.730 (0.660–0.810)	1.36 (1.14–1.67)	2.97 (2.53–3.33)	5.16 (3.84–9.38)	1,077
	2009–2010	0.731 (0.674–0.793)	0.630 (0.580–0.690)	1.13 (1.01–1.25)	2.76 (2.29–3.30)	5.16 (3.79–6.46)	1,206
	2011–2012	0.700 (0.609–0.805)	0.563 (0.519–0.619)	1.08 (0.885–1.33)	2.89 (1.79–3.78)	5.75 (3.27–9.67)	811
	2013–2014	0.615 (0.557–0.679)	0.521 (0.476–0.570)	1.05 (0.906–1.24)	2.22 (1.88–2.78)	3.64 (3.01–5.71)	987
All Hispanics	2011–2012	1.10 (0.919–1.31)	0.870 (0.700–1.12)	2.00 (1.54–2.72)	5.70 (3.96–9.26)	14.7 (6.37–43.5)	571
	2013–2014	0.780 (0.628–0.970)	0.629 (0.508–0.774)	1.30 (0.980–1.98)	4.48 (3.03–6.81)	11.1 (6.16–23.8)	690

Table 5-8. Geometric Mean and Selected Percentiles of Urinary 2,4-Dichlorophenol Concentrations (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2014

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Asians	2011–2012	0.832 (0.629–1.10)	0.667 (0.513–0.952)	1.42 (1.01–2.12)	3.50 (2.31–7.82)	8.00 (3.50–17.0)	352
	2013–2014	0.720 (0.540–0.961)	0.588 (0.469–0.813)	1.38 (1.06–1.71)	3.51 (1.95–6.78)	7.65 (2.54–54.1)	288

[a]The LODs for survey years 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2104 are 0.17, 0.2, 0.2, 0.2, 0.2, and 0.1, respectively.

CI = confidence interval; LOD = limit of detection

Source: CDC 2019

Table 5-9. Geometric Mean and Selected Percentiles of Urinary 2,5-Dichlorophenol Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2014

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total population	2003–2004	12.9 (10.1–16.3)	10.5 (8.00–14.2)	40.9 (29.8–54.7)	190 (133–282)	705 (342–1,330)	2,525
	2005–2006	9.55 (6.67–13.7)	8.10 (5.60–11.5)	26.4 (19.0–36.6)	111 (69.9–166)	332 (175–794)	2,548
	2007–2008	9.04 (7.22–11.3)	6.60 (5.50–8.30)	25.7 (19.2–34.7)	131 (90.2–222)	473 (296–753)	2,604
	2009–2010	6.10 (4.94–7.53)	4.70 (3.70–5.90)	18.4 (13.3–26.0)	101 (68.0–146)	301 (168–618)	2,749
	2011–2012	4.21 (3.15–5.62)	3.10 (2.30–3.90)	13.4 (9.40–18.9)	69.9 (40.9–117)	213 (121–404)	2,489
	2013–2014	2.78 (2.15–3.59)	1.80 (1.40–2.50)	7.50 (5.30–11.4)	37.7 (23.8–58.0)	148 (78.4–266)	2,686
Age group							
Age 6–11 years	2003–2004	12.5 (8.22–18.9)	9.10 (5.60–17.4)	42.1 (21.7–83.9)	161 (111–626)	928 (249–1,640)	314
	2005–2006	10.5 (8.29–13.4)	7.80 (5.90–10.6)	28.1 (17.8–40.2)	104 (55.4–226)	336 (189–785)	356
	2007–2008	9.31 (6.20–14.0)	6.50 (4.60–10.9)	23.3 (12.2–45.6)	151 (61.1–306)	464 (222–934)	389
	2009–2010	7.19 (4.36–11.8)	4.80 (2.70–9.90)	30.4 (12.4–50.7)	146 (63.7–368)	503 (103–4,940)	415
	2011–2012	3.45 (2.11–5.64)	2.30 (1.60–3.30)	9.20 (4.40–21.2)	69.1 (27.8–168)	369 (99.9–986)	396
	2013–2014	2.90 (1.98–4.24)	2.00 (1.30–3.00)	8.20 (4.30–14.9)	29.6 (19.7–73.8)	123 (38.0–438)	409

Table 5-9. Geometric Mean and Selected Percentiles of Urinary 2,5-Dichlorophenol Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2014

			Selected percentiles (95% CI)				
	Survey years[a]	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
Age 12–19 years	2003–2004	16.9 (11.1–26.0)	11.5 (8.20–20.6)	49.9 (26.8–94.0)	233 (94.5–1,060)	1,080 (287–3,970)	722
	2005–2006	11.9 (8.47–16.8)	9.60 (6.40–16.7)	36.0 (22.3–54.4)	127 (89.9–160)	459 (160–894)	702
	2007–2008	11.3 (8.78–14.5)	7.40 (6.20–9.10)	30.1 (18.5–52.6)	193 (66.7–448)	611 (254–1,560)	401
	2009–2010	8.01 (5.53–11.6)	4.80 (3.50–8.80)	24.9 (19.1–42.7)	191 (61.2–368)	526 (243–1,140)	420
	2011–2012	4.15 (2.43–7.10)	3.20 (1.60–8.00)	14.0 (7.30–28.8)	55.7 (28.6–209)	236 (71.2–468)	388
	2013–2014	2.72 (1.75–4.24)	2.10 (1.30–3.30)	6.00 (3.80–14.0)	21.7 (10.6–77.7)	77.7 (21.7–315)	462
Age 20+ years	2003–2004	12.3 (9.97–15.3)	10.4 (8.00–14.0)	40.5 (30.1–49.2)	181 (141–250)	583 (316–924)	1,489
	2005–2006	9.12 (6.15–13.5)	7.80 (5.20–11.5)	24.9 (17.3–35.3)	110 (62.9–183)	327 (159–852)	1,490
	2007–2008	8.71 (6.83–11.1)	6.60 (5.10–8.70)	24.6 (18.8–34.5)	124 (95.9–186)	452 (286–672)	1,814
	2009–2010	5.75 (4.77–6.92)	4.60 (3.70–5.70)	16.9 (12.7–23.1)	88.4 (66.4–117)	266 (156–450)	1,914
	2011–2012	4.31 (3.21–5.78)	3.20 (2.30–4.10)	14.2 (9.40–19.2)	71.4 (39.5–118)	198 (118–408)	1,705
	2013–2014	2.78 (2.20–3.51)	1.80 (1.40–2.40)	7.80 (5.50–11.5)	42.7 (25.2–61.2)	169 (87.2–308)	1,815
Gender							
Males	2003–2004	14.9 (11.8–18.8)	12.5 (9.00–16.5)	40.5 (30.7–54.5)	152 (120–259)	631 (259–1,950)	1,231
	2005–2006	12.0 (8.55–16.7)	9.90 (7.80–13.8)	29.0 (21.8–40.5)	114 (71.7–200)	396 (175–916)	1,270
	2007–2008	10.9 (8.86–13.4)	8.30 (6.30–9.90)	29.4 (23.2–39.6)	139 (100–248)	546 (311–727)	1,294
	2009–2010	7.09 (5.68–8.85)	5.30 (4.40–6.70)	21.9 (15.2–33.5)	103 (63.3–191)	311 (133–736)	1,399
	2011–2012	4.42 (3.38–5.78)	3.30 (2.40–4.50)	13.2 (9.40–20.8)	55.5 (37.1–106)	194 (99.8–341)	1,259
	2013–2014	2.96 (2.31–3.80)	2.00 (1.50–2.60)	7.20 (5.20–11.5)	36.1 (23.1–52.6)	175 (77.6–250)	1,285
Females	2003–2004	11.2 (8.51–14.7)	8.50 (6.30–12.0)	42.8 (26.0–64.2)	212 (141–364)	732 (371–1,100)	1,294
	2005–2006	7.69 (5.17–11.4)	5.90 (3.90–9.40)	21.1 (14.3–35.7)	110 (60.5–183)	317 (141–794)	1,278
	2007–2008	7.57 (5.70–10.1)	5.50 (4.40–7.30)	20.6 (13.9–31.8)	118 (57.4–268)	442 (213–838)	1,310
	2009–2010	5.28 (4.17–6.69)	3.90 (3.00–5.10)	16.7 (12.1–22.1)	99.5 (58.2–156)	287 (158–591)	1,350
	2011–2012	4.01 (2.86–5.61)	2.80 (2.00–3.70)	13.9 (9.20–17.7)	83.3 (42.4–124)	352 (117–614)	1,230
	2013–2014	2.61 (1.96–3.48)	1.70 (1.30–2.50)	7.80 (5.20–11.9)	38.3 (21.6–63.8)	136 (63.2–376)	1,401
Race/ethnicity							
Mexican Americans	2003–2004	30.1 (19.2–47.2)	23.7 (14.7–39.8)	103 (57.4–156)	841 (282–2,040)	2,370 (2,040–3,710)	617
	2005–2006	32.2 (22.2–46.7)	23.0 (14.9–37.1)	120 (69.6–228)	867 (298–1,320)	1,630 (916–3,650)	637
	2007–2008	22.2 (9.88–49.8)	16.4 (5.40–60.7)	104 (35.2–364)	566 (313–1,710)	1,920 (672–3,460)	531
	2009–2010	13.0 (5.80–29.1)	10.3 (3.30–26.2)	53.6 (19.4–199)	361 (124–900)	998 (247–3,700)	566
	2011–2012	5.92 (3.36–10.4)	4.00 (2.20–8.40)	21.2 (14.2–42.7)	178 (58.4–341)	362 (119–1,130)	316
	2013–2014	4.60 (2.78–7.61)	2.70 (1.40–6.30)	14.5 (6.70–29.2)	90.5 (32.9–486)	584 (85.3–1,840)	438

Table 5-9. Geometric Mean and Selected Percentiles of Urinary 2,5-Dichlorophenol Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2014

		Geometric mean	Selected percentiles (95% CI)				Sample
	Survey years[a]	(95% CI)	50th	75th	90th	95th	size
Non-Hispanic blacks	2003–2004	54.0 (35.9–81.2)	43.9 (26.2–65.6)	159 (97.0–338)	817 (342–2,330)	2,330 (887–3,730)	636
	2005–2006	43.9 (33.2–58.1)	33.2 (25.3–47.6)	161 (79.9–255)	722 (360–1,370)	1,700 (886–6,440)	678
	2007–2008	27.4 (21.3–35.2)	18.5 (13.2–26.7)	102 (61.9–147)	682 (364–943)	1,490 (933–1,870)	597
	2009–2010	23.0 (13.0–40.8)	17.3 (8.00–42.7)	82.7 (38.6–168)	443 (119–2,180)	1,240 (273–4,940)	516
	2011–2012	16.6 (10.4–26.2)	13.4 (8.80–19.4)	47.9 (24.9–100)	227 (108–569)	759 (341–2,480)	665
	2013–2014	9.58 (5.03–18.2)	7.20 (3.90–14.2)	27.6 (15.6–70.7)	175 (51.4–874)	843 (150–3,710)	609
Non-Hispanic whites	2003–2004	8.94 (7.15–11.2)	7.80 (6.30–9.40)	25.9 (19.3–36.6)	115 (61.8–171)	255 (148–522)	1,077
	2005–2006	6.19 (4.18–9.17)	5.90 (3.80–9.20)	15.7 (11.4–21.9)	43.7 (31.2–73.1)	105 (62.2–166)	1,038
	2007–2008	6.24 (5.04–7.74)	5.10 (4.20–6.20)	15.4 (12.2–19.9)	49.8 (37.0–90.2)	142 (103–294)	1,077
	2009–2010	4.10 (3.22–5.21)	3.30 (2.60–4.40)	10.9 (8.10–15.5)	45.5 (29.0–82.7)	124 (79.3–215)	1,206
	2011–2012	2.78 (2.13–3.63)	2.00 (1.60–2.50)	7.40 (5.40–9.70)	34.4 (18.1–67.6)	112 (52.1–178)	813
	2013–2014	1.95 (1.54–2.46)	1.40 (1.10–1.90)	4.70 (3.30–6.50)	19.0 (12.8–25.9)	53.7 (25.2–131)	988
All Hispanics	2011–2012	7.96 (4.50–14.1)	6.30 (3.20–14.9)	29.1 (16.0–66.7)	196 (84.1–399)	536 (194–1,630)	571
	2013–2014	4.26 (2.84–6.40)	2.80 (1.50–5.00)	11.8 (7.20–22.4)	77.7 (42.7–236)	420 (112–807)	690
Asians	2011–2012	3.77 (2.17–6.53)	2.40 (1.40–5.40)	13.0 (5.40–43.4)	86.8 (38.6–160)	378 (86.8–810)	352
	2013–2014	2.66 (1.64–4.32)	1.70 (1.20–2.90)	6.20 (3.30–18.5)	50.3 (13.0–154)	154 (38.7–2,450)	289

[a]The LODs for survey years 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2104 are 0.12, 0.2, 0.2, 0.2, 0.2, and 0.1, respectively.

CI = confidence interval; LOD = limit of detection

Source: CDC 2019

Table 5-10. Geometric Mean and Selected Percentiles of Urinary 2,5-Dichlorophenol Concentrations (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2014

			Selected percentiles (95% CI)				
	Survey years[a]	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
Total population	2003–2004	12.5 (10.1–15.6)	9.29 (7.25–12.5)	34.4 (26.8–45.4)	141 (100–251)	578 (313–851)	2,522
	2005–2006	9.31 (6.70–12.9)	7.32 (5.33–10.2)	20.4 (14.8–30.5)	89.3 (54.9–176)	292 (176–640)	2,548
	2007–2008	9.12 (7.35–11.3)	6.24 (5.00–7.77)	24.2 (17.2–30.3)	109 (70.8–175)	409 (234–745)	2,604
	2009–2010	6.36 (5.07–7.99)	4.12 (3.31–5.16)	16.2 (11.7–22.8)	80.2 (59.5–127)	269 (144–505)	2,749
	2011–2012	4.80 (3.65–6.32)	3.19 (2.38–4.43)	11.4 (7.97–17.9)	66.4 (39.9–125)	215 (145–342)	2,487
	2013–2014	2.77 (2.12–3.62)	1.82 (1.43–2.40)	6.80 (4.62–9.72)	32.2 (21.9–45.5)	108 (58.4–270)	2,684
Age group							
Age 6–11 years	2003–2004	15.2 (9.93–23.1)	10.6 (5.87–26.7)	44.7 (28.9–80.0)	183 (95.3–617)	830 (330–2,150)	314
	2005–2006	11.6 (8.90–15.1)	8.00 (5.95–12.6)	24.7 (16.8–37.8)	129 (55.8–242)	419 (151–709)	356
	2007–2008	11.5 (7.95–16.5)	7.70 (5.41–11.7)	29.5 (19.6–50.9)	131 (59.9–239)	420 (170–1,110)	389
	2009–2010	9.36 (5.65–15.5)	6.25 (4.09–9.60)	33.9 (12.6–65.0)	177 (66.1–496)	536 (111–5,950)	415
	2011–2012	5.01 (3.10–8.09)	3.02 (2.00–5.00)	10.6 (5.53–21.7)	98.1 (32.9–166)	377 (125–1,180)	395
	2013–2014	3.66 (2.50–5.36)	2.41 (1.62–3.54)	9.73 (5.25–15.6)	37.6 (16.9–110)	172 (70.4–615)	409
Age 12–19 years	2003–2004	12.7 (8.50–18.9)	9.05 (6.17–13.3)	34.8 (18.6–67.0)	177 (67.0–516)	549 (187–2,120)	720
	2005–2006	8.88 (6.34–12.4)	6.91 (4.15–11.1)	23.4 (17.7–30.0)	78.0 (58.5–112)	279 (112–659)	702
	2007–2008	8.79 (6.81–11.4)	5.56 (4.42–7.50)	20.9 (13.8–34.9)	130 (41.8–251)	353 (158–799)	401
	2009–2010	6.44 (4.40–9.42)	4.05 (2.34–8.69)	19.4 (11.6–37.7)	121 (49.3–218)	257 (119–1,180)	420
	2011–2012	4.04 (2.51–6.52)	2.41 (1.54–5.34)	12.1 (5.67–27.6)	47.9 (26.3–99.5)	157 (55.1–324)	388
	2013–2014	2.21 (1.44–3.40)	1.53 (0.915–2.52)	5.16 (2.63–12.0)	22.7 (12.2–38.9)	54.2 (21.7–236)	462
Age 20+ years	2003–2004	12.2 (10.1–14.8)	9.13 (7.25–12.4)	32.7 (26.7–42.9)	140 (103–203)	552 (283–838)	1,488
	2005–2006	9.15 (6.43–13.0)	7.29 (5.29–10.0)	19.6 (14.2–30.4)	90.7 (48.5–197)	274 (163–701)	1,490
	2007–2008	8.94 (7.07–11.3)	6.15 (4.93–8.00)	24.3 (16.6–30.6)	101 (70.0–162)	422 (234–729)	1,814
	2009–2010	6.09 (4.97–7.45)	3.97 (3.27–4.78)	14.7 (11.0–20.5)	72.5 (56.6–97.2)	261 (141–446)	1,914
	2011–2012	4.90 (3.67–6.56)	3.33 (2.50–4.51)	11.5 (8.04–18.0)	70.3 (38.8–136)	226 (145–342)	1,704
	2013–2014	2.78 (2.15–3.59)	1.81 (1.44–2.29)	6.67 (4.62–9.47)	32.6 (21.1–51.0)	126 (58.4–325)	1,813

Table 5-10. Geometric Mean and Selected Percentiles of Urinary 2,5-Dichlorophenol Concentrations (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2014

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2003–2004	12.2 (9.73–15.3)	9.65 (7.23–12.7)	32.7 (25.3–39.1)	108 (79.0–183)	358 (161–1,080)	1,230
	2005–2006	9.60 (7.17–12.9)	8.11 (5.95–10.5)	20.5 (15.9–28.2)	74.9 (50.5–141)	249 (137–534)	1,270
	2007–2008	9.17 (7.63–11.0)	6.24 (5.22–7.81)	25.5 (19.7–32.4)	110 (70.7–167)	353 (234–572)	1,294
	2009–2010	6.36 (5.04–8.02)	4.21 (3.36–4.97)	16.7 (11.7–24.0)	83.2 (53.7–141)	280 (111–727)	1,399
	2011–2012	4.15 (3.14–5.49)	2.87 (2.14–4.13)	9.73 (6.88–16.1)	52.8 (31.4–106)	157 (125–233)	1,258
	2013–2014	2.49 (1.93–3.22)	1.69 (1.23–2.22)	5.49 (4.18–8.11)	27.4 (19.6–45.8)	88.7 (58.4–160)	1,284
Females	2003–2004	12.9 (9.91–16.8)	8.95 (6.98–13.2)	37.1 (26.7–56.9)	209 (124–362)	660 (408–940)	1,292
	2005–2006	9.04 (6.18–13.2)	6.60 (4.56–10.4)	20.4 (14.1–33.8)	104 (55.8–199)	309 (149–933)	1,278
	2007–2008	9.07 (6.91–11.9)	6.08 (4.71–8.04)	22.4 (14.7–30.6)	107 (59.2–216)	509 (185–908)	1,310
	2009–2010	6.37 (4.92–8.25)	4.10 (3.09–5.69)	15.6 (11.3–22.1)	77.1 (53.3–148)	267 (151–481)	1,350
	2011–2012	5.53 (4.14–7.37)	3.39 (2.57–5.00)	13.1 (8.84–19.5)	90.1 (45.2–147)	331 (145–557)	1,229
	2013–2014	3.07 (2.30–4.09)	1.96 (1.52–2.54)	8.22 (5.07–11.9)	33.8 (21.7–56.2)	140 (50.4–374)	1,400
Race/ethnicity							
Mexican Americans	2003–2004	27.3 (17.4–42.9)	17.8 (9.86–36.3)	79.8 (45.8–138)	809 (196–2,110)	2,200 (1,250–2,480)	616
	2005–2006	29.0 (20.5–41.0)	18.6 (12.9–27.3)	99.4 (61.6–165)	675 (296–1,400)	1,680 (718–2,720)	637
	2007–2008	21.6 (9.44–49.6)	16.4 (5.09–58.9)	83.9 (30.8–281)	572 (182–1,490)	1,490 (700–2,220)	531
	2009–2010	12.9 (5.78–28.8)	9.12 (3.38–26.7)	45.0 (17.3–236)	460 (105–1,000)	1,000 (380–2,800)	566
	2011–2012	6.67 (4.04–11.0)	4.85 (2.25–8.69)	22.4 (12.6–37.6)	189 (49.2–249)	383 (213–981)	316
	2013–2014	4.68 (2.72–8.06)	2.47 (1.36–5.71)	14.5 (7.24–25.0)	91.8 (26.9–559)	559 (89.0–1,330)	438
Non-Hispanic blacks	2003–2004	37.1 (24.3–56.7)	27.4 (17.5–47.7)	103 (63.8–216)	609 (248–1,210)	1,240 (627–2,430)	635
	2005–2006	30.9 (23.6–40.3)	20.5 (17.3–29.1)	104 (57.7–180)	480 (294–1,080)	1,480 (515–3,100)	678
	2007–2008	21.3 (16.2–27.9)	14.6 (10.2–19.7)	64.6 (48.0–101)	529 (217–884)	1,130 (793–1,560)	597
	2009–2010	16.7 (9.19–30.2)	12.5 (6.74–22.0)	58.9 (22.3–106)	349 (92.6–878)	878 (277–3,890)	516
	2011–2012	12.9 (8.32–19.9)	9.41 (6.35–15.1)	34.5 (18.1–75.0)	174 (83.7–567)	744 (236–1,790)	665
	2013–2014	7.07 (3.87–12.9)	5.62 (2.55–10.4)	21.2 (10.0–54.1)	128 (32.7–527)	415 (103–2,580)	609
Non-Hispanic whites	2003–2004	9.24 (7.48–11.4)	7.14 (5.67–8.76)	24.8 (18.7–31.7)	79.7 (50.2–141)	216 (124–516)	1,076
	2005–2006	6.52 (4.51–9.43)	5.60 (3.86–8.51)	14.1 (10.7–19.7)	40.2 (28.4–61.6)	110 (47.3–224)	1,038
	2007–2008	6.52 (5.26–8.07)	4.89 (3.95–6.20)	14.4 (11.4–19.2)	53.2 (40.1–75.9)	131 (82.5–249)	1,077

Table 5-10. Geometric Mean and Selected Percentiles of Urinary 2,5-Dichlorophenol Concentrations (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2014

			Selected percentiles (95% CI)				
	Survey years[a]	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
	2009–2010	4.60 (3.59–5.90)	3.27 (2.77–4.10)	10.4 (7.22–15.2)	41.3 (25.0–69.1)	130 (73.4–180)	1,206
	2011–2012	3.40 (2.57–4.49)	2.36 (1.76–3.19)	6.96 (4.70–9.67)	34.5 (16.4–80.1)	126 (55.3–232)	811
	2013–2014	2.03 (1.53–2.69)	1.48 (1.13–1.91)	4.15 (2.96–6.34)	18.2 (10.6–32.5)	45.8 (26.0–86.3)	987
All Hispanics	2011–2012	8.92 (5.45–14.6)	6.55 (3.50–13.8)	28.8 (16.6–53.6)	184 (97.2–266)	383 (213–1,240)	571
	2013–2014	4.23 (2.77–6.47)	2.50 (1.41–5.07)	11.5 (6.84–18.7)	84.6 (32.2–226)	401 (135–993)	690
Asians	2011–2012	5.05 (2.93–8.69)	2.99 (1.74–7.04)	15.3 (6.51–45.6)	106 (58.7–177)	236 (97.5–632)	352
	2013–2014	3.40 (2.10–5.52)	2.06 (1.33–3.26)	8.99 (3.21–20.8)	45.2 (17.3–158)	207 (32.6–3,020)	288

[a]The LODs for survey years 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2104 are 0.12, 0.2, 0.2, 0.2, 0.2, and 0.1, respectively.

CI = confidence interval; LOD = limit of detection

Source: CDC 2019

Table 5-11. Geometric Mean and Selected Percentiles of Urinary 2,4,5-Trichlorophenol Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2010

			Selected percentiles (95% CI)				
	Survey years[a]	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
Total population	1999–2000	*	<LOD	1.40 (1.00–3.20)	(5.40 (2.50–16.0)	16.0 (4.3–40.0)	1,994
	2001–2002	*	<LOD	<LOD	<LOD	2.42 (<LOD–8.27)	2,497
	2003–2004	*	<LOD	0.100 (0.100–0.100)	0.200 (0.200–0.300)	0.400 (0.300–0.400)	2,525
	2005–2006	*	<LOD	0.100 (0.100–0.200)	0.300 (0.200–0.300)	0.400 (0.300–0.500)	2,548
	2007–2008	*	<LOD	0.100 (<LOD–0.100)	0.200 (0.200–0.200)	0.300 (0.200–0.300)	2,604
	2009–2010	*	<LOD	<LOD	0.200 (0.200–0.200)	0.300 (0.200–0.300)	2,749

Table 5-11. Geometric Mean and Selected Percentiles of Urinary 2,4,5-Trichlorophenol Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2010

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Age group							
Age 6–11 years	1999–2000	*	<LOD	1.4 (1.10–3.40)	4.80 (2.30–11.0)	11/0 (4.20–36.0)	482
	2001–2002	*	<LOD	<LOD	<LOD	2.42 (<LOD–12.7)	570
	2003–2004	*	<LOD	0.100 (0.100–0.200)	0.200 (0.200–0.300)	0.300 (0.200–0.500)	314
	2005–2006	*	<LOD	0.100 (0.100–0.200)	0.300 (0.200–0.400)	0.400 (0.300–0.500)	356
	2007–2008	*	<LOD	0.100 (<LOD–0.100)	0.200 (0.100–0.300)	0.300 (0.200–0.500)	389
	2009–2010	*	<LOD	<LOD	0.200 (0.100–0.200)	0.200 (0.200–0.300)	415
Age 12–19 years	1999–2000	*	<LOD	1.60 (0.940–3.72)	5.40 (2.5–25.0)	24.0 (3.80–41.0)	681
	2001–2002	*	<LOD	<LOD	<LOD	2.19 (<LOD–6.63)	815
	2003–2004	*	<LOD	0.100 (0.100–0.200)	0.200 (0.200–0.300)	0.300 (0.200–0.500)	722
	2005–2006	*	<LOD	0.100 (0.100–0.200)	0.300 (0.200–0.300)	0.400 (0.300–0.500)	702
	2007–2008	*	<LOD	0.100 (<LOD–0.100)	0.200 (0.100–0.200)	0.200 (0.200–0.500)	401
	2009–2010	*	<LOD	0.100 (<LOD–0.100)	0.200 (0.200–0.300)	0.300 (0.200–0.500)	420
Age 20+ years	1999–2000	*	<LOD	1.40 (0.980–3.30)	5.40 (2.40–18.0)	18.0 (4.3–44.0)	831
	2001–2002	*	<LOD	<LOD	<LOD	2.71 (<LOD–8.27)	1,112
	2003–2004	*	<LOD	0.100 (0.100–0.100)	0.300 (0.200–0.300)	0.400 (0.300–0.500)	1,489
	2005–2006	*	<LOD	0.100 (0.100–0.200)	0.300 (0.200–0.300)	0.400 (0.300–0.500)	1,490
	2007–2008	*	<LOD	0.100 (<LOD–0.100)	0.200 (0.200–0.300)	0.300 (0.200–0.400)	1,814
	2009–2010	*	<LOD	<LOD	0.200 (0.200–0.200)	0.300 (0.200–0.300)	1,914
Gender							
Males	1999–2000	*	<LOD	1.40 (0.980–3.80)	5.4 (2.60–8.40)	11.0 (5.30–27.0)	973
	2001–2002	*	<LOD	<LOD	<LOD	5.57 (<LOD–15.8)	1,178
	2003–2004	*	<LOD	0.100 (0.100–0.100)	0.200 (0.200–0.300)	0.400 (0.300–0.400)	1,231
	2005–2006	*	<LOD	0.100 (0.100–0.200)	0.200 (0.200–0.300)	0.400 (0.300–0.500)	1,270
	2007–2008	*	<LOD	0.100 (<LOD–0.100)	0.200 (0.200–0.200)	0.300 (0.200–0.300)	1,294
	2009–2010	*	<LOD	<LOD	0.200 (0.200–0.200)	0.300 (0.200–0.300)	1,399

Table 5-11. Geometric Mean and Selected Percentiles of Urinary 2,4,5-Trichlorophenol Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2010

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Females	1999–2000	*	<LOD	1.50 (1.00–3.20)	6.50 (2.30–27.0)	21.0 (3.20–71.0)	1,021
	2001–2002	*	<LOD	<LOD	<LOD	<LOD	1,319
	2003–2004	*	<LOD	0.100 (0.100–0.200)	0.200 (0.200–0.300)	0.400 (0.300–0.400)	1,294
	2005–2006	*	<LOD	0.100 (0.100–0.200)	0.300 (0.200–0.400)	0.500 (0.300–0.500)	1,278
	2007–2008	*	<LOD	0.100 (<LOD–0.100)	0.200 (0.200–0.300)	0.300 (0.200–0.400)	1,310
	2009–2010	*	<LOD	0.100 (<LOD–0.100)	0.200 (0.200–0.200)	0.300 (0.200–0.300)	1,350
Race/ethnicity							
Mexican Americans	1999–2000	*	0.950 (<LOD–1.30)	1.80 (1.30–3.50)	8.60 (4.60–18.0)	21.0 (8.90–33.0)	696
	2001–2002	*	<LOD	<LOD	<LOD	14.9 (<LOD–121)	661
	2003–2004	*	<LOD	0.100 (<LOD–0.200)	0.200 (0.200–0.300)	0.300 (0.200–0.400)	617
	2005–2006	*	<LOD	0.100 (<LOD–0.200)	0.300 (0.200–0.300)	0.400 (0.300–0.500)	637
	2007–2008	*	<LOD	<LOD	0.200 (0.100–0.200)	0.200 (0.200–0.300)	531
	2009–2010	*	<LOD	<LOD	0.100 (<LOD–0.200)	0.200 (0.100–0.300)	566
Non-Hispanic blacks	1999–2000	*	<LOD	1.30 (0.900–2.20)	5.00 (2.00–8.40)	9.00 (3.50–63.0)	521
	2001–2002	*	<LOD	<LOD	<LOD	2.31 (<LOD–9.03)	696
	2003–2004	*	<LOD	0.200 (0.100–0.200)	0.300 (0.200–0.500)	0.400 (0.300–0.700)	636
	2005–2006	*	<LOD	0.200 (0.100–0.200)	0.300 (0.200–0.400)	0.500 (0.300–0.500)	678
	2007–2008	*	<LOD	0.100 (0.100–0.200)	0.200 (0.200–0.300)	0.400 (0.300–0.500)	597
	2009–2010	*	<LOD	0.100 (<LOD–0.100)	0.200 (0.200–0.200)	0.200 (0.200–0.300)	516
Non-Hispanic whites	1999–2000	*	<LOD	1.5 (0.920–3.60)	4.60 (2.40–11.0)	9.20 (4.30–27.0)	603
	2001–2002	*	<LOD	<LOD	<LOD	2.71 (<LOD–8.27)	939
	2003–2004	*	<LOD	0.100 (0.100–0.100)	0.200 (0.200–0.300)	0.400 (0.300–0.400)	1,077
	2005–2006	*	<LOD	0.100 (0.100–0.200)	0.300 (0.200–0.300)	0.400 (0.300–0.600)	1,038
	2007–2008	*	<LOD	0.100 (<LOD–0.100)	0.200 (0.200–0.300)	0.300 (0.200–0.400)	1,077
	2009–2010	*	<LOD	<LOD	0.200 (0.200–0.200)	0.300 (0.200–0.300)	1,206

[a]The LODs for survey years 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, and 2009–2010 are 0.9, 0.9, 0.1, 0.1, 0.1, and 0.1, respectively.

* = not calculated; the proportion of results below the LOD was too high to provide a valid result; CI = confidence interval; LOD = limit of detection

Source: CDC 2009, 2019

Table 5-12. Geometric Mean and Selected Percentiles of Urinary 2,4,5-Trichlorophenol Concentrations (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2010

		Geometric mean	Selected percentiles (95% CI)				Sample
	Survey years[a]	(95% CI)	50th	75th	90th	95th	size
Total population	1999–2000	*	<LOD	2.36 (1.53–3.16)	5.57 (3.24–11.2)	11.9 (5.00–19.6)	1,994
	2001–2002	*	<LOD	<LOD	<LOD	457 (<LOD–7.11)	2,496
	2003–2004	*	<LOD	0.170 (0.160–0.180)	0.280 (0.260–0.310)	0.370 (0.330–0.420)	2,522
	2005–2006	*	<LOD	0.160 (0.150–0.180)	0.290 (0.260–0.320)	0.410 (0.360–0.450)	2,548
	2007–2008	*	<LOD	0.150 (<LOD–0.160)	0.280 (0.230–0.320)	0.390 (0.330–0.470)	2,604
	2009–2010	*	<LOD	<LOD	0.260 (0.240–0.280)	0.350 (0.320–0.390)	2,749
Age group							
Age 6–11 years	1999–2000	*	<LOD	2.29 (1.19–4.78)	5.86 (3.8312.4)	12.8 (5.28–25.4)	482
	2001–2002	*	<LOD	<LOD	<LOD	5.82 (<LOD–32.5)	570
	2003–2004	*	<LOD	0.180 (0.150–0.230)	0.290 (0.250–0.320)	0.370 (0.310–0.540)	314
	2005–2006	*	<LOD	0.180 (0.140–0.200)	0.310 (0.210–0.450)	0.450 (0.320–0.610)	356
	2007–2008	*	<LOD	0.180 (<LOD–0.190)	0.270 (0.210–0.390)	0.430 (0.270–0.580)	389
	2009–2010	*	<LOD	<LOD	0.320 (0.240–0.350)	0.390 (0.320–0.470)	415
Age 12–19 years	1999–2000	*	<LOD	1.44 (0.920–2.50)	3.80 (1.93–11.2)	11.2 (2.62–20.1)	681
	2001–2002	*	<LOD	<LOD	<LOD	2.75 (<LOD–6.74)	814
	2003–2004	*	<LOD	0.120 (0.100–0.140)	0.200 (0.170–0.220)	0.240 (0.220–0.280)	720
	2005–2006	*	<LOD	0.120 (0.110–0.130)	0.210 (0.180–0.240)	0.290 (0.240–0.330)	702
	2007–2008	*	<LOD	0.100 (<LOD–0.120)	0.170 (0.150–0.210)	0.250 (0.170–0.310)	401
	2009–2010	*	<LOD	0.110 (<LOD–0.130)	0.190 (0.150–0.250)	0.280 (0.190–0.380)	420
Age 20+ years	1999–2000	*	<LOD	2.46 (1.60–3.24)	5.75 (3.37–11.5)	11.7 (4.78–19.6)	831
	2001–2002	*	<LOD	<LOD	<LOD	4.57 (<LOD–7.11)	1,112
	2003–2004	*	<LOD	0.180 (0.160–0.180)	0.290 (0.270–0.320)	0.390 (0.350–0.470)	1,488
	2005–2006	*	<LOD	0.170 (0.150–0.190)	0.300 (0.260–0.330)	0.410 (0.370–0.470)	1,490
	2007–2008	*	<LOD	0.150 (<LOD–0.180)	0.290 (0.230–0.350)	0.410 (0.340–0.500)	1,814
	2009–2010	*	<LOD	<LOD	0.270 (0.240–0.280)	0.350 (0.320–0.410)	1,914

Table 5-12. Geometric Mean and Selected Percentiles of Urinary 2,4,5-Trichlorophenol Concentrations (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2010

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	1999–2000	*	<LOD	1.67 (1.02–3.15)	4.24 (3.05–8.02)	9.55 (4.13–13.6)	973
	2001–2002	*	<LOD	<LOD	<LOD	4.68 (<LOD–8.37)	1,178
	2003–2004	*	<LOD	0.130 (0.110–0.150)	0.230 (0.190–0.260)	0.320 (0.270–0.350)	1,230
	2005–2006	*	<LOD	0.130 (0.120–0.140)	0.220 (0.190–0.240)	0.310 (0.260–0.360)	1,270
	2007–2008	*	<LOD	0.110 (<LOD–0.120)	0.190 (0.180–0.230)	0.300 (0.230–0.340)	1,294
	2009–2010	*	<LOD	<LOD	0.210 (0.190–0.230)	0.280 (0.240–0.330)	1,399
Females	1999–2000	*	<LOD	2.67 (1.79–4.00)	7.95 (3.05–17.8)	16.3 (5.00–29.3)	1,021
	2001–2002	*	<LOD	<LOD	<LOD	<LOD	1,318
	2003–2004	*	<LOD	0.200 (0.180–0.210)	0.320 (0.290–0.350)	0.440 (0.350–0.510)	1,292
	2005–2006	*	<LOD	0.210 (0.180–0.230)	0.350 (0.300–0.410)	0.470 (0.410–0.550)	1,278
	2007–2008	*	<LOD	0.190 (<LOD–0.230)	0.330 (0.280–0.410)	0.470 (0.370–0.580)	1,310
	2009–2010	*	<LOD	0.180 (<LOD–0.190)	0.300 (0.280–0.330)	0.420 (0.330–0.470)	1,350
Race/ethnicity							
Mexican Americans	1999–2000	*	0.980 (<LOD–1.33)	2.49 (1.68–4.24)	6.90 (4.19–12.4)	12.4 (6.88–16.9)	696
	2001–2002	*	<LOD	<LOD	<LOD	12.1 (<LOD–58.0)	661
	2003–2004	*	<LOD	0.140 (<LOD–0.150)	0.240 (0.200–0.280)	0.330 (0.280–0.460)	616
	2005–2006	*	<LOD	0.140 (<LOD–0.160)	0.240 (0.190–0.320)	0.350 (0.290–0.380)	637
	2007–2008	*	<LOD	<LOD	0.210 (0.180–0.250)	0.270 (0.240–0.320)	531
	2009–2010	*	<LOD	<LOD	0.190 (<LOD–0.230)	0.290 (0.220–0.330)	566
Non-Hispanic blacks	1999–2000	*	<LOD	1.16 (0.820–2.31)	3.43 (2.20–6.32)	7.96 (2.69–18.2)	521
	2001–2002	*	<LOD	<LOD	<LOD	2.81 (<LOD–9.17)	695
	2003–2004	*	<LOD	0.120 (0.100–0.150)	0.230 (0.170–0.290)	0.310 (0.230–0.390)	635
	2005–2006	*	<LOD	0.110 (0.100–0.140)	0.210 (0.170–0.260)	0.320 (0.260–0.360)	678
	2007–2008	*	<LOD	0.120 (0.100–0.140)	0.200 (0.170–0.250)	0.290 (0.230–0.420)	597
	2009–2010	*	<LOD	0.090 (<LOD–0.110)	0.160 (0.130–0.200)	0.220 (0.160–0.380)	516

Table 5-12. Geometric Mean and Selected Percentiles of Urinary 2,4,5-Trichlorophenol Concentrations (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2010

			Selected percentiles (95% CI)				
	Survey years[a]	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
Non-Hispanic whites	1999–2000	*	<LOD	2.44 (1.53–3.24)	4.78 (3.47–8.43	9.64 (4.27–17.8)	603
	2001–2002	*	<LOD	<LOD	<LOD	4.73 (<LOD–8.37)	939
	2003–2004	*	<LOD	0.180 (0.160–0.190)	0.290 (0.260–0.320)	0.370 (0.340–0.440)	1,076
	2005–2006	*	<LOD	0.180 (0.160–0.190)	0.300 (0.270–0.350)	0.410 (0.360–0.500)	1,038
	2007–2008	*	<LOD	0.160 (<LOD–0.190)	0.300 (0.250–0.360)	0.440 (0.330–0.510)	1,077
	2009–2010	*	<LOD	<LOD	0.280 (0.250–0.320)	0.370 (0.330–0.410)	1,206

[a]The LODs for survey years 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, and 2009–2010 are 0.9, 0.9, 0.1, 0.1, 0.1, and 0.1, respectively.

* = not calculated; the proportion of results below the LOD was too high to provide a valid result; CI = confidence interval; LOD = limit of detection

Source: CDC 2009, 2019

Table 5-13. Geometric Mean and Selected Percentiles of Urinary 2,4,6-Trichlorophenol Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2010

			Selected percentiles (95% CI)				
	Survey years[a]	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
Total population	1999–2000	2.85 (2.55–3.18)	2.50 (2.40–2.70)	4.9 (3.80–7.70)	15.0 (7.80–25.0)	25.0 (15.0–44.0)	1,989
	2001–2002	*	1.68 (<LOD–2.44)	5.95 (4.89–6.63)	10.8 (9.98–11.7)	14.9 (13.4–17.9)	2,502
	2003–2004	*	<LOD	0.500 (<LOD–0.600)	1.00 (0.800–1.20)	1.40 (1.20–1.80)	2,525
	2005–2006	*	<LOD	0.600 (<LOD–0.700)	1.00 (0.800–1.20)	1.40 (1.20–1.80)	2,548
	2007–2008	*	<LOD	<LOD	0.800 (0.700–0.900)	1.20 (1.00–1.30)	2,604
	2009–2010	*	<LOD	0.500 (<LOD–0.600)	0.800 (0.700–0.900)	1.10 (1.00–1.40)	2,749

Table 5-13. Geometric Mean and Selected Percentiles of Urinary 2,4,6-Trichlorophenol Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2010

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Age group							
Age 6–11 years	1999–2000	4.47 (3.36–5.95)	3.80 (2.70–6.40)	11.0 (4.80–20.0)	24.0 (14.0–38.0)	33.0 (20.5–46.0)	481
	2001–2002	3.08 (2.52–3.76)	3.00 (1.91–4.32)	7.79 (5.73–9.99)	13.4 (10.6–17.3)	19.2 (14.1–25.3)	574
	2003–2004	*	<LOD	0.600 (0.500–0.700)	1.10 (0.800–1.40)	1.90 (1.10–3.10)	314
	2005–2006	*	<LOD	0.700 (0.600–0.900)	1.30 (1.00–2.30)	2.70 (1.30–5.40)	356
	2007–2008	*	<LOD	0.600 (<LOD–0.700)	1.10 (0.900–1.40)	1.60 (1.30–2.10)	389
	2009–2010	*	<LOD	0.500 (<LOD–0.600)	0.900 (0.700–1.20)	1.30 (0.900–2.20)	415
Age 12–19 years	1999–2000	3.56 (3.0–4.23)	3.00 (2.60–3.70)	6.00 (4.30–11.0)	20.4 (9.60–37.0)	37.0 (20.0–54.0)	678
	2001–2002	3.24 (2.74–3.84)	3.26 (2.33–4.40)	7.49 (6.45–9.40)	13.6 (11.0–18.2)	19.4 (17.3–26.6)	820
	2003–2004	*	<LOD	0.600 (0.500–0.800)	1.20 (0.900–1.70)	1.80 (1.50–2.10)	722
	2005–2006	*	<LOD	0.600 (<LOD–0.800)	1.00 (0.800–1.30)	1.30 (1.20–1.70)	702
	2007–2008	*	<LOD	0.600 (<LOD–0.700)	0.800 (0.700–1.10)	1.10 (0.800–1.70)	401
	2009–2010	*	<LOD	0.600 (<LOD–0.700)	0.900 (0.700–1.30)	1.30 (0.900–1.90)	420
Age 20+ years	1999–2000	2.52 (2.23–2.85)	2.40 (2.10–2.45)	4.20 (3.50–5.30)	12.0 (6.00–21.0)	21.0 (11.0–41.0)	830
	2001–2002	*	<LOD	4.89 (3.70–6.28)	9.66 (8.72–10.7)	13.3 (11.8–15.2)	1,109
	2003–2004	*	<LOD	0.500 (<LOD–0.600)	1.00 (0.800–1.10)	1.30 (1.10–1.70)	1,489
	2005–2006	*	<LOD	0.600 (<LOD–0.700)	1.00 (0.800–1.20)	1.30 (1.20–1.80)	1,490
	2007–2008	*	<LOD	<LOD	0.800 (0.700–0.900)	1.10 (0.900–1.30)	1,814
	2009–2010	*	<LOD	<LOD	0.800 (0.700–0.900)	1.10 (1.00–1.20)	1,914
Gender							
Males	1999–2000	2.92 (2.58–3.31)	2.60 (2.40–2.90)	5.20 (3.90–8.10)	15.0 (8.48–26.0)	26.0 (15.0–38.0)	970
	2001–2002	*	2.36 (1.70–3.04)	6.65 (5.98–7.53)	12.1 (10.8–13.1)	17.0 (13.6–22.2)	1,178
	2003–2004	*	<LOD	0.600 (<LOD–0.600)	1.00 (0.800–1.10)	1.30 (1.10–1.80)	1,231
	2005–2006	*	<LOD	0.600 (<LOD–0.800)	1.10 (0.900–1.30)	1.60 (1.20–2.00)	1,270
	2007–2008	*	<LOD	0.500 (<LOD–0.600)	0.900 (0.700–1.00)	1.20 (1.10–1.40)	1,294
	2009–2010	*	<LOD	<LOD	0.800 (0.700–0.900)	1.10 (1.00–1.20)	1,399

Table 5-13. Geometric Mean and Selected Percentiles of Urinary 2,4,6-Trichlorophenol Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2010

			Selected percentiles (95% CI)				
	Survey years[a]	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
Females	1999–2000	2.78 (2.35–3.28)	2.40 (2.30–2.60)	4.80 (3.40–7.59)	16.0 (6.40–32.0)	25.0 (14.0–50.0)	1,019
	2001–2002	*	<LOD	4.69 (3.59–6.09)	9.75 (8.25–11.6)	13.3 (11.7–16.6)	1,325
	2003–2004	*	<LOD	0.500 (<LOD–0.600)	1.10 (0.900–1.20)	1.40 (1.10–2.00)	1,294
	2005–2006	*	<LOD	0.500 (<LOD–0.600)	0.900 (0.800–1.20)	1.30 (1.10–1.70)	1,278
	2007–2008	*	<LOD	<LOD	0.800 (0.700–0.900)	1.10 (0.900–1.40)	1,310
	2009–2010	*	<LOD	0.500 (<LOD–0.600)	0.800 (0.700–1.00)	1.10 (0.900–1.60)	1,350
Race/ethnicity							
Mexican Americans	1999–2000	2.70 (2.20–3.32)	2.70 (2.10–3.10)	4.90 (4.20–6.70)	15.0 (8.20–23.0)	23.0 (14.0–43.0)	694
	2001–2002	*	2.07 (<LOD–3.23)	5.31 (3.95–6.54)	11.4 (8.51–12.8)	15.6 (12.6–19.8)	677
	2003–2004	*	<LOD	0.700 (0.600–0.800)	1.20 (1.10–1.60)	1.80 (1.30–2.00)	617
	2005–2006	*	<LOD	0.600 (0.500–0.700)	1.00 (0.800–1.20)	1.30 (1.20–1.70)	637
	2007–2008	*	<LOD	<LOD	0.700 (0.700–0.900)	1.00 (0.900–1.20)	531
	2009–2010	*	<LOD	0.500 (<LOD–0.600)	0.900 (0.700–1.10)	1.10 (0.900–1.30)	566
Non-Hispanic blacks	1999–2000	3.14 (2.40–4.12)	2.80 (2.10–3.40)	6.60 (3.40–14.0)	18.0 (9.30–33.0)	32.0 (16.0–68.0)	519
	2001–2002	2.78 (2.18–3.53)	2.58 (1.32–4.02)	6.45 (5.09–7.67)	11.1 (8.87–14.9)	17.9 (11.8–24.7)	696
	2003–2004	*	<LOD	0.900 (0.700–1.00)	1.40 (1.10–1.90)	2.00 (1.50–2.70)	636
	2005–2006	*	<LOD	0.800 (0.700–1.10)	1.50 (1.20–1.90)	2.20 (1.60–3.30)	678
	2007–2008	*	<LOD	0.600 (0.500–0.600)	1.00 (0.900–1.10)	1.30 (1.10–1.60)	597
	2009–2010	*	<LOD	0.700 (0.600–0.800)	1.10 (0.900–1.30)	1.50 (1.20–2.00)	516
Non-Hispanic whites	1999–2000	2.74 (2.46–3.06)	2.45 (2.30–2.80)	4.60 (3.80–6.60)	13.0 (6.60–21.0)	21.0 (12.0–37.0)	602
	2001–2002	*	1.57 (<LOD–2.20)	6.10 (5.01–6.65)	10.7 (9.67–12.3)	14.7 (13.3–17.9)	931
	2003–2004	*	<LOD	<LOD	0.800 (0.700–1.00)	1.20 (1.00–1.50)	1,077
	2005–2006	*	<LOD	0.500 (<LOD–0.700)	0.900 (0.700–1.30)	1.30 (1.10–1.80)	1,038
	2007–2008	*	<LOD	<LOD	0.800 (0.700–0.900)	1.20 (1.00–1.40)	1,077
	2009–2010	*	<LOD	<LOD	0.700 (0.600–0.900)	1.00 (0.800–1.30)	1,206

[a]The LODs for survey years 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, and 2009–2010 are 1.0, 1.3, 0.5, 0.5, 0.5, and 0.5, respectively.

* = not calculated; the proportion of results below the LOD was too high to provide a valid result; CI = confidence interval; LOD = limit of detection

Source: CDC 2009, 2019

Table 5-14. Geometric Mean and Selected Percentiles of Urinary 2,4,6-Trichlorophenol Concentrations (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2010

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total population	1999–2000	2.54 (2.30–2.81)	2.38 (2.14–2.68)	4.91 (3.83–6.49)	12.1 (8.67–17.0)	21.2 (13.6–31.5)	1,989
	2001–2002	*	2.43 (<LOD–2.75)	4.38 (4.184.78)	8.33 (7.10–9.26)	11.6 (9.25–15.6)	2,502
	2003–2004	*	<LOD	0.710 (<LOD–0.780)	1.25 (1.17–1.35)	1.75 (1.59–2.06)	2,522
	2005–2006	*	<LOD	0.720 (<LOD–0.760)	1.27 (1.17–1.38)	1.75 (1.59–1.94)	2,548
	2007–2008	*	<LOD	<LOD	1.25 (1.06–1.42)	1.75 (1.52–2.19)	2,604
	2009–2010	*	<LOD	0.710 (<LOD–0.760)	1.21 (1.13–1.35)	1.67 (1.55–1.84)	2,749
Age group							
Age 6–11 years	1999–2000	4.82 (3.87–6.00)	4.71 (3.41–6.53)	11.5 (7.63–15.3)	22.7 (14.1–32.6)	32.6 (22.7–36.8)	481
	2001–2002	4.00 (3.28–4.87)	4.01 (3.29–4.81)	8.26 (6.16–10.4)	13.9 (9.51–21.5)	21.2 (12.9–64.1)	574
	2003–2004	*	<LOD	0.920 (0.850–1.13)	1.59 (1.22–1.91)	2.11 (1.46–4.55)	314
	2005–2006	*	<LOD	0.880 (0.740–1.06)	1.59 (1.21–2.06)	2.50 (1.61–5.20)	356
	2007–2008	*	<LOD	0.900 (<LOD–0.930)	1.46 (1.14–1.67)	2.33 (1.52–2.92)	389
	2009–2010	*	<LOD	0.850 (<LOD–1.03)	1.59 (1.17–1.74)	1.85 (1.67–2.33)	415
Age 12–19 years	1999–2000	2.40 (2.08–2.78)	2.33 (1.95–2.68)	4.35 (3.13–6.00)	11.6 (6.94–13.6)	14.4 (11.3–23.6)	678
	2001–2002	2.51 (2.18–2.90)	2.78 (2.09–3.17)	4.52 (3.83–5.92)	8.29 (6.81–9.89)	12.5 (8.73–22.8)	819
	2003–2004	*	<LOD	0.580 (0.510–0.660)	0.970 (0.830–1.10)	1.21 (1.09–1.49)	720
	2005–2006	*	<LOD	0.550 (<LOD–0.630)	0.970 (0.690–1.17)	1.40 (1.08–1.59)	702
	2007–2008	*	<LOD	0.550 (<LOD–0.610)	0.830 (0.730–1.03)	1.30 (0.930–1.48)	401
	2009–2010	*	<LOD	0.590 (<LOD–0.700)	0.970 (0.690–1.23)	1.23 (0.920–1.66)	420
Age 20+ years	1999–2000	2.32 (2.04–2.63)	2.22 (1.89–2.56)	4.25 (3.38–5.63)	10.0 (6.72–16.9)	19.6 (10.9–34.4)	830
	2001–2002	*	<LOD	4.05 (3.66–4.38)	7.10 (6.43–7.72)	9.82 (8.53–11.9)	1,109
	2003–2004	*	<LOD	0.710 (<LOD–0.770)	1.25 (1.17–1.35)	1.75 (1.59–2.00)	1,488
	2005–2006	*	<LOD	0.730 (<LOD–0.780)	1.30 (1.17–1.40)	1.75 (1.57–2.06)	1,490
	2007–2008	*	<LOD	<LOD	1.30 (1.06–1.46)	1.84 (1.52–2.33)	1,814
	2009–2010	*	<LOD	<LOD	1.21 (1.13–1.35)	1.67 (1.52–1.94)	1,914

Table 5-14. Geometric Mean and Selected Percentiles of Urinary 2,4,6-Trichlorophenol Concentrations (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2010

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	1999–2000	2.24 (1.99–2.53)	2.15 (1.82–2.42)	4.41 (3.56–5.88)	10.8 (7.04–16.4)	18.0 (11.5–28.5)	970
	2001–2002	*	2.23 (1.91–2.65)	4.22 (3.77–4.73)	8.04 (6.70–9.17)	12.2 (8.79–17.7)	1,178
	2003–2004	*	<LOD	0.560 (<LOD–0.600)	0.920 (0.820–1.10)	1.30 (1.17–1.46)	1,230
	2005–2006	*	<LOD	0.600 (<LOD–0.650)	1.00 (0.850–1.13)	1.43 (1.25–1.59)	1,270
	2007–2008	*	<LOD	0.530 (<LOD–0.600)	0.930 (0.830–1.06)	1.46 (1.18–1.59)	1,294
	2009–2010	*	<LOD	<LOD	0.980 (0.850–1.12)	1.33 (1.13–1.59)	1,399
Females	1999–2000	2.88 (2.49–3.33)	2.63 (2.25–2.96)	5.53 (3.88 –7.23)	13.3 (9.65–21.9)	25.1 (13.3–37.0)	1,019
	2001–2002	*	<LOD	4.58 (4.19–5.11)	8.40 (7.27–9.51)	10.9 (9.26–13.6)	1,324
	2003–2004	*	<LOD	0.900 (<LOD–0.960)	1.59 (1.35–1.75)	2.19 (1.75–2.63)	1,292
	2005–2006	*	<LOD	0.850 (<LOD–0.970)	1.46 (1.30–1.67)	2.06 (1.67–2.50)	1,278
	2007–2008	*	<LOD	<LOD	1.46 (1.23–1.75)	2.19 (1.67–2.50)	1,310
	2009–2010	*	<LOD	0.850 (<LOD–0.920)	1.46 (1.30–1.59)	2.06 (1.62–2.33)	1,350
Race/ethnicity							
Mexican Americans	1999–2000	2.43 (2.06–2.87)	2.50 (2.22–2.82)	5.44 (3.87–7.10)	10.8 (8.46–14.9)	18.4 (12.1–21.8)	694
	2001–2002	*	2.22 (<LOD–2.88)	4.25 (3.47–5.76)	8.15 (6.21–11.1)	11.6 (9.63–13.9)	677
	2003–2004	*	<LOD	0.760 (0.600–0.900)	1.15 (0.970–1.38)	1.59 (1.18–2.42)	616
	2005–2006	*	<LOD	0.650 (0.570–0.700)	1.03 (0.860–1.19)	1.46 (1.11–1.94)	637
	2007–2008	*	<LOD	<LOD	1.05 (0.910–1.17)	1.35 (1.13–1.57)	531
	2009–2010	*	<LOD	0.690 (<LOD–0.760)	1.00 (0.900–1.33)	1.67 (1.13–2.18)	566
Non-Hispanic blacks	1999–2000	2.13 (1.65–2.76)	1.90 (1.60–2.52)	4.00 (2.76–8.02)	11.6 (5.32–19.7)	19.5 (10.9–29.5)	519
	2001–2002	1.98 (1.55–2.52)	2.02 (1.48–2.76)	3.83 (3.17–4.88)	6.52 (5.50–8.06)	9.91 (7.14–13.2)	695
	2003–2004	*	<LOD	0.600 (0.560–0.640)	0.950 (0.800–1.10)	1.34 (1.06–1.67)	635
	2005–2006	*	<LOD	0.630 (0.540–0.740)	1.03 (0.830–1.49)	1.59 (1.13–2.07)	678
	2007–2008	*	<LOD	0.520 (0.470–0.620)	1.00 (0.830–1.13)	1.40 (1.13–1.52)	597
	2009–2010	*	<LOD	0.560 (0.490–0.610)	0.830 (0.750–0.950)	1.17 (0.920–1.52)	516

Table 5-14. Geometric Mean and Selected Percentiles of Urinary 2,4,6-Trichlorophenol Concentrations (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2010

			Selected percentiles (95% CI)				
	Survey years[a]	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
Non-Hispanic whites	1999–2000	2.59 (2.33–2.88)	2.42 (2.20–2.77)	4.87 (3.83–6.06)	11.2 (7.62–15.5)	19.6 (12.9–32.8)	602
	2001–2002	*	2.63 (<LOD–2.88)	4.60 (4.29–4.98)	8.56 (7.22–9.65)	12.0 (9.25–17.1)	931
	2003–2004	*	<LOD	<LOD	1.30 (1.17–1.46)	1.75 (1.59–2.11)	1,076
	2005–2006	*	<LOD	0.760 (<LOD–0.830)	1.35 (1.25–1.50)	1.79 (1.60–2.06)	1,038
	2007–2008	*	<LOD	<LOD	1.35 (1.13–1.52)	1.84 (1.52–2.50)	1,077
	2009–2010	*	<LOD	<LOD	1.30 (1.18–1.46)	1.73 (1.59–2.06)	1,206

[a]The LODs for survey years 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, and 2009–2010 are 1.0, 1.3, 0.5, 0.5, 0.5, and 0.5, respectively.

* = not calculated; the proportion of results below the LOD was too high to provide a valid result; CI = confidence interval; LOD = limit of detection

Source: CDC 2009, 2019

As with the general population, occupational exposure to chlorophenols can also occur following accidents that result in the release of these chemicals to the environment, such as the previously discussed train derailment. On the day of the accident, 2-CP air concentrations of 0.02–0.7 mg/m^3 (0.004–0.19 ppm) were detected in the immediate vicinity (EPA 1982). Eighteen days after the spill, air concentrations were reduced to <2 µg/m^3 (<0.5 ppb). Urine levels in the clean-up workers were 1.98 mg/L approximately 2 months following the spill; however, the pathways, duration, and time of exposure were not recorded, so that the exposure levels cannot be estimated (EPA 1982).

Potential exposure to chlorophenols tends to be limited because of the pronounced odor and taste imparted by the presence of these substances. While taste and odor thresholds do vary across the population, low concentrations of chlorophenols can be detected by most people. For example, the odor of 2,4-DCP can be detected in water at 0.35 µg/L (Hoak 1957), and 2,4-DCP can be tasted in water at 8 pg/L (Burttschell et al. 1959). Odor thresholds as low as 0.3–9.15 µg/L in water have also been reported for chlorophenols (Hoak 1957). Although chlorophenols have low odor thresholds in water, 2-CP, 4-CP, 2,4-DCP, and 2,4,6-TCP have been noted to affect the flavor of fish at concentrations of about 2–43 times lower than the odor thresholds for these compounds in water (Persson 1984). Data for the other chlorophenols discussed in this profile were not available.

Ye et al. (2006) reported that 2,4-DCP, 2,4,5-TCP and 2,4,6-TCP were each detected in 5% of 20 pooled breast milk samples (detection limits 0.10–1.22 ng/mL) obtained from a group of females who had no known occupational exposure to these compounds. 2,5-DCP was tested for, but not identified in any samples. The 95th percentile concentration of 2,5-DCP in amniotic fluid from 97 pregnant females referred for amniocentesis screening at the Mount Sinai Medical Center in New York, New York was 5.2 µg/L (Philippat et al. 2013). 2,4-DCP levels were below the detection limits in each case; however, only 11 amniotic fluid samples were tested for 2,4-DCP.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In comparison to members of the general population, workers in certain occupational groups have much greater potential for exposure to high concentrations of chlorophenols (EPA 1982). While quantitative data are not available, workers involved in the production of either chlorophenols or chemicals synthesized from chlorophenols are potentially the most heavily exposed (WHO 1989). Exposure may occur through both inhalation and dermal absorption. Workers in plants that use chlorobenzene are also likely to be heavily exposed to monochlorophenols via the metabolism of inhaled chlorobenzene to

monochlorophenols (Kusters and Lauwerys 1990; Ogata et al. 1991; Yoshida et al. 1986). However, most of the inhaled chlorobenzene was metabolized to 4-chlorocatechol rather than chlorophenols, as the average exposed worker excreted 3 times more 4-chlorocatechol than chlorophenols in the urine (Kusters and Lauwerys 1990; Yoshida et al. 1986); thus, exposure via metabolism of chlorobenzene is not an important route of exposure.

Workers at sawmills where the higher chlorinated phenols are used as wood preservatives have the highest potential for being exposed to tetrachlorophenols (WHO 1989). The observation of higher urinary concentrations of tetrachlorophenols during hot humid weather when use of protective clothing was minimal (geometric means of 196.7 ppm in hot humid weather and 98.5 ppm in cooler weather) suggests that dermal contact is an important route of exposure to tetrachlorophenols in these workers (Kleinman et al. 1986). The higher volatility of tetrachlorophenols in warmer weather may have also contributed to the higher urinary concentrations of tetrachlorophenols found when the weather was hot. Higher general population exposure may occur through dermal or oral contact with contaminated soils and/or groundwater in the vicinity of disposal or accident sites and through dermal or oral contact with surface waters into which chlorinated effluents have been discharged (EPA 1982). In addition, inhalation and metabolism of chlorobenzene found in urban air can result in higher exposure to monochlorophenols (Angerer et al. 1992b, 1993).

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 chlorophenols 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 chlorophenols.

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

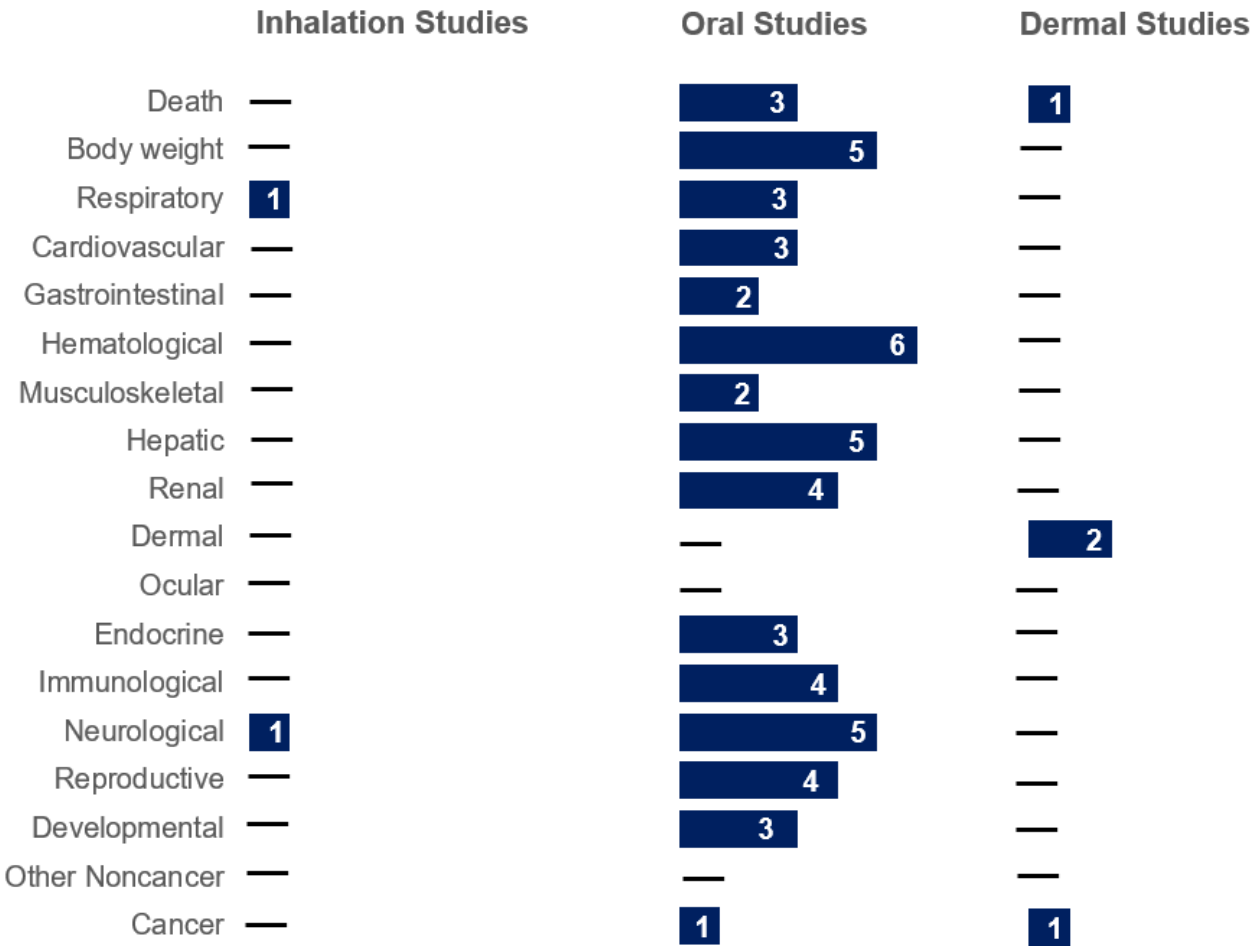
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to chlorophenols that are discussed in Chapter 2 are summarized in Figures 6-1 (2-CP), 6-2 (4-CP), 6-3 (2,4-DCP), 6-4 (2,4,5-TCP), 6-5 (2,4,6-TCP), 6-6 (2,3,4,6-TeCP), and 6-7 (other chlorophenols). The purpose of these figures is to illustrate the information concerning the health effects of chlorophenols. 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.

The preponderance of data on the toxicity of chlorophenols come from oral studies in laboratory animals, as shown in Figures 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, and 6-7. The most examined endpoints were body weight, neurological, hepatic, renal, hematological, and reproductive effects. There were two human case reports of dermal exposures to 2,4-DCP alone in which neurological effects and deaths were reported; these are included in the figures. The remaining human studies largely consisted of occupational cohort or case-control studies and population-based, cross-sectional studies. The former (n=18) were of populations exposed to multiple chlorophenols through inhalation and dermal routes; these studies primarily evaluated cancers and mortality. The population-based studies (n=24) used urinary chlorophenols, usually 2,4-DCP and 2,5-DCP and occasionally other compounds, to measure exposure, and evaluated associations with birth outcomes, obesity, blood pressure, thyroid levels, or reproductive endpoints.

Figure 6-1. Summary of Existing Health Effects Studies on 2-Chlorophenol By Route and Endpoint*

Potential hematological, neurological, body weight, and hepatic effects were the most studied endpoints

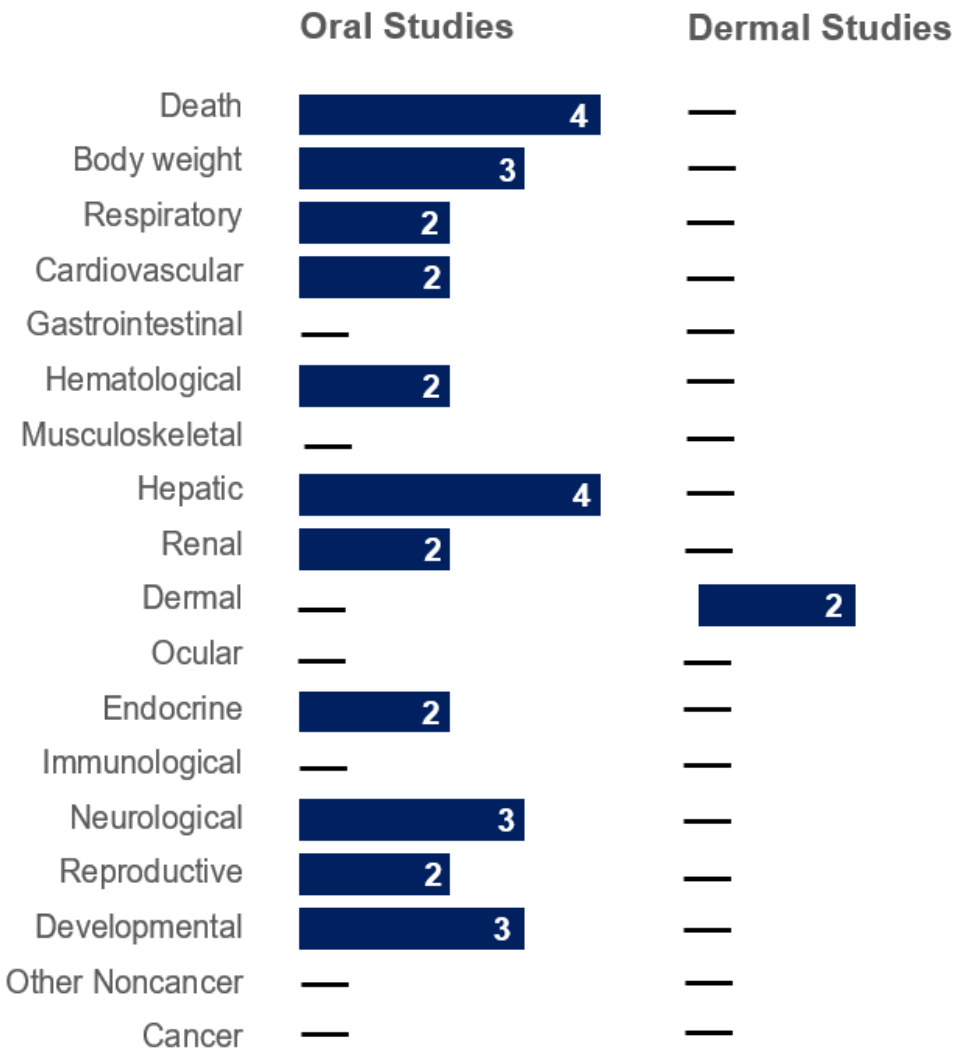
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. More than one endpoint may have been investigated in each study.

Figure 6-2. Summary of Existing Health Effects Studies on 4-Chlorophenol By Route and Endpoint*

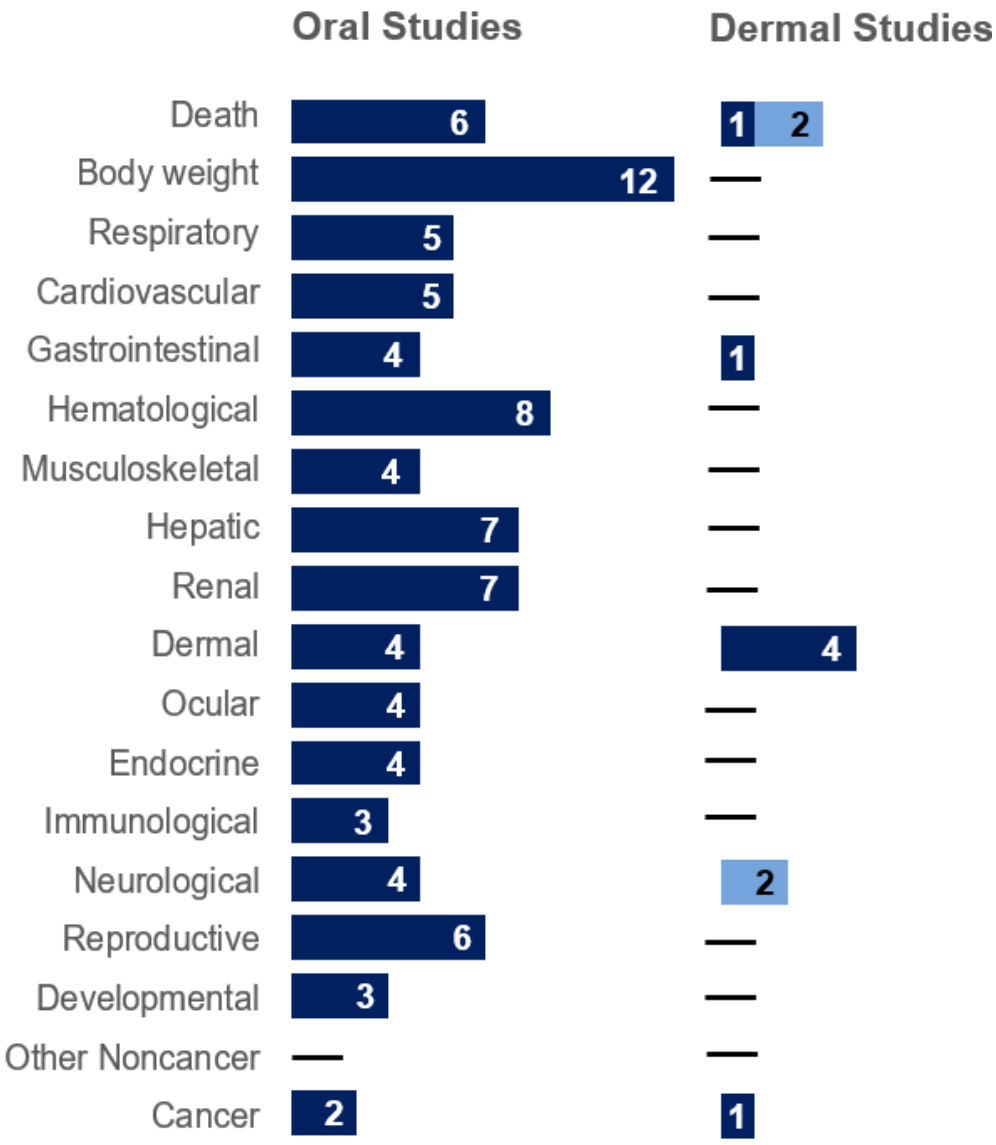
Potential mortality and hepatic effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. More than one endpoint may have been investigated in each study. No inhalation studies in humans or animals were located.

Figure 6-3. Summary of Existing Health Effects Studies on 2,4-Dichlorophenol By Route and Endpoint*

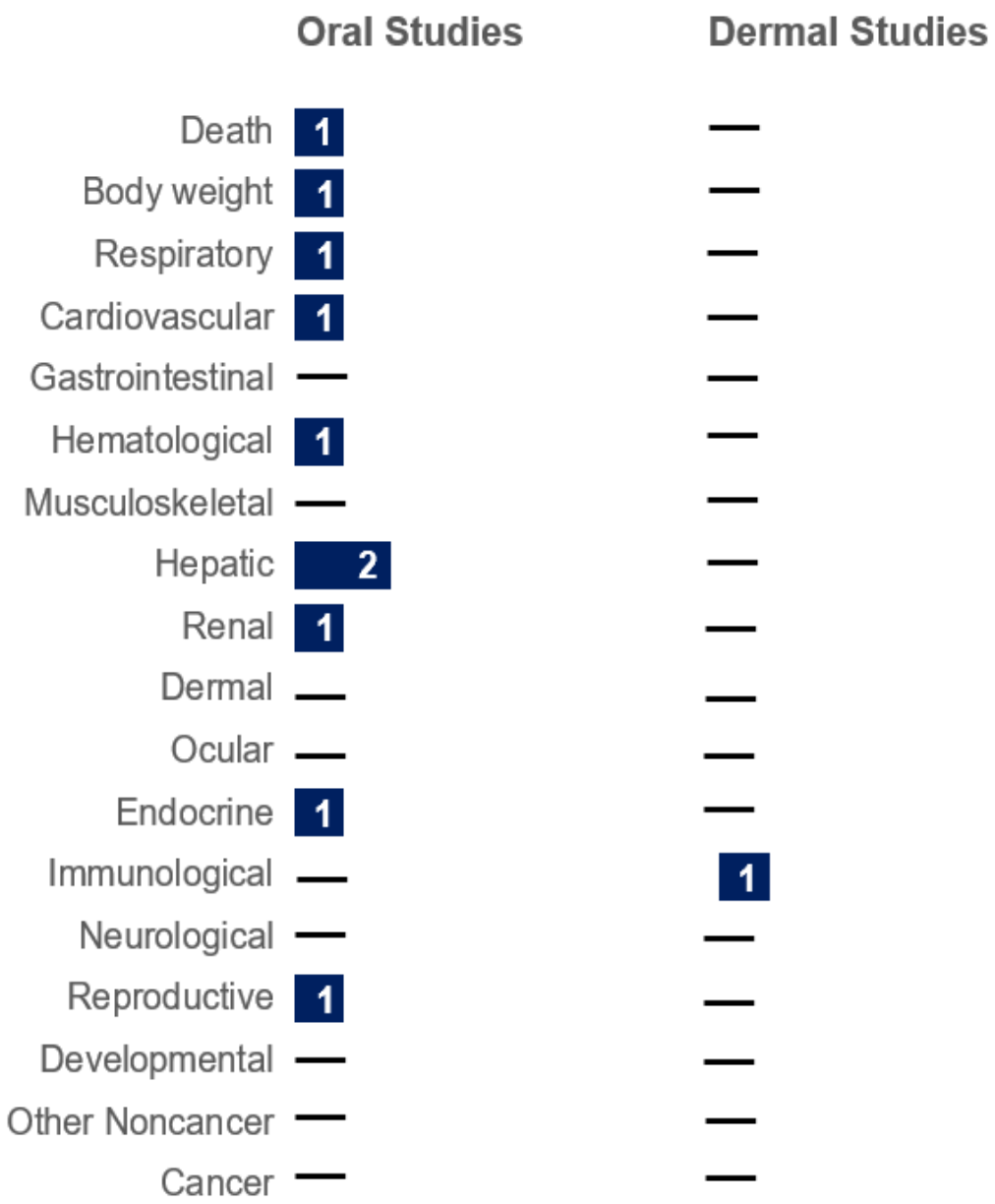
Potential mortality, body weight, hematological, and dermal were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. More than one endpoint may have been investigated in each study. No inhalation studies in humans or animals were located.

Figure 6-4. Summary of Existing Health Effects Studies on 2,4,5-Trichlorophenol By Route and Endpoint*

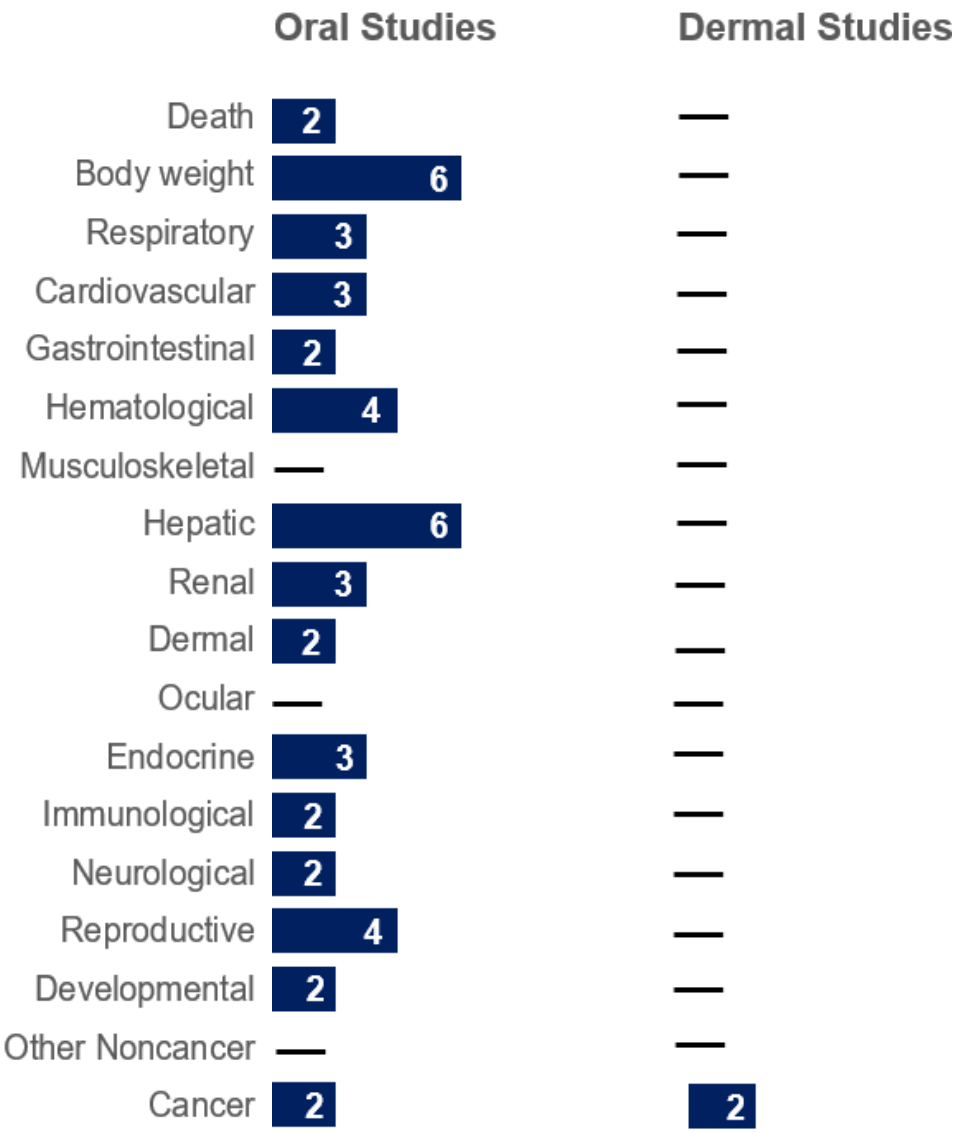
Potential hepatic effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. More than one endpoint may have been investigated in each study. No inhalation studies in humans or animals were located.

Figure 6-5. Summary of Existing Health Effects Studies on 2,4,6-Trichlorophenol By Route and Endpoint*

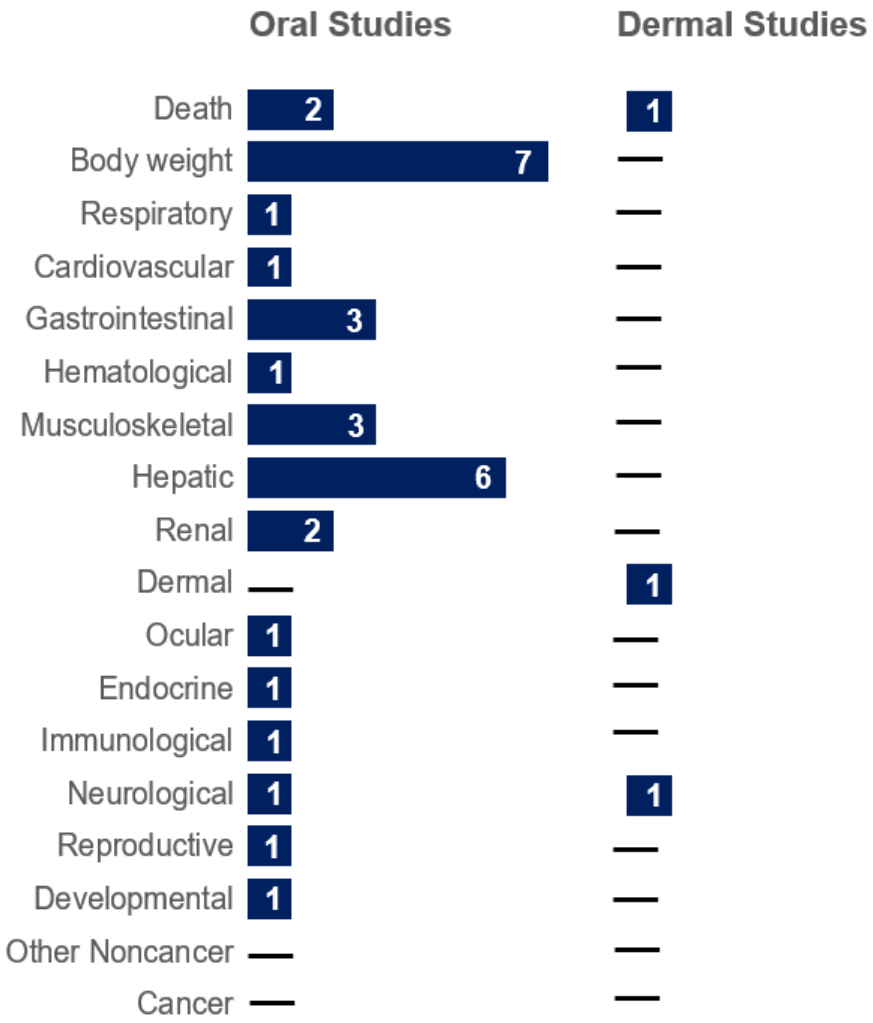
Potential body weight and hepatic effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. More than one endpoint may have been investigated in each study. No inhalation studies in humans or animals were located.

Figure 6-6. Summary of Existing Health Effects Studies on 2,3,4,6-Tetrachlorophenol By Route and Endpoint*

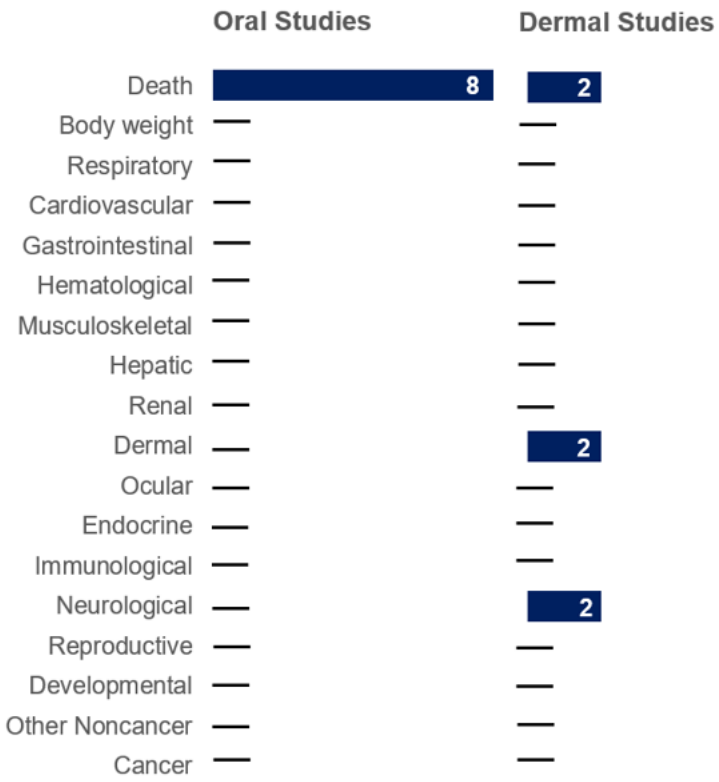
Potential body weight and hepatic effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. More than one endpoint may have been investigated in each study. No inhalation studies in humans or animals were located.

Figure 6-7. Summary of Existing Health Effects Studies on Other Chlorophenols By Route and Endpoint*

Potential mortality, neurological, and dermal effects were the only 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. More than one endpoint may have been investigated in each study.

The latter studies included multiple chlorophenols, and their interpretation is further complicated by the fact that urinary chlorophenols may occur as a result of metabolism of other compounds such as chlorinated benzenes. The databases of studies in laboratory animals exposed by inhalation and dermal routes include small numbers of studies evaluating limited endpoints. Among animal studies of oral exposure shown in the figures, most studies examined effects of 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, or 2,3,4,6-TeCP. Only a single study was located on the health effects in animals of oral exposure to 2,3-, 2,5-, 3,4-, and 3,5-DCP (Borzelleca et al. 1985b) or 2,3,4,5- and 2,3,5,6-TeCP (Ahlborg and Larsson 1978).

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figures 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, and 6-7 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.

Acute-Duration MRLs. No adequate acute-duration inhalation data were available for any of the chlorophenols discussed in this profile. The acute-duration oral data were considered adequate for derivation of MRLs for 2-CP and 2,3,4,6-TeCP. For 4-CP, available acute-duration data were not considered adequate because deaths were observed at the lowest LOAEL. Acute-duration oral data for 2,3-DCP, 2,5-DCP, 3,4-DCP, 3,5-DCP, 2,3,4,5-TeCP, and 2,3,5,6-TeCP were limited to acute lethality studies.

Intermediate-Duration MRLs. No adequate intermediate-duration inhalation data were available for any of the chlorophenols discussed in this profile. Studies in animals exposed by oral administration were considered adequate to derive intermediate-duration oral MRLs for 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP. There were no intermediate-duration oral studies for 2,3-DCP, 2,5-DCP, 3,4-DCP, 3,5-DCP, 2,3,4,5-TeCP, or 2,3,5,6-TeCP. Studies examining sensitive immunological endpoints following oral exposure to chlorophenols other than 2-CP, 2,4-DCP, and 2,4,6-TCP are needed to evaluate potential immunotoxicity of the other compounds.

Chronic-Duration MRLs. No adequate chronic-duration inhalation data were available for any of the chlorophenols discussed in this profile. In addition, there were no adequate chronic-duration oral data in

humans or animals for 4-CP, 2,4-DCP, 2,5-DCP, 3,4-DCP, 3,5-DCP, 2,4,5-TCP, 2,3,4,5-TeCP, 2,3,4,6-TeCP, or 2,3,5,6-TeCP. While a well-conducted chronic study of 2,4-DCP in rats and mice (NTP 1989) is available, this study did not examine sensitive measures of immunotoxicity, and identified effect levels higher than seen in the intermediate-duration study (Exon and Koller 1985; Exon et al. 1984), precluding its use for a chronic-duration oral MRL for 2,4-DCP.

Health Effects. Studies of health effects in humans exposed to chlorophenols are limited by the absence of specific, reliable biomarkers of exposure and by co-exposures to phenoxy herbicides and polychlorinated dibenzodioxins and furans in occupational and environmental settings. Furthermore, no repeated-exposure studies of animals exposed to chlorophenols by inhalation were located. Studies examining comprehensive endpoints in animals exposed by inhalation for acute, intermediate, and chronic durations would enable identification of target organs and exposure-response relationships for this exposure route; these are particularly important for the more volatile monochlorophenols. Finally, only acute lethality data are available for 2,3-DCP, 2,5-DCP, 3,4-DCP, 3,5-DCP, 2,3,4,5-TeCP, and 2,3,5,6-TeCP; thus, oral studies to identify target organs and establish exposure-response relationships for these compounds are needed.

Reproductive. Reproductive effects consisting of reduced numbers of implantations, litter sizes, and/or live births per litter have been observed in animals after oral exposure to 4-CP, 2,4-DCP, and 2,4,6-TCP (BSRC 2011; Exon and Koller 1985; Exon et al. 1984). Only 2,4-DCP has been tested in a multigeneration study examining comprehensive reproductive endpoints in exposed male and female animals (Aoyama et al. 2005); thus, multigeneration reproduction toxicity studies of other chlorophenols are needed.

Developmental. While results from animal studies showed minor effects occurring at doses that are maternally toxic (Blackburn et al. 1986; EPA 1987a, 1987b; Exon and Koller 1985; Rodwell et al. 1989), few developmental toxicity studies that included teratogenicity evaluations are available. Therefore, animal developmental toxicity studies that include evaluation of teratogenicity endpoints are needed. More epidemiological studies of developmental effects in humans exposed to chlorophenols would be beneficial as well.

Immunotoxicity. Only 2-CP, 2,4-DCP, and 2,4,6-TCP have been tested for sensitive measures of immune function (Exon and Koller 1982, 1983a, 1983b, 1985; Exon et al. 1984). Evidence of

effects on both cell-mediated and humoral immunity in rats exposed to 2,4-DCP suggests that additional chlorophenols may warrant testing.

Neurotoxicity. Available data on neurotoxicity of chlorophenols show serious effects including convulsions after acute- and intermediate-duration, oral, dermal, and intraperitoneal exposures in humans and animals (Borzelleca et al. 1985a, 1985b; Rhone-Poulenc 1991; Farquharson et al. 1958; Hasegawa et al. 2005; Kintz et al. 1992; Kobayashi et al. 1972; Phornchirasilp et al. 1989b; Shen et al. 1983; Spencer and Williams 1950; Wil Research Laboratories 1982). Although Borzelleca et al. (1985a, 1985b) reported a decrease in brain weight in mice exposed to 2-CP for 14 days, the authors reported few details of the experiment and results. No clinical signs or changes in brain weight, brain histology, and/or sciatic nerve histology were observed after acute- and intermediate-duration exposure of rats to 2-CP (Daniel et al. 1993; Hasegawa et al. 2005) or intermediate-duration exposure of rats or mice to 4-CP, 2,4-DCP, trichlorophenols, or tetrachlorophenols (Bercz et al. 1990; EPA 1986; Hasegawa et al. 2005; NCI 1979; NTP 1989). While inhibition of oxidative phosphorylation and cellular respiration are possible mechanisms for the clinical signs of neurotoxicity, studies to clarify the mechanism(s) may inform the dose-response assessment for these effects. There are no studies examining sensitive measures of neurotoxicity (e.g., functional observational battery, neurobehavioral changes); these studies are warranted based on the observed clinical signs. Finally, studies of 2-CP (Borzelleca et al. 1985b; Daniel et al. 1993) suggest that mice may be more sensitive to the neurological effects of chlorophenols than rats; further investigation of this possible species difference and its implications for extrapolation to humans would be beneficial.

Cancer. Apart from 2,4-DCP and 2,4,6-TCP, the chlorophenols discussed in this profile have not been adequately tested for potential carcinogenicity. Available chronic studies with rats and mice and predominantly negative results in studies of mutagenicity have indicated that 2,4,6-TCP may produce carcinogenicity in animal models through mechanisms other than direct gene mutation (Armstrong et al. 1993; Jansson and Jansson 1992; NCI 1979); however, candidate mode(s) of action have not been proposed. Additional animal and/or *in vitro* studies designed to evaluate potential key events in the mode(s) of action for 2,4,6-TCP carcinogenicity would be beneficial.

Epidemiology and Human Dosimetry Studies. Accurate human dosimetry studies may not be possible because environmental and occupational chlorophenols typically exist only in association with

other chlorinated organics, and urinary chlorophenol concentrations are not specific for chlorophenol exposure (see below). Consequently, it would be difficult to ascribe any observed health effect to a single chemical or a single group of compounds. Additional studies in workers, such as sawmill employees, who are exposed specifically to chlorophenols are needed. Careful monitoring of chlorophenol air concentrations and skin exposure combined with kinetic measures of urinary output for specific isomers may provide important data for human dosimetry and enable more reliable epidemiological studies.

Biomarkers of Exposure and Effect. Currently, no specific biomarkers for chlorophenol exposure or effect are available. The presence of chlorophenols or their metabolites in urine is not necessarily diagnostic for chlorophenol exposure because these compounds are also detectable in urine after exposure to other pesticides (Hill et al. 1989; Karapally et al. 1973; Shafik et al. 1973), dichlorobenzenes (Yoshida et al. 2002), and hexachlorocyclohexanes (Engst et al. 1976; Koransky et al. 1975). Research to identify specific biomarkers of chlorophenol exposure or effects would be useful to improve human epidemiological studies and/or medical surveillance of exposed populations.

Absorption, Distribution, Metabolism, and Excretion. Studies concerning the inhalation absorption and oral absorption of chlorophenols from different media (e.g., water, soil) and the effect of ionization on dermal absorption are needed for estimating exposure at a hazardous waste site. Available data on the toxicokinetics of chlorophenols are limited, but clearly establish the rapid and nearly complete absorption and rapid elimination of most chlorophenols after oral exposure. Data on the toxicokinetic behavior of the chlorophenols after inhalation exposure in humans or animals are lacking. Metabolism studies demonstrate that glucuronide and sulfate conjugates comprise the major portion of urinary chlorophenol metabolites. Semiquinones and quinones metabolites have been detected after oral exposure (Juhl et al. 1991; Phornchirasilp et al. 1989b); these compounds, while short-lived, are reactive and potentially toxic. Experiments to establish rate constants for the formation of both reactive intermediates and conjugates might provide data for the development of PBPK models. Finally, studies of differences in the rates of formation of reactive intermediates and conjugates after oral, inhalation, and dermal exposure, and/or in different species, would inform route- and species-specific differences in the toxic manifestations of chlorophenols.

Comparative Toxicokinetics. Toxicokinetic studies with chlorophenols have been conducted in humans, rats, rabbits, and dogs (Azouz et al. 1953; Bray et al. 1952a, 1952b; Exon and Koller 1982; Fenske et al. 1987; Hattula et al. 1981; Phomchirasilp et al. 1989a; Somani and Khalique 1982; Spencer and Williams 1950). Limited data suggest that mice may be more sensitive to the toxic effects of orally-

administered chlorophenols than rats; thus, toxicokinetic studies comparing metabolites and rates of elimination in mice and rats would be beneficial. Furthermore, the human fatalities seen after dermal and/or inhalation exposure to 2,4-DCP raise the question of whether humans may be more sensitive than rodents to the effects of this compound. Studies comparing human and rodent toxicokinetics of 2,4-DCP would provide data to inform this question.

Children's Susceptibility. There is inadequate experimental evidence to evaluate whether pharmacokinetics of chlorophenols are different in children. Higher chlorinated phenols (trichloro- and tetrachlorophenols) have been detected in human adipose tissue (Mussalo-Rauhamaa et al. 1989; Williams et al. 1984), suggesting that chlorophenols could be stored in maternal tissues. These studies did not examine whether mono- or dichlorophenols accumulate in adipose tissue; studies examining this issue would help to determine whether children have increased exposure from mobilization of contaminants stored in fat. Similarly, there are limited data showing detectable levels of 2,4-DCP; 2,4,5-TCP, and 2,4,6-TCP in breast milk (Ye et al. 2006) and 2,4-DCP, but not 2,4-DCP in amniotic fluid (Philippat et al. 2013), but these studies did not include analysis for other chlorophenols. There are no direct data on whether chlorophenols cross the placenta in humans or animals, but evidence of embryotoxicity in rats exposed to chlorophenols suggests that transplacental transfer may occur. In summary, the data on chlorophenol accumulation in human adipose tissue, breast milk, and amniotic fluid are incomplete, and there is a lack of data on transplacental transfer of chlorophenols. There is no experimental evidence to evaluate whether metabolism of chlorophenols or their mechanism of action may be different in children. Since the metabolic enzymes for detoxification exhibit age-dependent expression, there is a need for such data.

Physical and Chemical Properties. The physical and chemical properties of chlorophenols have been well studied, and reliable values for key parameters for most chlorophenols are available for use in environmental fate and transport models. Therefore, further studies of the physical and chemical properties of chlorophenols are not essential at the present time.

Production, Import/Export, Use, Release, and Disposal. Chlorophenols have a variety of different uses (Muller and Caillard 2011). 2,4-DCP is used as an intermediate in the production of herbicides and the manufacture of compounds used in mothproofing, antiseptics, and seed disinfectants. It is also used to produce miticides and wood preservatives. 4-CP is used as an intermediate in the production of acaricides, rodenticides, and dyes; it is used most commonly as a local antiseptic for dental procedures. 2-CP is used in the production of higher chlorinated phenols, dyestuffs, preservatives, and as

a disinfectant/bactericide/germicide. It is also used for extracting sulfur and nitrogen compounds from coal. 2,4,5-TCP is used as a fungicide/bactericide; an intermediate in the manufacture of herbicides, hide and leather processing; and as a disinfectant in swimming pool and sick-room related surfaces. Chlorophenols are potentially hazardous chemicals and are subject to a variety of regulations (see Chapter 7).

Data regarding the production methods for the chlorophenols are available; however, data regarding current production and import/export of the chlorophenols are extremely limited (Krijgsheld and van de Gen 1986; Muller and Caillard 2011). More complete and up-to-date production and import/export information would provide a better understanding of potential exposure in the United States. General disposal information for chlorophenols is adequately described in the literature. At low concentrations in aqueous media, microbial degradation followed by adsorption on activated charcoal is the common disposal method (WHO 1989).

Environmental Fate. The behavior of chlorophenols in solid and aqueous media depends on numerous physicochemical variables. These chemicals are partitioned to and transported in the air, soil, and water. The pH of soil and water is a major factor controlling their partitioning among the media, their mobility, and their ultimate fate in the environment. These processes are well characterized.

Atmospheric chlorophenols, primarily associated with production processes, are apparently removed by free radical oxidation, photolysis, and both wet and dry deposition (Bunce and Nakai 1989; EPA 1982). More specific data regarding atmospheric dispersion and photochemical reaction rates are needed for occupational settings. Volatilization of the higher chlorinated phenols from water and soil is expected to be a slow process, but there were no experimental data located in the available literature. Experimental data are available pertaining to many of the transformations of chlorophenols in the environment including biodegradation in water, soil, and sediment and photodegradation in water. Confirmation of the estimated slow rate of volatilization in addition to data regarding the overall half-lives for chlorophenols in air are needed to estimate potential inhalation exposure near hazardous waste sites that contain chlorophenols. Data regarding the overall half-life in water and soil are needed to estimate potential oral and dermal exposure to chlorophenols.

Bioavailability from Environmental Media. The observation of systemic effects following inhalation, oral, and dermal exposure indicates that the chlorophenols are readily absorbed (see Chapter 3 for more details). Systematic studies of the bioavailability of the chlorophenols from different media

have not been completed. Because the compounds are relatively lipophilic and become adsorbed to soil and sediments, a study of the bioavailability of these compounds from soil relative to water following oral exposure would be useful.

Food Chain Bioaccumulation. Chlorophenols bioconcentrate in aquatic (fish) organisms to a limited extent, with the greatest bioaccumulation observed for the tetrachlorophenols (Carey et al. 1988). The extent of bioconcentration is limited by relatively rapid metabolism and excretion (Veith et al. 1980). Additional data on the bioaccumulation of chlorophenols within both aquatic and terrestrial organisms are needed.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of chlorophenols in contaminated media at hazardous waste sites are needed so that the information obtained on levels of chlorophenols in the environment can be used in combination with the known body burden of chlorophenols to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Few data are available concerning the levels of chlorophenols in ambient air or near known sources of atmospheric pollution. Limited monitoring data on chlorophenol levels in surface water are available. Additional monitoring for current data for better characterization of the ambient chlorophenol concentrations in air, surface water, groundwater, soils, and sediment are needed. These data are particularly needed in the vicinity of industrial and municipal chlorinated wastewater discharge points and hazardous waste sites, where individuals may be exposed by oral and/or dermal contact, such that estimates of human intake can be made. The presence or absence and any exposure levels of chlorophenols in food items is a data need.

Exposure Levels in Humans. This information is necessary for assessing the need to conduct health studies on these populations. Limited data regarding chlorophenol levels in urine in humans and adipose tissue are currently available. Toxicokinetic data on occupationally and environmentally exposed humans are needed to determine whether there are specific, reliable biomarkers of exposure. Because chlorophenols are metabolites of other chemicals, measurement of these compounds in biological samples (e.g., blood, urine) can provide an estimate of internal dose but may not provide information about the dose of chlorophenols to which individuals were exposed. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. No exposure and body burden studies have been conducted on children; therefore, it is not known whether children are different from adults in their weight-adjusted intake of

chlorophenols, or if unique exposure pathways for children exist. In NHANES surveys of chlorophenol levels in urine (see Tables 5-7 through 5-14), the differences between concentrations in the urine of 6- to 11-year-old children and concentrations in the urine of adults were small. However, as noted earlier, chlorophenols in urine may reflect metabolism of other compounds rather than exposure to chlorophenols, so urine levels in populations without known chlorophenol exposures may not provide a reliable basis for this comparison. There is also no monitoring of chlorophenol levels in food (crops, fish), nor in environmental media, following application of herbicides and wood preservatives. Children whose parents work in manufacturing facilities that produce or use chlorophenols may also potentially be exposed to chlorophenols via parents' work clothes, skin, hair, tools, or other objects removed from the workplace; however, no studies exist on this means of exposure. A take-home exposure study may be warranted if such occupational exposure settings are identified. More complete information on levels of chlorophenols and their metabolites in breast milk will also help to determine the chlorophenols to which children may be exposed via milk ingestion.

Since children may be more susceptible to chlorophenols, it may be helpful to conduct studies aimed at identifying methods to prevent, mitigate, or limit exposure of children to chlorophenols.

6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institutes of Health (NIH) Research Portfolio Online Reporting Tools Expenditures and Results Tool (RePORTER 2019).

CHAPTER 7. REGULATIONS AND GUIDELINES

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

Table 7-1. Regulations and Guidelines Applicable to Chlorophenols

Agency	Description	Information	Reference
	Air		
EPA	RfC	Not evaluated/ Not derived	IRIS, 1988, 1990, 2002a, 2002b, 2002c, 2019
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)		
	2-CP	0.5 mg/L	
	2,4-DCP	0.03 mg/L	
	2,4,6-TCP	0.03 mg/L	
	10-Day health advisory (10-kg child)		
	2-CP	0.5 mg/L	
	2,4-DCP	0.03 mg/L	
	2,4,6-TCP	0.03 mg/L	
	DWEL		
	2-CP	0.2 mg/L	
	2,4-DCP	0.1 mg/L	
	2,4,6-TCP	0.01 mg/L	
	Lifetime health advisory		
	2-CP	0.04 mg/L	
	2,4-DCP	0.02 mg/L	
	2,4,6-TCP	No data	
	10^{-4} Cancer risk		
	2-CP	No data	
	2,4-DCP	No data	
	2,4,6-TCP	0.3 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Chlorophenols

Agency	Description	Information	Reference
	National primary drinking water regulations	Not listed	EPA 2009
	RfD		IRIS 2019
	2-CP	$5x10^{-3}$ mg/kg/day	IRIS 2002a
	2,4-DCP	$3x10^{-3}$ mg/kg/day	IRIS 2002b
	2,4,5-TCP	$1x10^{-1}$ mg/kg/day	IRIS 2002c
	2,3,4,6-TeCP	$3x10^{-2}$ mg/kg/day	IRIS 1988
	Provisional RfD - Chronic		
	2,4,6-TCP	$1x10^{-3}$ mg/kg/day	EPA 2007a
	Provisional RfD - Subchronic		
	2-CP	$8x10^{-3}$ mg/kg/day	EPA 2007b
	2,4-DCP	$2x10^{-2}$ mg/kg/day	EPA 2007c
	2,4,5-TCP	$3x10^{-1}$ mg/kg/day	EPA 2007d
WHO	Drinking water quality guidelines		WHO 2017
	Guideline value[a]		
	2,4,6-TCP	0.2 mg/L	
FDA	Substances Added to Food	No data[b]	FDA 2019
	Cancer		
HHS	Carcinogenicity classification		
	2,4,6-TCP	Reasonably anticipated to be a human carcinogen (based on sufficient evidence in animal bioassays)	NTP 2016
EPA	Carcinogenicity classification		IRIS 2019
	2,4,6-TCP	Probably carcinogenic to humans—Group B2 (based on sufficient evidence in animal bioassays)	IRIS 1990
	Provisional carcinogenicity classification[c]		EPA 2007b, EPA 2007d
	2,4-DCP	Not likely to be carcinogenic to humans via oral exposure; inadequate information to assess the carcinogenic potential to humans via inhalation exposure	EPA 2007c

Table 7-1. Regulations and Guidelines Applicable to Chlorophenols

Agency	Description	Information	Reference
IARC	Carcinogenicity classification		
	Polychlorophenols or their sodium salts (combined exposures)	Possibly carcinogenic to humans—Group 2B (based on sufficient evidence in animal bioassays)	IARC 1999
	2,4-DCP	Evidence suggesting lack of carcinogenicity of 2,4-DCP in experimental animals	
	2,4,5-TCP	Inadequate evidence in experimental animals for carcinogenicity	
	2,4,6-TCP	Possibly carcinogenic to humans—Group 2B (based on sufficient evidence in animal bioassays)	IARC 2019
	Occupational		
ACGIH	TLV (TWA)	No data	ACGIH 2019
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction	No data	OSHA 2019a, 2019b, 2019c
NIOSH	REL (up to 10-hour TWA)	No data	NIOSH 2018
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2018
DOE	PACs-air[d]		DOE 2018a
	2-CP		
	PAC-1	2.3 mg/m^3	
	PAC-2	25 mg/m^3	
	PAC-3	150 mg/m^3	
	4-CP		
	PAC-1	1.5 mg/m^3	
	PAC-2	17 mg/m^3	
	PAC-3	99 mg/m^3	
	2,4-DCP		
	PAC-1	0.2 mg/m^3	
	PAC-2	2 mg/m^3	
	PAC-3	20 mg/m^3	
	2,4,5-TCP		
	PAC-1	2.5 mg/m^3	
	PAC-2	27 mg/m^3	
	PAC-3	160 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Chlorophenols

Agency	Description	Information	Reference
	2,4,6-TCP		
	PAC-1	2.5 mg/m^3	
	PAC-2	27 mg/m^3	
	PAC-3	160 mg/m^3	

[a]Available data inadequate to permit derivation of health-based guideline values for 2-CP and 2,4-DCP.
[b]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."
[c]For 2-CP and 2,4,5-TCP, available data were deemed inadequate for assessment of human carcinogenic potential.
[d]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; CP = chlorophenol; DCP = dichlorophenol; 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; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TCP = trichlorophenol; TeCP = tetrachlorophenol; TLV = threshold limit value; TWA = time-weighted average; WHO = World Health Organization

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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.

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2-Chlorophenol Chronic Inhalation MRL Worksheet....A-7
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2-Chlorophenol Intermediate Oral MRL Worksheet....A-10
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2,3,4-Trichlorophenol Acute Oral MRL Worksheet A-64
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2,4,5-Trichlorophenol Acute Oral MRL Worksheet A-70
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2,4,6-Trichlorophenol Intermediate Inhalation MRL Worksheet A-75
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2,3,5,6-Tetrachlorophenol Acute Oral MRL Worksheet A-115
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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Chlorophenol
CAS Numbers: 95-57-8
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 2-CP because the available studies evaluated limited endpoints and reported little detail.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. Available animal data consist of two rat studies of 2-CP with exposures for 4 or 6 hours (Monsanto 1975; Rhone-Poulenc 1991). These studies reported limited experimental details and evaluated limited endpoints. The only effects reported were clinical signs (tachypnea, restlessness, hunched posture) in the study by Rhone-Poulenc (1991). These data are not adequate for derivation of an acute-duration inhalation MRL.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Chlorophenol
CAS Numbers: 95-57-8
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 2-CP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Chlorophenol
CAS Numbers: 95-57-8
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for 2-CP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Chlorophenol
CAS Numbers: 95-57-8
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for 2-CP, because the only study that reported a LOAEL for effects other than death was very poorly reported.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Only two acute-duration studies (Borzelleca et al. 1985a; Daniel et al. 1993) examined toxicological endpoints other than death in animals exposed to 2-CP (see Table A-1). Daniel et al. (1993) exposed Sprague-Dawley rats (10/sex/dose) to 2-CP in corn oil by gavage at doses of 0, 13, 64, 129, and 257 mg/kg/day for 10 days. Endpoints evaluated in all animals included mortality, body weight, clinical signs, food and water consumption, hematology, clinical chemistry, gross necropsy, and organ weights. Histopathology was performed on a comprehensive list of tissues and organs in the control and high-dose groups. No effects were observed at any dose (Daniel et al. 1993). Borzelleca et al. (1985a) administered 2-CP (0, 35, 69, or 175 mg/kg/day) in corn oil by gavage to CD-1 ICR mice (12/sex/dose) for 14 days. Evaluations included mortality, clinical signs, body weight, hematology and clinical chemistry, hepatic microsomal mixed function oxidase activity, cell-mediated and humoral immune responses, organ weights, and gross pathology. All animals receiving 175 mg/kg/day died prior to scheduled sacrifice. In female mice, brain, liver, and spleen weights were reportedly reduced (magnitude of change and affected doses not reported). Body weights were reportedly reduced at 69 mg/kg/day on days 1, 8 and 15, but the publication did not provide any further detail. Hyperactivity was reported to occur in mice at both 35 and 69 mg/kg/day; this endpoint formed the basis for the LOAEL. The study by Borzelleca et al. (1985a) was very poorly reported; results were given qualitatively in tabular form, without any discussion of the incidence or severity of effects.

Table A-1. Summary of Acute-Duration Oral Studies of 2-Chlorophenol

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
CD-1 Mouse	14 days (GO)	ND	35	Hyperactivity	Borzelleca et al. 1985a
Body weight effects					
CD-1 Mouse	14 days (GO)	35	69	Reduced body weight (magnitude not reported)	Borzelleca et al. 1985a
Death					
CD-1 Mouse	14 days (GO)	69	175	20/20 mice died	Borzelleca et al. 1985a
Sprague-Dawley rat	9 days; PNDs 4–12 (GO)	ND	500	12/12 rats died by 9th day of dosing in range finding study	Hasegawa et al. 2005

Table A-1. Summary of Acute-Duration Oral Studies of 2-Chlorophenol

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Other					
Sprague-Dawley rat	10 days (GO)	257	ND	None	Daniel et al. 1993

(GO) = gavage in oil vehicle; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day

The finding of hyperactivity in mice exposed to 2-CP is not supported by other data for this compound or other chlorophenols (including 4-CP, 2,4-DCP, and tetrachlorophenols) that induce central nervous system depression, lethargy, tremors, and convulsions in humans (Kintz et al. 1992) and/or animals after oral or dermal exposure (Carreon et al. 1980a, 1980b; Hasegawa et al. 2005; Monsanto 1976; NTP 1989; Phornchirasilp et al. 1989b; Rhone-Poulenc 1991; Shen et al. 1983; Spencer and Williams 1950). Borzelleca et al. (1985a) also reported decreased body weight at the next higher dose (69 mg/kg/day), but the authors did not indicate the magnitude or statistical significance of this change, precluding its use as the basis for an acute-duration oral MRL.

The freestanding NOAEL of 257 mg/kg/day identified for the rat study by Daniel et al. (1993) is not a suitable basis for the oral MRL as it is higher than the dose that was lethal to all mice (175 mg/kg/day) in the study by Borzelleca et al. (1985a).

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Chlorophenol
CAS Numbers: 95-57-8
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
MRL: 0.08 mg/kg/day (provisional)
Critical Effect: Decreased litter size
References: Exon and Koller 1982, 1985
Point of Departure: NOAEL of 7.6 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 5
Species: Rats

MRL Summary: A provisional intermediate-duration oral MRL of 0.08 mg/kg/day is proposed for 2-CP based on a NOAEL of 7.6 mg/kg/day and LOAEL of 76 mg/kg/day for reproductive effects in rats administered 2-CP for 10 weeks premating and through mating and parturition (Exon and Koller 1982, 1985). A total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the NOAEL of 7.6 mg/kg/day.

Selection of the Critical Effect: No dose-response data are available for humans. Table A-2 summarizes results from candidate intermediate-duration oral studies in laboratory animals.

Table A-2. Summary of NOAELs and LOAELs from Candidate Intermediate-Duration Studies in Laboratory Animals Orally Exposed to 2-Chlorophenol

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Reproductive effects					
Rat (Sprague-Dawley)	Dams: from weaning through mating at PND 90, gestation, and lactation Offspring: from conception through weaning (PND 21) and for additional 12 weeks (W)	7.6	76	Increased percent of fetuses stillborn; decrease in litter size	Exon and Koller 1982, 1983a, 1983b, 1985
Neurological effects					
Rat (Sprague-Dawley)	18 days; PNDs 4–21 (GO)	50	300	Tremors	Hasegawa et al. 2005
Rat (Sprague-Dawley)	4 weeks (GO)	500	1,000	Tremors, hypoactivity, ataxia	Hasegawa et al. 2005

Table A-2. Summary of NOAELs and LOAELs from Candidate Intermediate-Duration Studies in Laboratory Animals Orally Exposed to 2-Chlorophenol

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Kidney effects					
Rat (Sprague-Dawley)	18 days; PNDs 4–21 (GO)	50	300	Renal basophilic tubules	Hasegawa et al. 2005
Other					
Rat (Sprague-Dawley)	13 weeks (GO)	150	ND	No effects on comprehensive parameters	Daniel et al. 1993

(GO) = gavage in oil vehicle; (W) = water; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day

The lowest LOAEL was identified based on decreased litter size and increased percent stillborn in the study reported by Exon and Koller (1982, 1985).

Selection of the Principal Study: The study by Exon and Koller (1982, 1983a, 1983b, 1985) was selected as the principal study. This study identified the lowest LOAEL for an endpoint (decreased litter size; increased percent stillborn pups) that has been observed for several other chlorophenols (2,4-DCP and 2,4,6-TCP).

Summary of the Principal Study:

Exon JH, Koller LD. 1982. Effects of transplacental exposure to chlorinated phenols. Environ Health Perspect 46:137-140.

Exon JH, Koller LD. 1983a. Alteration of transplacental carcinogenesis by chlorinated phenols. In: Jolley RL, Brungs WA, Cotruvo WA, et al., eds. Water chlorination: Environmental impact and health effects. Vol. 4, Book 2. Ann Arbor, MI: Ann Arbor Science, 1177-1188.

Exon JH, Koller LD. 1983b. Effects of chlorinated phenols on immunity in rats. Int J Immunopharmacol 5(2):131-136.

Exon JH, Koller LD. 1985. Toxicity of 2-chlorophenol, 2,4-dichlorophenol and 2,4,6-trichlorophenol. In: Jolley RL, ed. Water chlorination: Chemistry, environmental impact and health effects. Vol. 5. Chelsea, MI: Lewis Publishers, 307-330.

2-CP (97% pure) was administered in the drinking water of female Sprague-Dawley rats (12–20 rats/group) at concentrations of 0, 5, 50, or 500 ppm (0, 0.76, 7.6, or 76 mg/kg/day, respectively). Treatment with 2-CP was initiated at 3 weeks of age (weaning) and continued through mating (with untreated males at 90 days of age) and gestation. The treated dams were allowed to deliver. The reproductive/developmental parameters evaluated included conception, mean litter size, number of stillborn, birth and weaning pup weights, and survival of pups to weaning. At weaning, hematology evaluations (erythrocyte, leukocyte, hematocrit, hemoglobin, and mean corpuscular volume) were conducted in the offspring. After weaning, randomly selected offspring were exposed for an additional 12 weeks. Immune parameters (antibody production, delayed-type hypersensitivity response, and

phagocytic activity) were measured in 3–4 offspring/sex per group. At termination at the end of exposure, thymus, spleen, and liver weights of offspring were measured, and histological examinations of these organs were completed.

No changes in maternal body weight were observed. Mean litter size was reduced in rats treated at 76 mg/kg/day. The conception rate, pup birth and weaning weights, and survival of pups to weaning were similar in control and treated rats. No changes in hematological parameters were observed in the offspring at weaning. Treatment had no effect on any measure of humoral or cell-mediated immunity in offspring. In addition, there were no treatment-related changes in offspring liver, thymus, or spleen weights or histology. A LOAEL of 76 mg/kg/day and a NOAEL of 7.6 mg/kg/day were identified based on reduced litter size and increased percent of stillborn fetuses.

Selection of the Point of Departure for the MRL: The publications describing the principal study provided slightly different results for the litter size endpoint, as shown in Table A-3.

Table A-3. Litter Size and Percent Stillborn when Female Rats exposed to 2-Chlorophenol from Weaning through Mating (PND 90) to Parturition

	Dose (mg/kg/day)			
Endpoint (reference)	0	0.76	7.6	76
Number pregnant dams	8	9	9	12
Litter size (mean ± standard error) (Exon and Koller 1983b, 1985)	11.4±1.1	*11.6*±1.0	10.1±1.0	*9.1*±0.9[a]
Litter size (mean ± standard deviation) (Exon and Koller 1982)	11.4±1.2	*11.7*±3.5	10.1±2.3	*9.2*±4.3[b]
Percent stillborn (incidence of affected fetuses) (Exon and Koller 1982, 1985)	0 (0/91)	2 (2/105)	0 (0/91)	5 (6/*110*)[c,d]
Percent stillborn (incidence of affected fetuses) (Exon and Koller 1983b)	0 (0/91)	2 (2/105)	0 (0/91)	5 (6/*100*)[c,d]

[a]p≤0.1 compared with controls based on analysis of variance (ANOVA) and least squares means performed by the study authors (Exon and Koller 1985).
[b]Exon and Koller (1982) reported that "Litter size was significantly (p≤0.05) decreased in groups of dams treated with high levels of 2-CP;" however, the statistical test was not reported, and the accompanying table did not flag the dose level(s) at which the decrease was statistically significant.
[c]p≤0.1 compared with controls based on ANOVA and chi-square analysis performed by the study authors (Exon and Koller 1985).
[d]p≤0.05 (one-sided) compared with controls based on Fisher exact test performed for this review.

Italics indicates values reported inconsistently across the publications.

Sources: Exon and Koller 1982, 1983b, 1985

Because of the subtle inconsistencies in the data on litter size and percent stillborn, benchmark dose (BMD) modeling was not undertaken for these data. However, the reported information was considered adequate to define the middle dose (7.6 mg/kg/day) as a NOAEL; this value was used as the basis for the provisional intermediate-duration oral MRL for 2-CP.

Uncertainty Factor: The NOAEL was divided by a total uncertainty factor (UF) of 100:

- 10 UF for extrapolation from animals to humans
- 10 UF for human variability

Provisional MRL = NOAEL ÷ (UF)
7.6 mg/kg/day ÷ (10 x 10) = 0.08 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Decreases in litter size or the number of live pups per litter were reported in animals exposed to other chlorophenols, including 4-CP (BSRC 2011), 2,4-DCP and 2,4,6-TCP (Exon and Koller 1985).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Chlorophenol
CAS Numbers: 95-57-8
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 2-CP because the only available chronic study examined a limited number of endpoints.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. Only one chronic animal study of oral exposure to 2-CP was available (Exon and Koller 1985). Groups of 12–14 female Sprague-Dawley rats were exposed for 10 weeks before mating, and during gestation and lactation to one of three 2-CP concentrations (0, 5, 50, or 500 ppm, yielding estimated doses of 0.62, 6.2, or 62 mg/kg/day) in drinking water. Offspring (48–56/group) from these litters were kept on the same treatment regimen until death or 24 months of age. Hematological assessment of red and white cell counts, hemoglobin concentration, mean corpuscular volume (MCV), and packed-cell volume (PCV) was conducted on the offspring every two months. At termination, the animals were examined for tumors. In males and females exposed to 500 ppm, PCV, MCV, and the numbers of red cells were increased; this effect was especially pronounced after 14 months of exposure. Treatment with 2-CP had no effect on tumor incidence, latency, or type in males or females. No other endpoints were evaluated. These data are not considered adequate for use in deriving a chronic-duration oral MRL due to limitations in the evaluations conducted (only hematology and tumor assessments).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Chlorophenol
CAS Numbers: 106-48-9
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 4-CP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No acute-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Chlorophenol
CAS Numbers: 106-48-9
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 4-CP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Chlorophenol
CAS Numbers: 106-48-9
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for 4-CP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Chlorophenol
CAS Numbers: 106-48-9
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for 4-CP because the available studies examined limited endpoints, and because the lowest LOAEL was a serious LOAEL for mortality.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. Acute-duration oral studies of 4-CP are limited to a 2-week study examining hepatic endpoints (Phornchirasilp et al. 1989b) and a single-dose developmental toxicity screening study (Kavlock et al. 1990), both conducted in Sprague-Dawley rats. Table A-4 summarizes the available data.

Table A-4. Summary of Acute-Duration Oral Studies of 4-Chlorophenol

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Liver effects					
Rat (Sprague-Dawley)	2 weeks 7 days/week (GO)	2.58	ND	No adverse hepatic effects (see text)	Phornchirasilp et al. 1989b
Body weight effects					
Rat (Sprague-Dawley)	Once on GD 11 (GO)	667	1,000	Maternal body weight loss of 10 g	Kavlock 1990
Death					
Rat (Sprague-Dawley)	12 days (GO)	ND	1,000 (serious LOAEL)	Death (11/24 rats)	BSRC 2011

GD = gestation day; (GO) = gavage in oil vehicle); LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

In the developmental toxicity study, Kavlock et al. (1990) exposed groups of 12–13 female Sprague-Dawley rats by gavage on GD 11 and allowed them to deliver their litters. These authors examined maternal weight, clinical signs, implantations, and weight and viability of offspring through PND 6, and gross or external malformations detected until weaning. At 1,000 mg/kg, the dams lost an average of 10 g of body weight in the 24 hours postdosing; at 667 mg/kg, dams lost an average of 3 g. There were no effects on other parameters examined. In an intermediate-duration study (BSRC 2011), deaths were observed in the first 12 days of dosing at 1,000 mg/kg/day.

Phornchirasilp et al. (1989b) administered 4-CP in corn oil by gavage to groups of 4–6 male Sprague-Dawley rats for 1–2 weeks and examined hepatic microsomal protein and cytochrome P-450 levels, and electron microscopy of the liver. No changes in liver weights were seen. Hepatic microsomal protein levels were increased at doses ≥0.32 mg/kg/day, and cytochrome P-450 enzyme activities were increased at doses ≥0.64 mg/kg/day. After 2 weeks of exposure to 2.58 mg/kg/day, rats exhibited ultrastructural

changes in the liver, consisting of foamy cytoplasm and clustering of intracellular organelles. Microscopy findings were reported qualitatively (incidences and severity not reported). These effects were of uncertain significance because they were not supported by a later intermediate-duration study of Sprague-Dawley rats exposed to much higher doses (Hasegawa et al. 2005) in which no adverse hepatic effects (clinical chemistry, liver weight, or histopathological findings) were observed at doses up to 300 mg/kg/day for 18 days or 500 mg/kg/day for 4 weeks.

In summary, the lowest LOAEL (1,000 mg/kg/day) was also a serious LOAEL for mortality (BSRC 2011), and the other available studies (Kavlock 1990; Phornchirasilp et al. 1989b) examined limited endpoints (Kavlock 1990; Phornchirasilp et al. 1989b and) or exposed animals only once (Kavlock 1990). Thus, the data are not considered to be adequate for acute duration oral MRL derivation.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Chlorophenol
CAS Numbers: 106-48-9
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
MRL: 0.9 mg/kg/day (provisional)
Critical Effect: Decreased live births/litter
Reference: BSRC 2011
Point of Departure: $BMDL_{1SD}$ of 85.77 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 9
Species: Rat

MRL Summary: A provisional intermediate-duration oral MRL of 0.9 mg/kg/day was derived for 4-CP. It is derived from a $BMDL_{1SD}$ of 85.77 mg/kg/day based on reproductive effects (decreased number of live births per litter) in Sprague-Dawley rats given 4-CP by daily gavage in a 42–53-day reproductive/ developmental toxicity screening study (BSRC 2011). A total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied.

Selection of the Critical Effect: No dose-response data are available for humans. Table A-5 summarizes results from candidate intermediate-duration oral studies in experimental animals.

Phornchirasilp et al. (1989b) administered 4-CP in corn oil by gavage to groups of 4–6 male Sprague-Dawley rats for 4–8 weeks for examination of the liver by electron microscopy. Exposure for at least 4 weeks to 0.64 mg/kg/day resulted in morphological changes in hepatic ultrastructure (foamy cytoplasm and the proliferation and clustering of mitochondria and endoplasmic reticulum). Microscopy findings were reported qualitatively (incidences and severity not reported). These effects are of uncertain significance because a later study of Sprague-Dawley rats exposed to much higher doses (Hasegawa et al. 2005) did not observe any adverse hepatic effects (clinical chemistry, liver weight, or histopathological findings by light microscopy) at doses up to 300 mg/kg/day for 18 days (neonatal rats) or 500 mg/kg/day for 4 weeks (starting at 5–6 weeks of age). The lowest effect level was identified in the study by BSRC (2011) for reproductive effects.

Table A-5. Summary of Intermediate-Duration Oral Studies of 4-Chlorophenol

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Liver effects					
Rat (Sprague-Dawley)	4–8 weeks 7 days/week (GO)	0.64	ND	No adverse hepatic effects (see text)	Phornchirasilp et al. 1989b
Reproductive effects					
Rat (Sprague-Dawley)	41–53 days (GO)	40	200	Significantly reduced number live births; reduced number implantation sites	BSRC 2011

Table A-5. Summary of Intermediate-Duration Oral Studies of 4-Chlorophenol

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
Rat (Sprague-Dawley)	18 days, PNDs 4–21 (GO)	100	300 (serious LOAEL)	Tremors, hyperventilation, salivation	Hasegawa et al. 2005
Rat (Sprague-Dawley)	4 weeks (GO)	100	500 (serious LOAEL)	Tremors, hyperventilation, salivation	Hasegawa et al. 2005

(GO) = gavage in oil vehicle; LOAEL = lowest observed adverse effect level; NOAEL = no-observed-adverse-effect level; PND = postnatal day

Selection of the Principal Study: Of the four available studies of 4-CP, the lowest effect level was identified by BSRC (2011).

Summary of the Principal Study:

BSRC. 2011. Simplified reproductive toxicity testing of oral p-chlorophenol dosage using rats. Biosafety Research Center. Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare of Japan. Test No: C539 (115-222).

A reproductive/developmental toxicity screening study was conducted in Crl:CD (SD) rats (BSRC 2011). This study was unpublished and originally reported in Japanese; this summary is based on an official translation. Groups of 12 rats/sex/dose were given 4-CP (99.8% pure) in corn oil by gavage at doses of 0, 40, 200, or 1,000 mg/kg/day. Dosing began 14 days before mating and continued through a 14-day mating period (males) or until successfully mated (females). Males continued to be dosed for 14 additional days (total of 42 days) after mating, while females were dosed during gestation and through 3 days postpartum (total of 41–53 days). Evaluations in parental animals included clinical signs, body weight (weekly during most of the study), food intake, gross necropsy, reproductive organ weights, and histopathology (sites of gross anomalies, dead animals, animals that did not copulate, and males that did not impregnate females or females that did not become pregnant). Reproductive and developmental parameters were evaluated, including sperm formation cycle, estrus cyclicity, copulation index, fertility, gestation period, and implantations, litter size, offspring viability and weight, and external abnormalities.

Mortalities occurred in the high dose group (6/12 male and 5/12 female) but not in other groups; the deaths occurred within the first 12 days of dosing (BSRC 2011). Animals in this group exhibited a variety of clinical signs including salivation, prone position, lateral position, tremor, and clonic convulsion within a half hour of dosing and continuing up to 2 hours after dosing. Other clinical signs seen in this group (1,000 mg/kg/day) included dyspnea, abnormal respiratory noises, ptosis, and soiling of fur in the anogenital area. Salivation occurred at low frequency in males of the 200 mg/kg/day group. Body weights and food intake were decreased at the high dose but not affected at 200 mg/kg/day. Relative organ weight changes in the high dose group were attributable to the body weight changes. Gross and microscopic findings in parental animals were limited to the gastrointestinal tract and liver; these consisted of squamous epithelial hyperplasia and erosion or ulcers of the forestomach, ulcers in the esophagus, and centrilobular hepatocellular hypertrophy. These findings were observed in the high dose group; however, the low and mid-dose groups were not examined for histopathology. The number of live offspring at birth was significantly reduced in the 200 mg/kg/day group and lower at 1,000 mg/kg/day

(although not statistically significant, possibly due to the small number of survivors). Decreases in the numbers of implantation sites and offspring delivered were also seen at 200 mg/kg/day but were not significantly different from controls. No treatment-related effects were seen on other reproductive or developmental parameters. A LOAEL of 200 mg/kg/day and NOAEL of 40 mg/kg/day are identified for this study based on reduced numbers of live births and implantation sites.

Selection of the Point of Departure for the MRL: The $BMDL_{1SD}$ of 85.77 mg/kg/day for decreased live births/litter was selected as the basis of the MRL.

The numbers of live births/litter were subjected to BMD modeling to obtain a point of departure (POD) for MRL derivation. Numbers of implantations were not modeled because the changes were not statistically significant. The data on numbers of live births per litter were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 3.1.2). 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). Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the benchmark dose) was selected as the POD when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. For BMD modeling, the high dose group was omitted due to the substantial mortality in that group. A BMR of one standard deviation from the control mean was selected in the absence of a biologically-based BMR. The data as modeled are reported in Table A-6.

Table A-6. Live Births/litter in Sprague-Dawley Rats Exposed to 4-Chlorophenol by Gavage in Reproductive/ Developmental Toxicity Screening Study

		Live births/litter	
Dose	Number/group	Mean	SD
0	12	15.2	1.7
40	12	15.1	1.1
200	9	13.2	1.3

Source: BSRC 2011

The model predictions are shown in Table A-7.

Table A-7. Results from BMD Analysis (Constant Variance) of Live Births per Litter in Sprague-Dawley Rats Exposed to 4-Chlorophenol via Gavage in a Reproductive/Developmental Toxicity Screening Study (BSRC 2011)

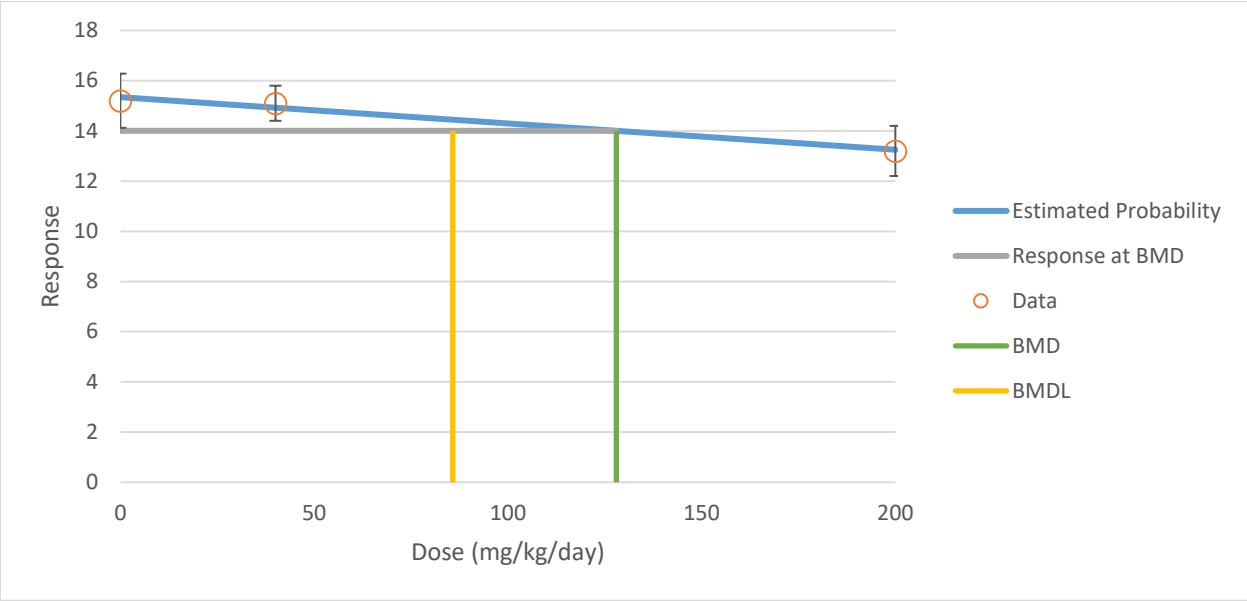
Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Exponential (model 2)[e]	0.01	0.31	0.52	0.50	-0.13	0.50	119.03	124.81	80.81
Exponential (model 3)[e]	0.01	0.31	NA	$-1.1x10^{-5}$	$-5.7 x10^{-5}$	$-9.12 x10^{-5}$	120.61	159.55	83.24
Exponential (model 4)[e]	0.01	0.31	0.52	0.50	-0.13	0.50	119.03	124.80	80.81
Exponential (model 5)[e]	0.01	0.31	<0.0001	$-2.01 x10^{-6}$	$-9.98 x10^{-6}$	$-5.0 x10^{-5}$	122.61	158.91	40.92
Hill[e]	0.01	0.31	<0.0001	-0.0003	$8.05 x10^{-5}$	-0.0003	122.61	54.43	41.50
Polynomial (2-degree)[e]	0.01	0.31	NA	$1.85 x10^{-6}$	$-1.92 x10^{-8}$	$-1.88 x10^{-6}$	120.61	162.09	87.75
Power[e]	0.01	0.31	NA	0.004	-0.0002	0.004	120.61	160.45	87.75
Linear[f]	**0.01**	**0.31**	**0.55**	**0.46**	**-0.11**	**0.46**	**118.97**	**127.96**	**85.77**

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[e]Restricted model
[f]Recommended model (lowest AIC). The variance model assuming constant variance was an adequate fit. The Exponential 2, exponential 4, and linear models provided adequate fit to the means. The BMDLs of the fit models were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (Linear).

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., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control)

The best-fitting model was the linear model with constant variance; this model yielded BMD_{1SD} and $BMDL_{1SD}$ values of 127.95 and 85.77 mg/kg/day. The fit of the selected model (linear, constant variance) is shown in Figure A-1.

Figure A-1. Fit of Linear Model (Constant Variance) to Data on Live Births/Litter in Rats Administered 4-Chlorophenol by Gavage Before Mating and During Mating and Gestation



Uncertainty Factor: The $BMDL_{1SD}$ is divided by a total uncertainty factor of 100:

- UF of 10 for extrapolation from animals to humans
- UF of 10 for human variability

Provisional MRL = $BMDL_{1SD}$ ÷ (UF)
85.77 mg/kg/day ÷ (10 x 10) = 0.9 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: While the data on reproductive toxicity of 4-CP are limited, other chlorophenols exhibit similar reproductive effects. In animals exposed to chlorophenols by oral administration, decreases in implantations, litter size, and/or live births per litter have been reported after intermediate-duration exposure to 2,4-DCP (46 mg/kg/day) (Exon and Koller 1985; Exon et al. 1984), and 2,4,6-TCP (46 mg/kg/day) (Exon and Koller 1985). 2,4-DCP also induced decreased numbers of implantation sites in a 2-generation study in Wistar-Hanover rats (Aoyama et al. 2005). Exposure of rats to 2,4,5-TCP on GD 14 resulted in an increased incidence of prenatal mortalities and resorptions (Hood et al. 1979).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 4-Chlorophenol
CAS Numbers: 106-48-9
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 4-CP.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. No chronic-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3-Dichlorophenol
CAS Numbers: 576-24-9
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 2,3-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No acute-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3-Dichlorophenol
CAS Numbers: 576-24-9
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 2,3-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3-Dichlorophenol
CAS Numbers: 576-24-9
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for 2,3-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3-Dichlorophenol
CAS Numbers: 576-24-9
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for 2,3-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. The only information on the health effects of 2,3-DCP following oral exposure in animals was acute lethality data following single exposures (Borzelleca et al. 1985b).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3-Dichlorophenol
CAS Numbers: 576-24-9
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for 2,3-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3-Dichlorophenol
CAS Numbers: 576-24-9
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 2,3-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. No chronic-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4-Dichlorophenol
CAS Numbers: 120-83-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 2,4-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No acute-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4-Dichlorophenol
CAS Numbers: 120-83-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 2,4-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4-Dichlorophenol
CAS Numbers: 120-83-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for 2,4-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4-Dichlorophenol
CAS Numbers: 120-83-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for 2,4-DCP because the lowest effect level represents a serious LOAEL in the absence of an identified NOAEL.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. Table A-8 summarizes results from candidate acute-duration oral studies in experimental animals.

Table A-8. Summary of Acute-Duration Studies in Experimental Animals Orally Exposed to 2,4-Dichlorophenol

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Reproductive effects					
Mouse (BALB/c)	14 days (W)	ND	270 (serious LOAEL)	Increased necrotic cell counts in seminiferous tubules, >3-fold increase in percent abnormal sperm, and decreased sperm motility	Aydin et al. 2009
Body weight effects					
Rat (Fischer 344)	10 days GDs 6–15 (GO)	200	375 (serious LOAEL)	Maternal toxicity: 23% decrease in weight gain; hair loss; red discharge from eyes, nose, and mouth	Rodwell et al. 1989
Rat (Fischer 344)	14 days (F)	500	1,000	19% decrease in body weight	NTP 1989

(F) = feed; GD = gestation day; (GO) = gavage in oil vehicle; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; (W) = water

It is not appropriate to derive an acute-duration oral MRL for 2,4-DCP because the lowest effect level (270 mg/kg/day; Aydin et al. 2009) represents a serious LOAEL in the absence of an identified NOAEL.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4-Dichlorophenol
CAS Numbers: 120-83-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
MRL: 0.02 mg/kg/day (provisional)
Critical Effect: Decreased delayed-type hypersensitivity response
References: Exon and Koller 1985, Exon et al. 1984
Point of Departure: $BMDL_{1SD}$ of 2.07 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 8
Species: Rats

MRL Summary: A provisional intermediate-duration oral MRL of 0.02 mg/kg/day is proposed for 2,4-DCP based on immunotoxicity in rats exposed from conception through weaning via maternal exposure and in drinking water for an additional 15 weeks (Exon and Koller 1985; Exon et al. 1984). BMD analysis of the data for delayed-type hypersensitivity response yielded a $BMDL_{1SD}$ of 2.07 mg/kg/day that was used as the POD. A total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the $BMDL_{1SD}$.

Selection of the Critical Effect: No dose-response data are available for humans. Table A-9 summarizes results from candidate intermediate-duration oral studies in laboratory animals.

Table A-9. Summary of Candidate Critical Effects for Provisional Intermediate-Duration Oral MRL for 2,4-DCP

Species (Strain)	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Immune system effects					
Rat (Sprague-Dawley)	Dams: from weaning through mating at PND 90, gestation, and lactation Offspring: from conception through weaning (PND 21) and for additional 15 weeks (W)	0.46[a]	4.6	Decreased delayed-type hypersensitivity response	Exon and Koller 1985; Exon et al. 1984

Table A-9. Summary of Candidate Critical Effects for Provisional Intermediate-Duration Oral MRL for 2,4-DCP

Species (Strain)	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Reproductive effects					
Rat (Sprague-Dawley)	Dams: from weaning through mating at PND 90, gestation, and lactation Offspring: from conception through weaning (PND 21) and for additional 15 weeks (W)	4.6	46	Decreased mean litter size	Exon and Koller 1985; Exon et al. 1984
Mouse (CD-1)	90 days (W)	500	ND	No adverse effect on sperm motility or acrosome integrity, or ovum penetration	Seyler et al. 1984
Liver effects					
Mouse (ICR, ddN)	6 months (F)	100	230	Hepatocyte swelling	Kobayashi et al. 1972
Mouse (B6C3F1)	13 weeks (F)	ND	325	Minimal hepatocellular necrosis	NTP 1989
Hematological effects					
Rat (Fischer 344)	13 weeks (F)	250	500 (serious LOAEL)	Bone marrow atrophy	NTP 1989
Body weight effects					
Rat (Wistar)	10 weeks premating through gestation and lactation until weaning of 3rd generation (F)	134	543	Decreased body weights in parental and F1 generations	Aoyama et al. 2005
Other					
Mouse (CD-1)	13 weeks (W)	383	ND	No adverse effects noted	Borzelleca et al. 1985a, 1985c

(F) = feed; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day; (W) = water

Selection of the Principal Study: The lowest LOAEL (4.6 mg/kg/day) was identified for immunotoxicity in Sprague-Dawley rats exposed to 2,4-DCP from conception through weaning via maternal exposure and for an additional 15 weeks after weaning. No other LOAEL was within a factor of 10 of the lowest value; thus, this study was considered the principal study for intermediate-duration oral MRL derivation.

Summary of the Principal Study:

Exon JH, Koller LD. 1985. Toxicity of 2-chlorophenol, 2,4-dichlorophenol and 2,4,6-trichlorophenol. In: Jolley RL, ed. Water chlorination: Chemistry, environmental impact and health effects. Vol. 5. Chelsea, MI: Lewis Publishers, 307-330.

Exon JH, Henningsen GM, Osborne CA, et al. 1984. Toxicologic, pathologic, and immunotoxic effects of 2,4-dichlorophenol in rats. J Toxicol Environ Health 14:723-730.

2,4-DCP (99% pure) was administered in the drinking water of female Sprague-Dawley rats (12–20 rats/group) at concentrations of 0, 3, 30, or 300 ppm (0, 0.46, 4.6, or 46 mg/kg/day, respectively). Treatment with 2,4-DCP was initiated at 3 weeks of age (weaning) and continued through mating (with untreated males at 90 days of age) and gestation. The treated dams were allowed to deliver. The reproductive/developmental parameters evaluated included conception, mean litter size, number of stillborn, birth and weaning pup weights, and survival of pups to weaning. At weaning, hematology evaluations (erythrocyte, leukocyte, hematocrit, hemoglobin, and mean corpuscular volume) were conducted in the offspring. After weaning, randomly selected offspring were exposed for an additional 12 weeks. Immune parameters (antibody production, delayed-type hypersensitivity response, phagocytic activity) were measured in 3–4 offspring/sex per group. At termination at the end of exposure, thymus, spleen, and liver weights of offspring were measured, and histological examinations of these organs were completed.

The conception rate, pup birth weight, and survival of pups to weaning were similar in control and treated rats. The percent of stillborn pups was increased in all treatment groups, but this increase was not statistically significant. Mean litter size was similar in rats treated with up to 0, 0.46, or 4.6 mg/kg/day; however, mean litter size was significantly reduced ($p<0.1$) in rats of the 46 mg/kg/day group (6.3±1.6 versus 9.8±1.3 in controls). No effects on body weight or thymus weight were observed. Delayed-type hypersensitivity was significantly ($p<0.05$) decreased at 4.6 and 46 mg/kg/day. Delayed-type hypersensitivity was evaluated by sensitizing the rats with a subcutaneous injection of bovine serum albumin and then administering a challenge injection of bovine serum albumin in the left rear footpad 1 week later. The right rear footpad received a sham injection of saline. The difference in footpad swelling between the left and right footpads is a measure of the immune response to bovine serum albumin. A decrease in footpad swelling indicates suppression of cell-mediated immunity. Antibody production was significantly ($p<0.05$) increased at 46 mg/kg/day. No effects on phagocytic activity were observed. Spleen and liver weights were significantly ($p<0.05$) increased at 46 mg/kg/day. 2,4-DCP treatment did not result in any microscopic changes in the liver, spleen or thymus. A LOAEL of 4.6 mg/kg/day and a NOAEL of 0.46 mg/kg/day were identified based on effects on cell-mediated immunity (reduced delayed-type hypersensitivity response).

Selection of the Point of Departure for the MRL: The data for decreased delayed-type hypersensitivity response (measured as footpad swelling in response to bovine serum albumin injection) are shown in Table A-10.

Table A-10. Cell-mediated Immunity Effects in Rats Exposed to 2,4-DCP from Conception Through Weaning and for an Additional 15 Weeks

		Footpad swelling (mm)			
Concentration in water	Dose (mg/kg/day)	Number of rats	Mean	Standard error of the mean	Standard deviation (calculated)
0	0	10	1.1	0.13	0.41
3	0.46	10	0.85	0.11	0.35
30	4.6	10	0.67	0.11	0.35
300	46	10	0.63	0.11	0.35

Sources: Exon and Koller 1985; Exon et al. 1984

These data were subjected to BMD modeling to obtain a POD for MRL derivation. Data were fit to all available continuous models in EPA's BMDS (version 3.1.2). 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 was selected as the POD when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen. A BMR of 1 standard deviation from the control mean was used.

In modeling of the data, the p-value for test 1 was 0.11, which exceeds the threshold of 0.05 and suggests lack of evidence for a dose-response. This result probably stems from the large standard deviations on the data points. The study authors reported a statistical difference ($p \leq 0.05$) between the high- and control-groups using analysis of variance and least squares means, and a t-test estimated for this document using the provided means and standard errors also showed a significant difference (two-tailed $p = 0.0129$). Therefore, the data were considered to show a dose-response despite the test 1 p-value. The model predictions for footpad swelling are shown in Table A-11 and the fit of the selected (Exponential 4) model is shown in Figure A-2.

Table A-11. Results from BMD Analysis (Constant Variance) of Delayed Type Hypersensitivity (Footpad Swelling) in Female Sprague-Dawley Rats Exposed to 2,4-Dichlorophenol

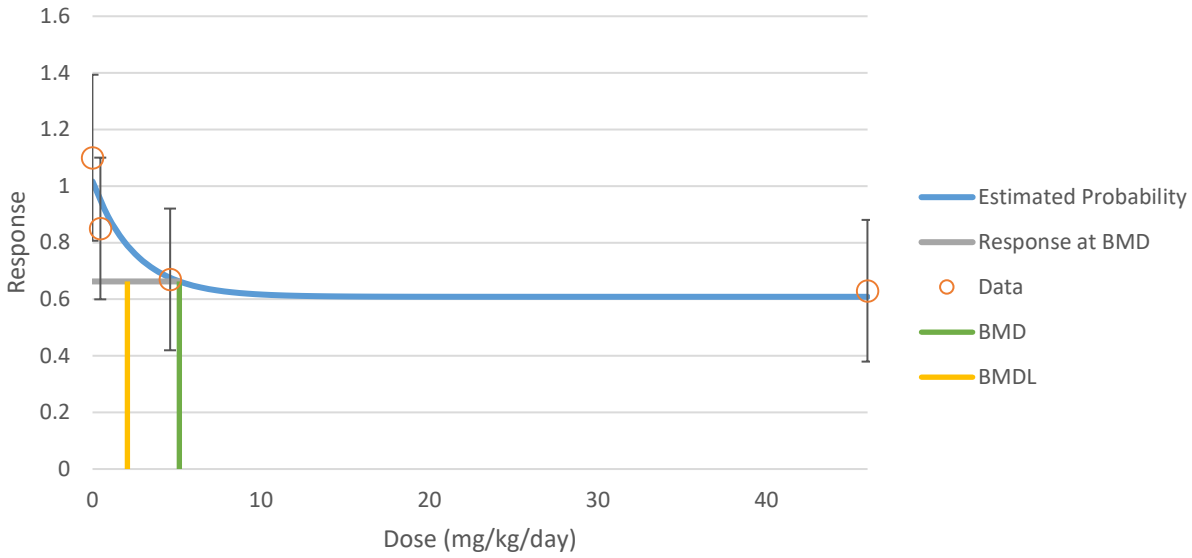
Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Exponential (model 2)[e]	0.11	0.94	0.05	0.23	ND	1.73	41.07	63.11	27.59
Exponential (model 3)[e]	0.11	0.94	0.05	0.23	ND	1.73	41.07	63.11	27.59
Exponential (model 4)[e,f]	**0.11**	**0.94**	**0.49**	**-0.05**	**0.19**	**-0.89**	**36.29**	**5.15**	**2.07**
Exponential (model 5)[e]	0.11	0.94	0.49	-0.05	0.19	-0.89	36.29	5.15	2.07
Hill[e]	0.11	0.94	0.97	-0.01	0.03	0.03	36.88	1.15	0.00
Polynomial (2-degree)[e]	0.11	0.94	0.04	0.16	ND	1.77	41.21	61.80	33.33
Polynomial (3-degree)[e]	0.11	0.94	0.04	0.16	ND	1.77	41.21	61.80	33.33
Power[e]	0.11	0.94	0.04	0.16	ND	1.77	41.21	61.80	33.33
Linear	0.11	0.94	0.04	0.16	ND	1.77	41.21	61.80	33.33

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[e]Restricted model
[f]Recommended model. There was an adequate fit to the variance when assuming constant variance. Only the Exponential 4, Exponential 5, and Hill models provided adequate fit to the means; however, the Hill model predicted a BMDL of 0 so it was not considered further. The Exponential models provided identical BMDs, BMDLs, and AICs.

The p-value for the test for significant difference was >0.05; there may not be a dose-response.

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., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control)

Figure A-2. Fit of Exponential 4 Model to Data on Decreased Delayed-Type Hypersensitivity Response (Footpad Swelling) in Rats Administered 2,4-Dichlorophenol from Conception Through Weaning and for 12 Additional Weeks in Drinking Water



The $BMDL_{1SD}$ from the selected (Exponential 4) model was 2.07 mg/kg/day; this value was selected as the POD for derivation of the provisional intermediate-duration oral MRL.

Uncertainty Factor: The $BMDL_{1SD}$ of 2.07 mg/kg/day was divided by a total uncertainty factor (UF) of 100:

- 10 UF for extrapolation from animals to humans
- 10 UF for human variability

Provisional MRL = $BMDL_{1SD}$ ÷ (UF)
2.07 mg/kg/day ÷ (10 x 10) = 0.02 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: In addition to effects on cell-mediated immunity, 2,4-DCP exposure resulted in increased serum antibodies to keyhole limpet hemocyanin in rats exposed to higher doses (46 mg/kg/day) in the principal study (Exon and Koller 1985; Exon et al. 1984).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4-Dichlorophenol
CAS Numbers: 120-83-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 2,4-DCP; the available chronic studies identified higher effect levels than the intermediate duration studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. Table A-12 summarizes results from candidate chronic-duration oral studies in experimental animals that identified the lowest NOAELs and/or LOAELs.

Table A-12. Summary of NOAELs and LOAELs from Candidate Chronic-Duration Studies in Experimental Animals Orally Exposed to 2,4-Dichlorophenol

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Respiratory effects					
Rat (Fischer 344)	103 weeks (F)	ND	210	Nasal lesions; multifocal degeneration of respiratory epithelium	NTP 1989
Body weight effects					
Mouse (B6C3F1)	103 weeks (F)	430	820	Maximum 19% decrease in body weight relative to controls	NTP 1989

(F) = feed; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

The lowest effect level identified in the chronic studies by NTP (1989) was the LOAEL of 210 mg/kg/day based on nasal and respiratory tract lesions in rats. This value is higher than intermediate-duration LOAELs identified for immunotoxicity (decreased delayed-type hypersensitivity response at 4.6 mg/kg/day) (Exon and Koller 1985; Exon et al. 1984) and reproductive toxicity (decreased mean litter size at 46 mg/kg/day) (Exon and Koller 1985; Exon et al. 1984; see Table A-9 above). As the available chronic studies did not evaluate these sensitive endpoints and identified higher effect levels than the intermediate-duration studies, they are not considered adequate for derivation of a chronic oral MRL for 2,4-DCP.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,5-Dichlorophenol
CAS Numbers: 583-78-8
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 2,5-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No acute-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,5-Dichlorophenol
CAS Numbers: 583-78-8
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 2,5-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,5-Dichlorophenol
CAS Numbers: 583-78-8
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for 2,5-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,5-Dichlorophenol
CAS Numbers: 583-78-8
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for 2,5-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans The only information on the health effects of 2,5-DCP following oral exposure in animals was acute lethality data following single exposures (Borzelleca et al. 1985b).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,5-Dichlorophenol
CAS Numbers: 583-78-8
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for 2,5-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,5-Dichlorophenol
CAS Numbers: 583-78-8
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 2,5-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. No chronic-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3,4-Dichlorophenol
CAS Numbers: 95-77-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 3,4-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No acute-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3,4-Dichlorophenol
CAS Numbers: 95-77-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 3,4-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3,4-Dichlorophenol
CAS Numbers: 95-77-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for 3,4-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3,4-Dichlorophenol
CAS Numbers: 95-77-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for 3,4-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. The only information on the health effects of 3,4-DCP following oral exposure in animals was acute lethality data following a single exposure (Borzelleca et al. 1985b).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3,4-Dichlorophenol
CAS Numbers: 95-77-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for 3,4-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3,4-Dichlorophenol
CAS Numbers: 95-77-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 3,4-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. No chronic-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3,5-Dichlorophenol
CAS Numbers: 591-35-5
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 3,5-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No acute-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3,5-Dichlorophenol
CAS Numbers: 591-35-5
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 3,5-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3,5-Dichlorophenol
CAS Numbers: 591-35-5
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for 3,5-DCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3,5-Dichlorophenol
CAS Numbers: 591-35-5
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for 3,5-DCP. The only acute-duration study that evaluated effects other than lethality was available only as an abstract and the full study report could not be located.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans for 3,5-DCP. The only information on the health effects of 3,5-DCP following oral exposure in animals was acute lethality data following a single exposure (Borzelleca et al. 1985b).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3,5-Dichlorophenol
CAS Numbers: 591-35-5
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for 3,5-DCP due to the lack of intermediate-duration studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans for 3,5-DCP. No intermediate-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3,5-Dichlorophenol
CAS Numbers: 591-35-5
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 3,5-DCP due to the lack of chronic-duration studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. No chronic-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4-Trichlorophenol
CAS Numbers: 15950-66-0
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 2,3,4-TCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No acute-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4-Trichlorophenol
CAS Numbers: 15950-66-0
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 2,3,4-TCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4-Trichlorophenol
CAS Numbers: 15950-66-0
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for 2,3,4-TCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4-Trichlorophenol
CAS Numbers: 15950-66-0
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for 2,3,4-TCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. No acute-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4-Trichlorophenol
CAS Numbers: 15950-66-0
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for 2,3,4-TCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4-Trichlorophenol
CAS Numbers: 15950-66-0
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 2,3,4-TCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. No chronic-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,5-Trichlorophenol
CAS Numbers: 95-95-4
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 2,4,5-TCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No acute-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,5-Trichlorophenol
CAS Numbers: 95-95-4
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 2,4,5-TCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,5-Trichlorophenol
CAS Numbers: 95-95-4
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for 2,4,5-TCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,5-Trichlorophenol
CAS Numbers: 95-95-4
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for 2,4,5-TCP, as the available studies examined limited endpoints and/or reported doses imprecisely.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans for 2,4,5-TCP. Available acute-duration animal studies of oral exposure to 2,4,5-TCP include a single dose acute lethality study in rats (McCollister et al. 1961), a 1- or 3-day developmental toxicity study in mice (Hood et al. 1979), a 14-day developmental toxicity study in rats (Chernoff et al. 1990), and a 14-day gavage study (Carlson 1978). In the 3-day developmental toxicity study, an increase in prenatal mortalities and resorptions occurred when pregnant mice were dosed with 800–900 mg/kg on GD 14 but not when dosed with 250–300 mg/kg/day on GDs 13–15. Maternal mortalities occurred at the only tested dose, 650 mg/kg/day in the 14-day developmental toxicity study in rats (Chernoff et al. 1990). No effects were observed on hepatic enzyme levels, the only endpoints evaluated, at doses up to 400 mg/kg/day in the 14-day gavage study in rats (Carlson 1978). These data are not considered adequate for acute-duration MRL derivation due to the limited evaluations in the study by Carlson (1978), mortalities in the 14-day developmental toxicity study (Chernoff et al. 1990), and imprecise doses and brief exposure duration (1 or 3 days) in the mouse developmental study by Hood et al. (1979).

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,5-Trichlorophenol
CAS Numbers: 95-95-4
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
MRL: 1.0 mg/kg/day (provisional)
Critical Effect: Degenerative changes in the kidneys and liver
Reference: McCollister et al. 1961
Point of Departure: NOAEL of 100 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 3
Species: Rats

MRL Summary: A provisional intermediate-duration oral MRL of 1.0 mg/kg/day was derived for 2,4,5-TCP based on degenerative changes in the kidneys and liver of rats administered 300 mg/kg/day 2,4,5-TCP in feed for 98 days (McCollister et al. 1961). A total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the NOAEL of 100 mg/kg/day.

Selection of the Critical Effect: No dose-response data are available for humans. McCollister et al. (1961) is the only adequate intermediate-duration oral study of 2,4,5-TCP. A series of studies in animals exposed orally to 2,4,5-TCP was performed by McCollister et al. 1961; these included an oral LD_{50} study in rats, a study of rats exposed to doses up to 1,000 mg/kg/day by gavage on 18 of 24 days, a study of rabbits exposed to doses up to 500 mg/kg by gavage on 20 of 28 days, and a 98-day rat study using dietary administration at doses up to 1,000 mg/kg/day. McCollister et al. (1961) reported temporary weight loss and a 15% increase in relative kidney weight in the rats exposed by gavage for 18 doses of 1,000 mg/kg. The authors reported very slight kidney changes in rabbits exposed to 100 mg/kg, and very slight kidney and liver changes at 500 mg/kg; no further details were provided on the nature of these changes. Only the 98-day study was reported with enough detail to identify effect levels; the rat and rabbit gavage studies were described briefly with limited information on results.

Selection of the Principal Study: Only the 98-day study was reported with enough detail to identify effect levels; the rat and rabbit gavage studies were described briefly with limited information on results.

Summary of the Principal Study:

McCollister DD, Lockwood DT, Rowe VK. 1961. Toxicologic information on 2,4,5-trichlorophenol. Toxicol Appl Pharmacol 3:63-70.

2,4,5-TCP was administered to 10 male and 10 female rats in the diet at 0, 0.01, 0.03, 0.1, 0.3, or 1% for 98 days. Doses of 0, 10, 30, 100, 300, and 1,000 mg/kg/day (respectively) were provided by the authors. Body weights were measured regularly and animals were observed for clinical signs of toxicity. Food intake was recorded for the first month of the experiment. At termination, hematological parameters (hematocrit, hemoglobin, white blood cell counts) and BUN were measured in a subgroup of female rats (number not reported). Organ weights (lungs, heart, liver, kidneys, spleen, testes, and brain) were recorded, and histologic examinations of these organs along with the pancreas and adrenal glands were completed. At 100 mg/kg/day, there were no adverse effects in either sex. At doses of 300 and

1,000 mg/kg/day, rats showed diarrhea and pathologic changes in the liver and kidneys. In the highest dose group, the changes in the kidneys were described as moderate degenerative changes in the epithelial lining of the convoluted tubules and early proliferation of the interstitial tissue, and the changes in the liver were described as cloudy swelling with occasional areas of focal necrosis, slight proliferation of the bile ducts and early portal cirrhosis. These liver and kidney changes in the 300 mg/kg/day group were described as similar but milder in severity than in the high-dose group. At the 1,000 mg/kg/day level, there was also a significant retardation (24% decrease in body weight gain) of growth in females. Relative kidney and liver weights were not affected by treatment, nor was BUN; no other clinical chemistry parameters were evaluated. A LOAEL of 300 mg/kg/day and NOAEL of 100 mg/kg/day were identified for degenerative changes in the kidneys and liver (incidences not reported) and diarrhea.

Selection of the Point of Departure for the MRL: The NOAEL of 100 mg/kg/day for degenerative changes in the liver and kidney was selected as the POD. BMD modeling of the data in the study by McCollister et al. (1961) was not possible because the study findings were reported qualitatively.

Uncertainty Factor: The NOAEL was divided by a total UF of 100:

- 10 UF for extrapolation from animals to humans
- 10 UF for human variability

Provisional MRL = NOAEL ÷ (UF x MF)
100 mg/kg/day ÷ (10 x 10) = 1.0 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The liver is a well-established target of chlorophenol toxicity in laboratory animals. Hepatic effects including clinical chemistry changes, increased liver weight, hepatocellular hypertrophy, and necrosis have been observed in rats or mice after oral exposure to 2-CP, 4-CP, 2,4-DCP, 2,4,6-TCP, and 2,3,4,6-TeCP (Aydin et al. 2009; Bercz et al. 1990; BSRC 2011; Dodd et al. 2012; Exon and Koller 1985; Exon et al. 1984; Hasegawa et al. 2005; Kobayashi et al. 1972; NCI 1979; NTP 1989).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,5-Trichlorophenol
CAS Numbers: 95-95-4
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 2,4,5-TCP due to the lack of chronic duration studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. No chronic-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,6-Trichlorophenol
CAS Numbers: 88-06-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 2,4,6-TCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No acute-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,6-Trichlorophenol
CAS Numbers: 88-06-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 2,4,6-TCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,6-Trichlorophenol
CAS Numbers: 88-06-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for 2,4,6-TCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,6-Trichlorophenol
CAS Numbers: 88-06-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for 2,4,6-TCP, as the only available study examined limited endpoints.

Rationale for Not Deriving an MRL: The acute-duration oral data were not considered adequate for derivation of an acute-duration oral MRL for 2,4,6-TCP.

No adequate exposure-response data were available for humans. Only one acute-duration animal study of oral exposure to 2,4,6-TCP was located. In that study (Carlson 1978), no effects were observed on hepatic enzyme levels, the only endpoints evaluated, in rats exposed to doses up to 400 mg/kg/day administered by gavage for 14 days (Carlson 1978). These data were not considered adequate for MRL derivation due to the limited evaluations performed and the lack of information needed to identify the critical effect.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,6-Trichlorophenol
CAS Numbers: 88-06-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
MRL: 0.005 mg/kg/day (provisional)
Critical Effect: Increased absolute liver weight
Reference: Exon and Koller 1985
Point of Departure: NOAEL of 0.46 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 6
Species: Rats

MRL Summary: A provisional intermediate-duration oral MRL of 0.005 mg/kg/day was derived for 2,4,6-TCP based on increased absolute liver weight in rats exposed to 2,4,6-TCP from conception through weaning (via maternal exposure) and for 12 additional weeks in drinking water (Exon and Koller 1985). The NOAEL of 0.46 mg/kg/day was used as the POD. A total uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability) was applied to the NOAEL to obtain the provisional intermediate-duration oral MRL.

Selection of the Critical Effect: No dose-response data are available for humans. Table A-13 summarizes results from candidate intermediate-duration oral studies in laboratory animals. The lowest LOAEL was for increased absolute liver weight in the rat study by Exon and Koller (1985). Exon and Koller (1985) did not evaluate clinical chemistry or histopathology. Bercz et al. (1990) did not observe liver effects at a much higher dose (80 mg/kg/day) in the same strain of rat. However, Exon and Koller (1985) exposed Sprague-Dawley rats beginning at conception, while Bercz et al. (1990) exposed Sprague-Dawley rats beginning at 49 days of age. Thus, the lower dose at which liver effects were seen by Exon and Koller (1985) may reflect greater sensitivity of younger rats. The liver is a well-established target organ for chlorophenol toxicity, supporting the selection of this endpoint for the critical effect. Hepatic effects including clinical chemistry changes, increased liver weights, hepatocellular hypertrophy, vacuolation, and necrosis have been observed in rats or mice after oral exposure to 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, and 2,3,4,6-TeCP (Aydin et al. 2009; BSRC 2011; Dodd et al. 2012; Exon and Koller 1985; Exon et al. 1984; Hasegawa et al. 2005; Kobayashi et al. 1972; McCollister et al. 1961; NTP 1989).

Table A-13. Summary of Intermediate-Duration Studies in Experimental Animals Orally Exposed to 2,4,6-Trichlorophenol

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Liver effects					
Rat (Sprague-Dawley)	Dams: from weaning through mating at PND 90, gestation, and lactation Offspring: from conception through weaning (PND 21) and for additional 12 weeks (W)	0.46	4.6	15% increase in offspring absolute liver weight	Exon and Koller 1985

Table A-13. Summary of Intermediate-Duration Studies in Experimental Animals Orally Exposed to 2,4,6-Trichlorophenol

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Rat (Sprague-Dawley)	90 days (GO)	80	240	14% increase in relative liver weight	Bercz et al. 1990
Reproductive effects					
Rat (Sprague-Dawley)	Dams: from weaning through mating at PND 90, gestation, and lactation Offspring: from conception through weaning (PND 21) and for additional 12 weeks (W)	4.6	46	Decreased mean litter size	Exon and Koller 1985
Developmental effects					
Rat (Long-Evans hooded)	2 week premating at 5 days/week; then GDs 1–21 at 7 days/week (GO)	100	500	10–11% reduction in litter weight	Blackburn et al. 1986
Body weight effects					
Rat (F344)	7 weeks, 7 days/week (F)	500	735	11–16% decreased body weight	NCI 1979

(F) = feed; (GO) = gavage in oil vehicle; GD = gestation day; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day; (W) = water

Selection of the Principal Study: The Exon and Koller (1985) study was selected as the principal study because this study identified the lowest LOAEL and NOAEL (4.6 and 0.46 mg/kg/day, respectively, for hepatic effects).

Summary of the Principal Study:

Exon JH, Koller LD. 1985. Toxicity of 2-chlorophenol, 2,4-dichlorophenol and 2,4,6-trichlorophenol. In: Jolley RL, ed. Water chlorination: Chemistry, environmental impact and health effects. Vol. 5. Chelsea, MI: Lewis Publishers, 307-330.

The effect of pre- and postnatal exposure to 2,4,6-TCP on body and organ weights was evaluated in rats. 2,4,6-TCP (purity=98%) was administered in the drinking water of female Sprague-Dawley rats (12–14 rats/group) at concentrations of either 0, 3, 30, or 300 ppm (0, 0.46, 4.6, or 46 mg/kg/day, respectively). Treatment with 2,4,6-TCP was initiated at 3 weeks of age and continued through breeding (at 90 days of age), parturition, and lactation. The reproductive/developmental parameters evaluated included conception (%), mean litter size, number of stillborn, birth weight of pups, and survival of pups to weaning (%). Ten randomly selected pups (sex not specified) from each group were weaned at 3 weeks and continued on 2,4,6-TCP treatment for 12 weeks. Mean body weight and mean weights of thymus, spleen, and liver were recorded. Histopathology examination was not performed. Mean body and organ weights were evaluated statistically by analysis of variance and least-square means.

The conception, pup birth weight, and survival of pups to weaning were similar in control and treated rats. The percentage of stillborn pups was increased in all treatment groups, but this increase was not statistically significant. Mean litter size was similar in rats treated with 0, 0.46, or 4.6 mg/kg/day; however, mean litter size was significantly reduced ($p<0.1$) in rats of the 46 mg/kg/day group. The mean litter sizes were 12.1, 11.3, 11.2, and 9.1 in control through high dose respectively. Mean terminal body weight and mean thymus weight of offspring exposed pre- and postnatally to 2,4,6-TCP were comparable to those of controls. Mean spleen weight was significantly increased ($p< 0.05$) in offspring treated with 46 mg/kg/day, and mean liver weight was significantly increased at 4.6 (15% higher than controls) and 46 mg/kg/day (29% higher than controls). The LOAEL and NOAEL for this study were 4.6 and 0.46 mg/kg/day (respectively) based on increased liver weight.

Selection of the Point of Departure for the MRL: The NOAEL of 0.46 mg/kg/day was used as the POD for the MRL.

The lowest LOAEL of 4.6 mg/kg/day for increased absolute liver weight (Exon and Koller 1985) was 10-fold lower than the nearest LOAEL (46 mg/kg/day); thus, only this endpoint and study was considered for the POD. The absolute liver weight reported by Exon and Koller (1985) are shown in Table A-14.

Table A-14. Absolute Liver Weight in Rats Exposed to 2,4,6-Trichlorophenol from Conception Through Weaning and for 12 Additional Weeks

	Dose (mg/kg/day)			
Endpoint (reference)	0	0.46	4.6	46
Liver weight (mean±standard error)	10.9±0.4	11.9±0.3	12.5±0.5[a]	14.1±0.6[a]
Calculated standard deviation	1.26	0.95	1.58	1.90
Number/group	10	10	10	10

[a]$p \leq 0.05$ compared with controls based on analysis of variance (ANOVA) and least squares means performed by study authors.

Source: Exon and Koller 1985

The liver weight data were fit to all available continuous models in EPA's BMDS (version 3.1.2). 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 was selected as the POD when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen. A BMR of 1 standard deviation from the control mean was selected for the liver weight data.

The model predictions for absolute liver weight are shown in Table A-15 and the fit of the selected (Hill) model is shown in Figure A-3.

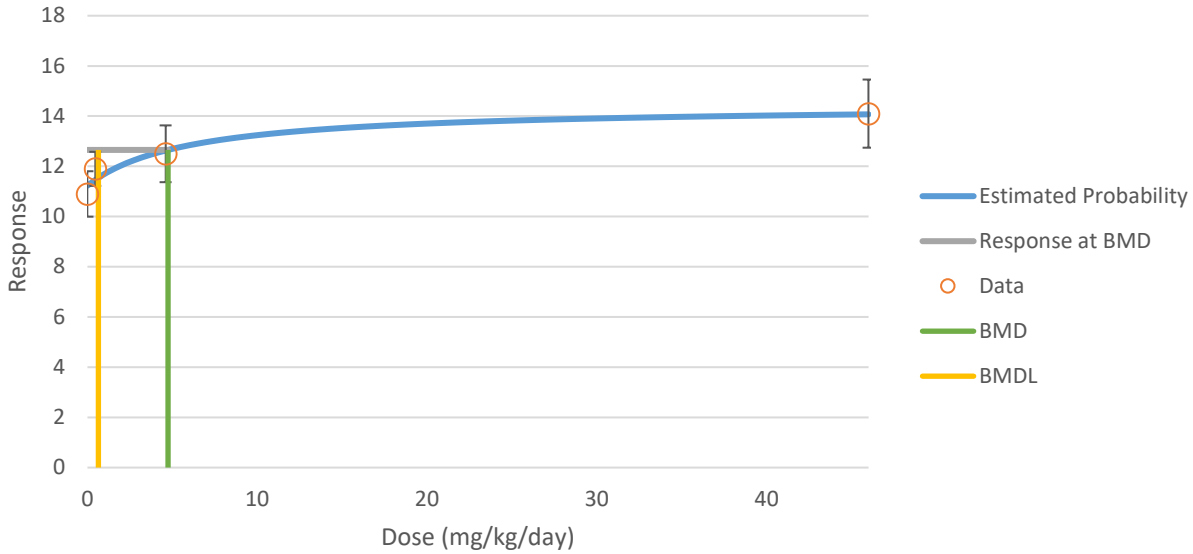
Table A-15. Results from BMD Analysis (Constant Variance) of Absolute Liver Weights in Male and Female Sprague-Dawley Rats Exposed to 2,4,6-Trichlorophenol

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Exponential (model 2)[e]	<0.001	0.17	0.09	1.30	-0.11	-1.64	150.79	ND	ND
Exponential (model 3)[e]	<0.001	0.17	0.09	1.30	-0.11	-1.64	150.79	ND	ND
Exponential (model 4)[e]	<0.001	0.17	0.18	-0.18	0.02	1.00	149.71	5.24	1.97
Exponential (model 5)[e]	<0.001	0.17	0.18	-0.18	0.02	1.00	149.71	5.24	1.97
Hill[e,f]	***<0.001***	***0.17***	***0.20***	***-0.29***	***0.06***	***0.97***	***149.54***	***4.75***	***0.64***
Polynomial (2-degree)[e]	<0.001	0.17	0.09	1.27	-0.13	-1.62	150.67	ND	ND
Polynomial (3-degree)[e]	<0.001	0.17	0.09	1.27	-0.13	-1.62	150.67	ND	ND
Power[e]	<0.001	0.17	0.09	1.27	-0.13	-1.62	150.67	ND	ND
Linear	<0.001	0.17	0.09	1.27	-0.13	-1.62	150.67	ND	ND

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[e]Restricted model.
[f]Recommended model. There was an adequate fit to the variance when assuming constant variance. Only the Exponential 4, Exponential 5, and Hill models provided adequate fit to the means. Of the adequately fit models, the BMDLs were not sufficiently close (differed by >3-fold), suggesting that the model with the lowest BMDL should be selected (Hill). However, EPA's BMDS guidance notes that models with an asymptote term (which includes the Hill and Exponential 4 and 5 models) may not support reasonable BMD and BMDL values when the observed data appear to be supralinear. As the modeled data appear supralinear, the BMD results were not selected for use in deriving the MRL.

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., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control);
BMDS =Benchmark Dose Software; EPA = U.S. Environmental Protection Agency; MRL = Minimal Risk Level;
ND = not determined, the test for the means failed to meet conventional goodness-of-fit criteria

Figure A-3. Fit of Hill Model to Absolute Liver Weight Data in Rats Administered 2,4,6-Trichlorophenol from Conception Through Weaning and for 12 Additional Weeks in Drinking Water



Three models provided adequate fit to the liver weight data: the Hill and Exponential 4 and 5 models. However, EPA's BMDS guidance notes that models with an asymptote term (which includes the Hill and Exponential 4 and 5 models) may not support reasonable BMD and BMDL values when the observed data appear to be supralinear. Because the liver weight data from Exon and Koller (1985) do appear supralinear, the BMD results were not selected for use in deriving the MRL. The NOAEL of 0.46 mg/kg/day was selected as the POD for the provisional intermediate-duration oral MRL for 2,4,6-TCP.

Uncertainty Factor: The NOAEL was divided by a total uncertainty factor (UF) of 100:

- 10 UF for extrapolation from animals to humans
- 10 UF for human variability

Provisional MRL = NOAEL ÷ (UF)
0.46 mg/kg/day ÷ (10 x 10) = 0.005 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The liver is a well-established target of chlorophenol toxicity in laboratory animals. Hepatic effects including clinical chemistry changes, increased liver weight, hepatocellular hypertrophy, and necrosis have been observed in rats or mice after oral exposure to 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, and 2,3,4,6-TeCP (Aydin et al. 2009; Bercz et al. 1990; BSRC 2011; Dodd et al. 2012; Exon and Koller 1985; Exon et al. 1984; Hasegawa et al. 2005; Kobayashi et al. 1972; McCollister et al. 1961; NCI 1979; NTP 1989).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,6-Trichlorophenol
CAS Numbers: 88-06-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 2,4,6-TCP; available studies identified only serious LOAELs in the absence of NOAELs.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. Table A-16 summarizes results from available chronic-duration oral studies in experimental animals.

Table A-16. Summary of NOAELs and LOAELs from Candidate Chronic-Duration Studies in Experimental Animals Orally Exposed to 2,4,6-Trichlorophenol

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Rat (F344)	2 years (F)	ND	250 (serious LOAEL)	High incidence of bone marrow hyperplasia; remaining animals had leukemia	NCI 1979
Mouse (B6C3F1)	2 years (F)	ND	650 (serious LOAEL)	Hepatic hyperplasia; hepatocellular carcinomas or adenomas; 24% decrease in body weight	NCI 1979

(F) = feed; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

It is not appropriate to derive a chronic-duration oral MRL for 2,4,6-TCP because the lowest effect levels from chronic studies represent serious LOAELs in the absence of identified NOAELs, and because the lowest doses tested were higher than LOAELs identified for intermediate-duration exposures.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,5-Tetrachlorophenol
CAS Numbers: 4901-51-3
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 2,3,4,5-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No acute-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,5-Tetrachlorophenol
CAS Numbers: 4901-51-3
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 2,3,4,5-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,5-Tetrachlorophenol
CAS Numbers: 4901-51-3
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for 2,3,4,5-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,5-Tetrachlorophenol
CAS Numbers: 4901-51-3
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for 2,3,4,5-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. The only information on the health effects of 2,3,4,5-TeCP following oral exposure in animals was acute lethality data following a single exposure (Ahlborg and Larsson 1978).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,5-Tetrachlorophenol
CAS Numbers: 4901-51-3
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for 2,3,4,5-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,5-Tetrachlorophenol
CAS Numbers: 4901-51-3
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 2,3,4,5-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. No chronic-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,6-Tetrachlorophenol
CAS Numbers: 58-90-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 2,3,4,6-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No acute-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,6-Tetrachlorophenol
CAS Numbers: 58-90-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 2,3,4,6-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,6-Tetrachlorophenol
CAS Numbers: 58-90-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for 2,3,4,6-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,6-Tetrachlorophenol
CAS Numbers: 58-90-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute
MRL: 0.08 mg/kg/day (provisional)
Critical Effect: Hepatic effects (liver weight increases and histopathology)
Reference: Dodd et al. 2012
Point of Departure: $BMDL_{1SD}$ of 8.45 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 5
Species: Rats

MRL Summary: A provisional acute-duration oral MRL of 0.08 mg/kg/day has been derived for 2,3,4,6-TeCP, based on hepatic effects in rats administered 2,3,4,6-TeCP by daily gavage for 14 days (Dodd et al. 2012). A $BMDL_{1SD}$ of 8.45 mg/kg/day was calculated for increased relative liver weight and used as the POD; this value was divided by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability) to derive the MRL.

Selection of the Critical Effect: No adequate exposure-response data were available for humans. Two studies were considered candidate principal studies for deriving an acute-duration oral MRL for 2,3,4,6-TeCP. A third acute-duration study (Hattula et al. 1981) was not considered because the test material used in the study contained a large proportion of contaminants including pentachlorophenol and dioxins (IRIS 1988). Table A-17 summarizes results from candidate acute-duration oral studies in experimental animals. EPA (1987a, 1987b) was a developmental toxicity study, while Dodd et al. (2012) evaluated liver effects in adult animals; both studies were 14 days in duration.

Table A-17. Summary of Acute-Duration Studies in Experimental Animals Orally Exposed to 2,3,4,6-TeCP

Species	Duration (Route)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Liver effects					
Sprague-Dawley rat	14 days (GO)	10	25	Increased absolute and relative liver weights; low incidence of vacuolation	Dodd et al. 2012
Body weight effects					
CD rat	14 days (GDs 6–15) (GO)	25	100	13% decrease in maternal body weight gain	EPA 1987a, 1987b

GD = gestation day; (GO) = gavage in oil vehicle); LOAEL = lowest observed adverse effect level; NOAEL = no-observed-adverse-effect level

The lowest LOAEL for an acute-duration study was 25 mg/kg/day for liver effects in the study by Dodd et al. (2012).

Selection of the Principal Study: The Dodd et al. (2012) study was selected as the principal study as it was well-conducted, thoroughly reported, and identified the lowest LOAEL.

Summary of the Principal Study:

Dodd DE, Pluta LJ, Sochaski MA, et al. 2012. Subchronic hepatotoxicity evaluation of 2,3,4,6-tetra-chlorophenol in Sprague-Dawley rats. J Toxicol 2012:376246. http://doi.org/10.1155/2012/376246.

In the study by Dodd et al. (2012), male Sprague-Dawley rats (10/group) were administered 2,3,4,6-TeCP in olive oil (0, 10, 25, 50, 100, or 200 mg/kg/day) by daily gavage for 2 weeks. Clinical signs were recorded and body weights were measured daily. At sacrifice at the end of exposure, blood was collected for serum chemistry (ALT, AST, alkaline phosphatase, LDH, and bilirubin) and the liver was excised for weight and microscopic examination. No clinical signs of toxicity were noted and there was no adverse effect of treatment on body weight at any dose. Serum ALT levels were statistically significantly increased (70% relative to controls) at 200 mg/kg/day; lower doses were not affected, and no other serum chemistry changes were observed. Significantly increased absolute (≥15% at ≥25 mg/kg/day) and relative (≥9% at ≥10 mg/kg/day) liver weights were noted. Single cell necrosis and hepatocellular hypertrophy were observed at ≥50 mg/kg/day, with statistically significant increased incidences in the 100 and 200 mg/kg/day groups. Centrilobular hepatocytic vacuolation was observed at doses ≥25 mg/kg/day, but the incidence was statistically significantly increased only in the 200 mg/kg/day group. A LOAEL of 25 mg/kg/day and NOAEL of 10 mg/kg/day were identified for hepatic effects. Table A-18 presents summary data for hepatic effects among rats exposed to 2,3,4,6-TeCP for 2 weeks (Dodd et al. 2012).

Table A-18. Liver Weight and Histopathology Data for Rats Exposed to 2,3,4,6-Tetrachlorophenol by Gavage for 2 weeks

	Dose (mg/kg/day)					
Test	0	10	25	50	100	200
Absolute liver weight (g)	13.8±1.5[a]	15.2±1.3	15.9±1.7[b]	17.9±2.1[c]	19.5±1.8[c]	21.4±2.3[c]
Relative liver weight (%)	3.89±0.24	4.25±0.27[b]	4.43±0.25[c]	4.96±0.34[c]	5.56±0.23[c]	6.36±0.32[c]
Vacuolation (centrilobular)	0/11[d]	0/10	1/10 (1.0)	1/10 (1.0)	4/10 (1.5)	7/10[e] (1.6)
Hypertrophy (centrilobular)	0/11	0/10	0/10	4/10 (1.0)	10/10[c] (2.0)	10/10[c] (3.4)
Necrosis (centrilobular)	0/11	0/10	0/10	2/10 (1.0)	6/10[b] (1.0)	9/10[c] (2.3)

[a]Mean±standard deviation.
[b]p<0.05 compared to control based on analysis of variance (ANOVA) and Dunnet's test performed by study authors.
[c]p<0.001 compared to control.
[d] Incidence (average severity score). Severity scores were 1:minimal, 2: slight/mild, 3:moderate, 4: moderately severe, and 5: severe/high.
[e]p<0.01 compared to control.

Source: Dodd et al. 2012

Selection of the Point of Departure for the MRL: The $BMDL_{1SD}$ of 8.45 mg/kg/day for increased relative liver weight was selected as basis for deriving an acute-duration oral MRL for 2,3,4,6-TeCP.

The liver weight and histopathology data were fit to all available continuous or dichotomous models (respectively) in EPA's BMDS (version 3.1.2). 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 benchmark concentration) was selected as the POD when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen. For the liver weight data, a BMR of 1 standard deviation from the control mean was selected. For the histopathology incidence data, a BMR of 10% extra risk was used.

No model fit was achieved with the full dataset on centrilobular hypertrophy, or when the high dose was dropped. Dropping the two highest doses would result in only one dose with a nonzero incidence, so no additional modeling was done with this dataset. The model predictions for absolute and relative liver weights and hepatic vacuolation and necrosis are shown in Tables A-19, A-20, A-21, and A-22 (respectively), and the fit of the selected models are shown in Figures A-4, A-5, A-6, and A-7 (respectively).

Table A-19. Results from BMD Analysis (Constant Variance) of Absolute Liver Weights in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol for 2 Weeks (Dodd et al. 2012)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Exponential (model 2)[e]	<0.0001	0.50	0.00	1.99	1.91	-2.30	261.58	64.59	53.98
Exponential (model 3)[e]	<0.0001	0.50	0.00	1.99	1.91	-2.30	261.58	64.59	53.98
Exponential (model 4)[e]	<0.0001	0.50	0.84	0.55	-0.39	0.55	248.01	19.42	13.06
Exponential (model 5)[e]	<0.0001	0.50	0.84	0.55	-0.39	0.55	248.01	19.41	13.06
Hill[e,f]	***<0.0001***	***0.50***	***0.88***	***0.47***	***-0.55***	***-0.55***	***247.86***	***17.40***	***10.68***
Polynomial (2-degree)[e]	<0.0001	0.50	0.01	1.90	1.56	-2.00	258.12	53.03	43.40
Polynomial (3-degree)[e]	<0.0001	0.50	0.01	1.90	1.56	-2.00	258.12	53.03	43.40
Polynomial (4-degree)[e]	<0.0001	0.50	0.01	1.90	1.56	-2.00	258.12	53.03	43.40
Polynomial (5 degree)[e]	<00001	0.50	0.01	1.90	1.56	-2.00	258.12	53.03	43.41

Table A-19. Results from BMD Analysis (Constant Variance) of Absolute Liver Weights in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol for 2 Weeks (Dodd et al. 2012)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Power[e]	<0.0001	0.50	0.01	1.90	1.56	-2.00	258.12	53.03	43.40
Linear	<0.0001	0.50	0.01	1.90	1.56	-2.00	258.12	53.03	43.40

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[e]Restricted model
[f]Recommended model. There was an adequate fit to the variance when assuming constant variance. The Exponential 4, Exponential 5, and Hill models provided adequate fit to the means. Of the adequately fit models, the BMDLs were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Hill).

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., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control)

Figure A-4. Fit of Hill Model to Absolute Liver Weight Data in Rats administered 2,3,4,6-Tetrachlorophenol by Gavage for 14 Days

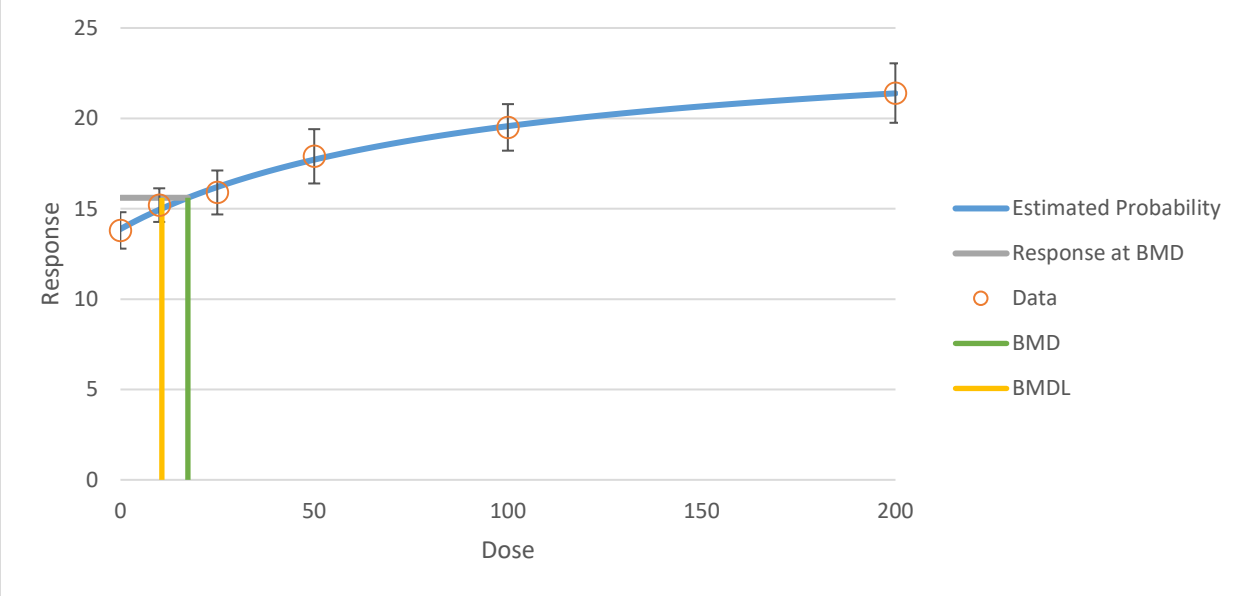


Table A-20. Results from BMD Analysis (Constant Variance) of Relative Liver Weights in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol for 2 Weeks (Dodd et al. 2012)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Exponential (model 2)[e]	<0.0001	0.76	<0.0001	-0.15	2.39	-3.04	50.17	36.12	31.08
Exponential (model 3)[e]	<0.0001	0.76	<0.0001	-0.15	2.39	-3.04	50.17	36.11	31.08
Exponential (model 4)[e]	<0.0001	0.76	0.57	0.99	-0.56	0.99	20.37	11.77	9.33
Exponential (model 5)[e]	<0.0001	0.76	0.57	0.99	-0.56	0.99	20.37	11.77	9.33
Hill[e,f]	***<0.0001***	***0.76***	***0.62***	***0.96***	***-0.71***	***0.96***	***20.15***	***11.01***	***8.45***
Polynomial (2-degree)[e]	<0.0001	0.76	0.00	-0.06	2.23	-2.56	39.76	26.68	22.75
Polynomial (3-degree)[e]	<0.0001	0.76	0.00	-0.06	2.23	-2.56	39.76	26.68	22.75
Polynomial (4-degree)[e]	<0.0001	0.76	0.00	-0.06	2.23	-2.56	39.76	26.68	22.75
Polynomial (5 degree)[e]	<0.0001	0.76	0.00	-0.06	2.23	-2.56	39.76	26.68	22.82
Power[e]	<0.0001	0.76	0.00	-0.06	2.23	-2.56	39.76	26.68	22.75
Linear	<0.0001	0.76	0.00	-0.06	2.23	-2.56	39.76	26.68	22.75

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[e]Restricted model
[f]Recommended model. There was an adequate fit to the variance when assuming constant variance. The Exponential 4, Exponential 5, and Hill models provided adequate fit to the means. Of the adequately fit models, the BMDLs were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Hill).

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., $_{1SD}$ = exposure dose associated with one standard deviation from the control mean)

Figure A-5. Fit of Hill Model to Relative Liver Weight Data in Rats Administered 2,3,4,6-Tetrachlorophenol by Gavage for 14 Days

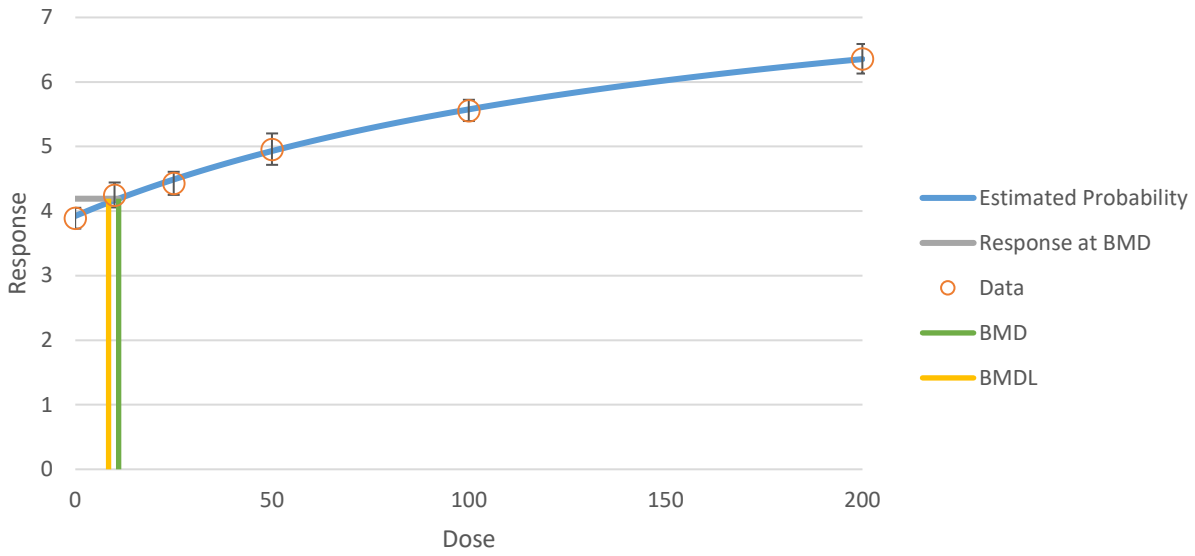


Table A-21. Model Predictions for Vacuolation (Centrilobular) in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol (Dodd et al. 2012)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b]			AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Dichotomous Hill	2	0.86	0.65	0.71	-0.49	0.71	47.56	37.62	16.33
Gamma[c]	4	0.78	0.94	0.63	-0.47	0.63	43.53	37.10	16.48
Logistic	4	2.29	0.68	-0.09	0.95	0.95	45.78	61.29	42.54
LogLogistic[d]	4	0.86	0.93	0.71	-0.49	0.71	43.56	37.62	16.33
LogProbit[d]	3	0.97	0.81	0.73	-0.60	0.73	45.64	35.86	16.67
Multistage (1-degree)[e,f]	***5***	***1.59***	***0.90***	***-0.69***	***-0.10***	***-0.84***	***42.87***	***22.60***	***14.62***
Multistage (2-degree)[e]	3	0.79	0.87	0.49	-0.40	0.49	45.67	36.95	16.23
Multistage (3-degree)[e]	4	0.79	0.94	0.49	-0.40	0.49	43.68	36.95	16.23
Multistage (4-degree)[e]	4	0.79	0.94	0.49	-0.40	0.49	43.67	36.95	16.23
Multistage (5-degree)[e]	4	0.79	0.94	0.49	-0.40	0.49	43.67	36.95	16.23

Table A-21. Model Predictions for Vacuolation (Centrilobular) in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol (Dodd et al. 2012)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b]			AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Probit	4	1.98	0.74	-0.09	0.85	0.85	45.29	57.15	40.15
Weibull[c]	3	0.76	0.86	0.58	-0.45	0.58	45.56	37.03	16.44

[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.
[ef]Betas restricted to ≥0.
[f]Selected model. All models provided adequate fits to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected (Multistage [1-degree]).

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 criteria, p<0.10

Figure A-6. Fit of Multistage Degree 1 Model to Hepatic Vacuolation Data in Rats Administered 2,3,4,6-Tetrachlorophenol by Gavage for 14 Days

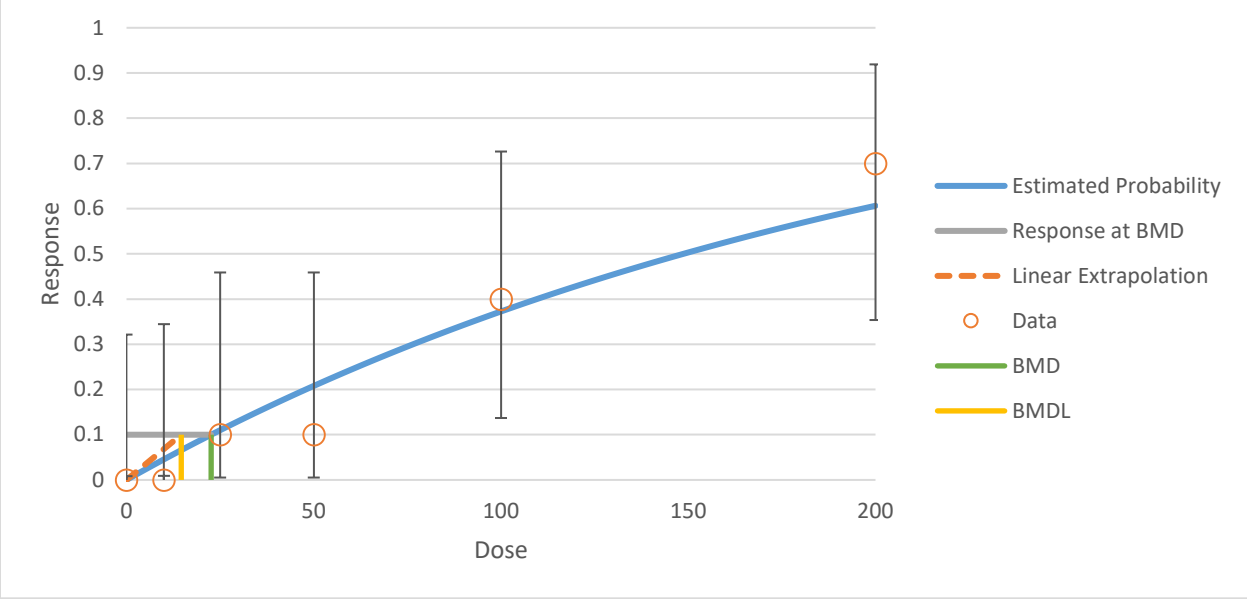


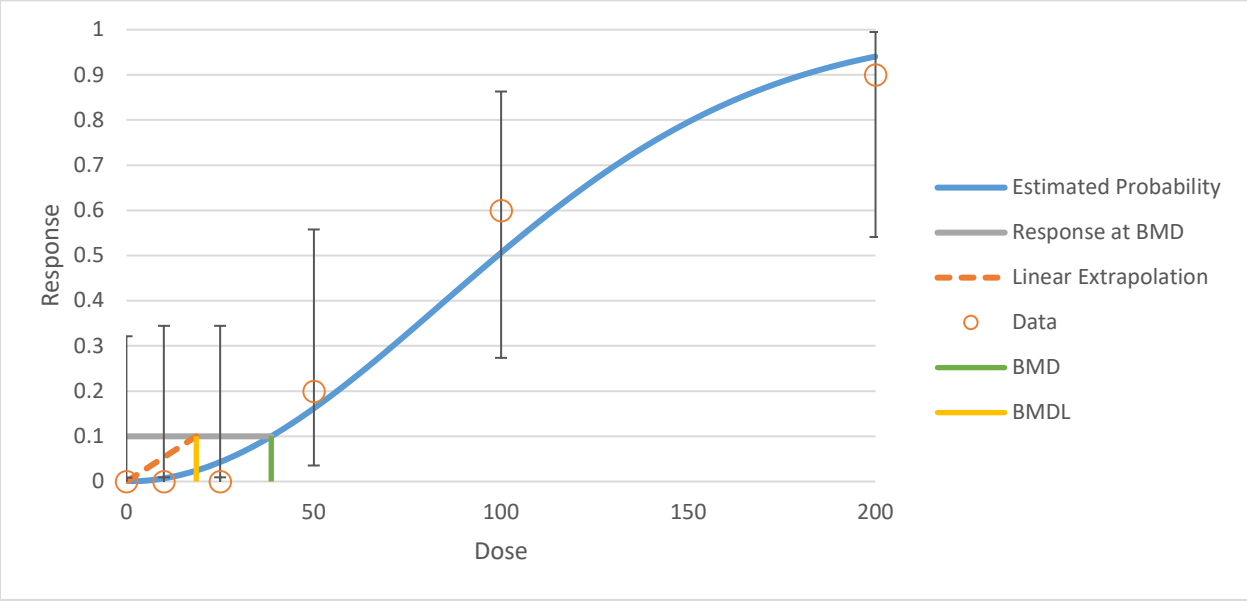
Table A-22. Model Predictions for Necrosis (Centrilobular) in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol (Dodd et al. 2012)

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_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Dichotomous Hill	3	0.37	0.95	-0.43	0.37	0.37	36.53	42.70	24.58
Gamma[c]	4	0.71	0.95	-0.56	0.30	-0.56	34.99	40.03	21.79
Logistic	4	3.95	0.41	-0.79	0.63	-1.29	38.48	47.49	32.48
LogLogistic[d]	3	0.42	0.94	-0.76	0.63	1.02	36.65	41.38	24.20
LogProbit[d]	3	0.28	0.96	-0.42	0.25	-0.41	36.42	41.15	24.79
Multistage (1-degree)[e,f]	5	4.54	0.47	-0.87	-1.41	-1.41	39.10	14.57	9.78
Multistage (2-degree)[e]	***5***	***1.28***	***0.94***	***-0.67***	***0.33***	***-0.67***	***33.70***	***38.65***	***18.62***
Multistage (3-degree)[e]	5	1.28	0.94	-0.67	0.33	-0.67	33.70	38.65	18.56
Multistage (4-degree)[e]	5	1.28	0.94	-0.67	0.33	-0.67	33.70	38.65	18.56
Multistage (5-degree)[e]	5	1.28	0.94	-0.67	0.33	-0.67	33.70	38.65	18.56
Probit	4	3.59	0.46	-0.77	0.63	-1.03	38.25	46.02	31.42
Weibull[c]	3	1.15	0.76	-0.71	0.24	-0.71	37.67	36.92	19.34

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[ef]Betas restricted to ≥0.
[f]Selected model. All models provided adequate fits to the data. BMDLs for models providing adequate fit differed by >3-fold. However, the model with the lowest BMDL (1-degree polynomial multistage) was an outlier and predicted a BMD below the NOAEL of 25 mg/kg/day. Therefore, the model with the lowest AIC was selected (Multistage [2-degree]).

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 criteria, p<0.10

Figure A-7. Fit of Multistage 2 Degree Model to Hepatic Necrosis Data in Rats Administered 2,3,4,6-Tetrachlorophenol by Gavage for 14 Days



A comparison of the BMDs and BMDLs for the selected models is shown in Table A-23.

Table A-23. Benchmark Dose Modeling Results for Hepatic Endpoints in 2-Week Rat Study by Dodd et al. (2012)

Endpoint	Selected model	BMD (mg/kg/day)	BMDL (mg/kg/day)
Absolute liver weight (g)	Hill	17.40	10.68
Relative liver weight (%)	Hill	11.01	8.45
Vacuolation (centrilobular)	1-degree multistage	22.60	14.62
Necrosis (centrilobular)	2-degree multistage	38.65	18.62

The lowest BMDL was the $BMDL_{1SD}$ of 8.45 mg/kg/day for increased relative liver weight; this value was selected as the POD.

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The $BMDL_{1SD}$ was divided by a total uncertainty factor (UF) of 100:

- 10 UF for extrapolation from animals to humans
- 10 UF for human variability

Provisional MRL = $BMDL_{1SD}$ ÷ (UF)
8.45 mg/kg/day ÷ (10 x 10) = 0.08 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The liver is a well-established target of chlorophenol toxicity in laboratory animals. Hepatic effects including clinical chemistry changes, increased liver weight, hepatocellular hypertrophy, and necrosis have been observed in rats or mice after oral exposure to 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, and 2,4,6-TCP (Bercz et al. 1990;

Aydin et al. 2009; BSRC 2011; Exon and Koller 1985; Exon et al. 1984; Hasegawa et al. 2005; Kobayashi et al. 1972; McCollister et al. 1961; NCI 1979; NTP 1989).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,6-Tetrachlorophenol
CAS Numbers: 58-90-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
MRL: 0.01 mg/kg/day (provisional)
Critical Effect: Hepatic Effects (liver weight increases and histopathology)
Reference: Dodd et al. 2012
Point of Departure: $BMDL_{10}$ of 1.02 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 8
Species: Rats

MRL Summary: A provisional intermediate-duration oral MRL of 0.01 mg/kg/day was derived for 2,3,4,6-TeCP based on hepatic effects in rats administered 2,3,4,6-TeCP by gavage for 13 weeks (Dodd et al. 2012). BMD analysis was used to identify a $BMDL_{10}$ of 1.02 mg/kg/day for hepatocellular hypertrophy. A total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the $BMDL_{10}$ of 1.02 mg/kg/day.

Selection of the Critical Effect: No dose-response data are available for humans. Table A-24 summarizes results from candidate intermediate-duration oral studies in experimental animals. Two studies were considered potential candidate principal studies for deriving an intermediate-duration oral MRL for 2,3,4,6-TeCP. A third intermediate-duration study (Hattula et al. 1981) was not considered because the test material used in the study contained a large proportion of contaminants including pentachlorophenol and dioxins (IRIS 1988).

Table A-24. Summary of NOAELs and LOAELs from Candidate Intermediate-Duration Studies in Experimental Animals Orally Exposed to 2,3,4,6-Tetrachlorophenol

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Liver effects					
Sprague-Dawley rat	13 weeks, 7 days/week (GO)	ND	10	Increased liver weights; centrilobular vacuolation and hypertrophy	Dodd et al. 2012
Sprague-Dawley rat	13 weeks, 7 days/week (GO)	25	100	Increased liver and kidney weights, centrilobular hypertrophy	EPA 1986

(GO) = gavage in oil vehicle; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study:

The study by Dodd et al. (2012) was selected because it tested lower doses and identified a lower LOAEL for the same endpoint (hepatic effects) as the EPA (1986) study.

Summary of the Principal Study:

Dodd DE, Pluta LJ, Sochaski MA, et al. 2012. Subchronic hepatotoxicity evaluation of 2,3,4,6-tetrachlorophenol in Sprague-Dawley rats. J Toxicol 2012:376246. http://doi.org/10.1155/2012/376246.

In the study by Dodd et al. (2012), male Sprague-Dawley rats (10/group) were administered 2,3,4,6-TeCP in olive oil (0, 10, 25, 50, 100, or 200 mg/kg/day) by daily gavage for 13 weeks. Clinical signs were recorded and body weights were measured daily. At sacrifice at the end of exposure, blood was collected for serum chemistry (ALT, AST, alkaline phosphatase, LDH, and bilirubin) and the liver was excised for weight and microscopic examination. No clinical signs of toxicity were noted. Mean body weights were decreased by 12 and 22% at 100 and 200 mg/kg/day, respectively. At lower doses, no statistically or biologically significant effect on body weight was observed. Serum ALT levels were increased at ≥50 mg/kg/day (61–216% compared to controls), and alkaline phosphatase and AST were increased at 200 mg/kg/day (92 and 95%, respectively). Increased absolute and relative liver weights were noted in the groups exposed to ≥25 mg/kg/day; the differences from controls were at least 27 and 18% for absolute and relative weights, respectively. Centrilobular vacuolation was seen in all groups including controls (4/12), but incidence and severity increased with dose such that all animals were affected at doses ≥25 mg/kg/day. Hypertrophy was not seen in controls, but the incidence increased with dose from 4/10 at 10 mg/kg/day to all animals (9/9 or 10/10) at doses of at least 50 mg/kg/day. Necrosis was observed at doses of ≥50 mg/kg/day, from 3/9 at 50 mg/kg/day to 10/10 at 200 mg/kg/day. Incidences of other histopathology lesions were not reported in tables. All high-dose (200 mg/kg/day) rats exhibited bile duct hyperplasia, as did 20% of rats in the 100 and 25 mg/kg/day groups. Finally, centrilobular and/or periportal fibrosis was observed at 10% incidence in groups exposed to 25 and 100 mg/kg/day and at 40–60% incidence in the 200 mg/kg/day group. The LOAEL for hepatic effects was 10 mg/kg/day; a NOAEL was not identified. Table A-25 presents summary data for hepatic effects among rats exposed to 2,3,4,6-TeCP for 13 weeks (Dodd et al. 2012).

Table A-25. Liver Weight and Histopathology Changes in Rats Exposed to 2,3,4,6-Tetrachlorophenol by Gavage for 13 Weeks

	Dose (mg/kg/day)					
Test	0	10	25	50	100	200
Absolute liver weight (g)	16.8±2.9	21.4±2.7	24.2±3.3[b]	27.5±5.5[c]	33.6±7.3[c]	38.9±7.2[c]
Relative liver weight (%)	3.10±0.20	3.65±0.13	4.36±0.42[c]	5.46±0.62[c]	7.11±0.86[c]	9.40±1.11[c]
Vacuolation, centrilobular	4/12 (1.0)[d]	9/10 (1.6)	9/9[e] (2.4)	9/9[e] (3.4)	10/10[b] (4.3)	10/10[b] (4.7)
Hypertrophy, centrilobular	0/12	4/10 (1.0)	8/9[c] (1.3)	9/9[c] (2.6)	0/10	0/10
Hypertrophy, diffuse	0/12	0/10	0/10	0/10	10/10[c] (3.0)	10/10[c] (4.2)
Necrosis, centrilobular	0/12	0/10	0/10	3/9 (1.0)	2/10 (1.5)	0/10
Necrosis, midzonal	0/12	0/10	0/10	0/10	1/10 (1.0)	10/10[c] (2.3)

[a]Mean±standard deviation.
[b]p<0.01 compared to control.
[c]p<0.001 compared to control.
[d]Incidence (average severity score). Severity scores were 1:minimal, 2: slight/mild, 3:moderate, 4: moderately severe, and 5: severe/high.
[e]p<0.05 compared to control based on Fisher's exact test with Bonferroni correction performed by study authors.

Source: Dodd et al. 2012

Selection of the Point of Departure for the MRL: The $BMDL_{1SD}$ of 1.02 mg/kg/day for centrilobular or diffuse hepatocellular hypertrophy was selected as basis for deriving an intermediate-duration oral MRL for 2,3,4,6-TeCP.

The absolute liver weight and selected histopathology data (vacuolation and hypertrophy) were fit to all available continuous or dichotomous models (respectively) in EPA's BMDS (version 3.1.1). Relative liver weights were not modeled, as these values were influenced by significantly decreased body weights (12 and 22% at doses of 100 and 200 mg/kg/day). Necrosis incidences were not modeled because this effect occurred at higher doses than vacuolation and hypertrophy. 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 was selected as the POD when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen. For the liver weight data, a BMR of 1 standard deviation from the control mean in the absence of information to suggest an alternative BMR. For the histopathology incidence data, a BMR of 10% extra risk was used.

No model fit was achieved with the data on centrilobular vacuolation, even when up to three dose groups were dropped from the analysis. The model predictions for absolute liver weight and hepatic hypertrophy are shown in Tables A-26 and A-27 (respectively), and the fit of the selected models is shown in Figures A-8 and A-9 (respectively).

Table A-26. Results from BMD Analysis of Absolute Liver Weights in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol for 13 Weeks (Dodd et al. 2012)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Constant variance									
Linear	<0.0001	0.001	0.01	1.15	1.74	-2.19	379.13	52.14	42.73
Nonconstant variance									
Exponential (model 2)[e]	<0.0001	0.56	<0.0001	1.27	1.73	-3.02	379.01	45.49	32.10
Exponential (model 3)[e]	<0.0001	0.56	<0.0001	1.28	1.74	-3.02	379.01	45.21	32.10
Exponential (model 4)[e]	<0.0001	0.56	0.67	-0.67	1.17	1.17	355.31	8.62	5.44
Exponential (model 5)[e]	<0.0001	0.56	0.67	-0.68	1.17	1.17	355.31	8.59	5.44
Hill[e,f]	***<0.0001***	***0.56***	***0.80***	***-0.48***	***0.97***	***0.97***	***354.80***	***7.43***	***4.47***
Polynomial (2-degree)[e]	<0.0001	0.56	0.002	1.43	1.27	-2.37	369.05	25.78	17.47
Polynomial (3-degree)[e]	<0.0001	0.56	0.002	1.43	1.27	-2.37	369.05	25.78	17.47
Polynomial (4-degree)[e]	<0.0001	0.56	0.002	1.43	1.27	-2.37	369.05	25.78	17.47
Polynomial (5 degree)[e]	<0.0001	0.56	0.002	1.43	1.27	-2.37	369.05	25.78	17.47
Power[e]	<0.0001	0.56	0.002	1.43	1.26	-2.37	369.05	25.78	17.47
Linear	<0.0001	0.56	0.002	1.43	1.26	-2.37	369.05	25.78	17.47

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[e]Restricted model.
[f]Recommended model. There was not an adequate fit to the variance when assuming constant variance. With the nonconstant variance model applied, an adequate fit to the variance was achieved. The Exponential 4, Exponential 5, and Hill models provided adequate fit to the means. Of the adequately fit models, the BMDLs were sufficiently close (differed by < 3-fold); therefore, the model with the lowest AIC was selected (Hill).

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., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control)

Figure A-8. Fit of Hill Model to Absolute Liver Weight Data in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol for 13 Weeks

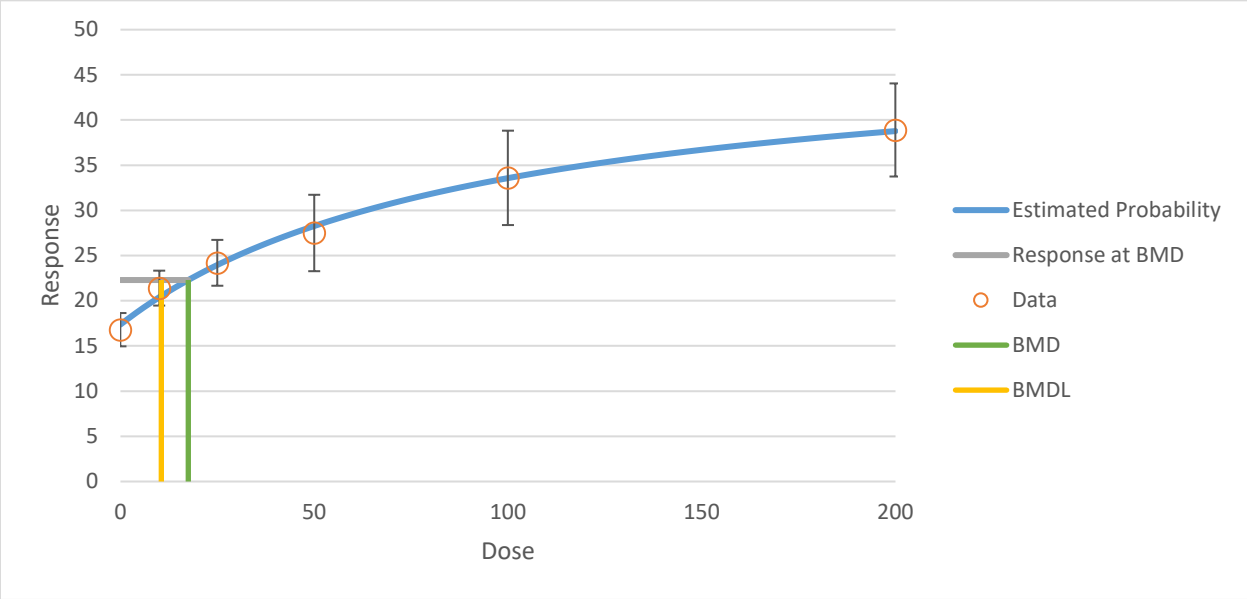


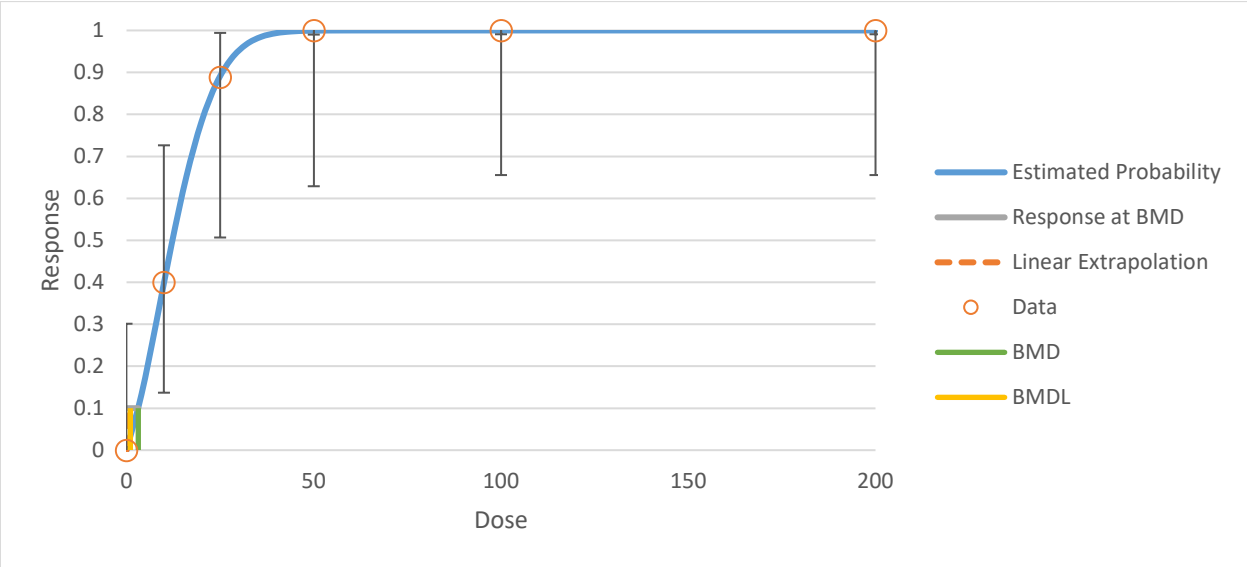
Table A-27. Model Predictions for Hypertrophy (Centrilobular and Diffuse) in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol for 13 Weeks (Dodd et al. 2012)

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_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma[c]	4	0.03	0.99989	-0.0004	0.03	0.15	23.79	4.49	1.02
LogLogistic[d]	4	0.19	0.99579	-0.0004	0.07	0.32	24.04	5.64	1.95
Multistage (5-degree)[e]	1	2.89×10^{-7}	0.99957	-0.0004	-0.0001	-0.0004	29.74	2.42	1.02
Multistage (4-degree)[e]	4	3.00×10^{-7}	1.00000	-0.0004	1.3×10^{-6}	-0.0004	23.74	2.17	1.02
Multistage (3-degree)[e]	3	0.0002	1.00000	-0.0004	0.0007	0.01	25.74	2.37	1.02
Multistage (2-degree)[e,f]	***3***	***0.005***	***0.99990***	***-0.0005***	***0.01***	***0.07***	***25.75***	***3.15***	***1.02***
Multistage (1-degree)[e]	5	0.99	0.96345	-0.0004	-0.79	-0.79	22.97	1.42	0.91
Weibull[c]	3	0.01	0.99967	-0.006	0.02	0.09	25.76	3.82	1.02
Dichotomous Hill	4	0.19	0.99579	-0.0004	0.07	0.32	24.04	5.64	1.95
Logistic	4	1.18	0.88197	-0.75	0.62	-0.75	25.41	5.52	3.18
LogProbit[d]	4	0.09	0.99911	-0.0004	0.05	0.23	23.88	5.58	1.75
Probit	5	1.70	0.88940	-1.10	0.44	-1.10	24.57	4.71	3.00

[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. All models provided an adequate fit to the dataset based on the χ2 goodness-of-fit p value; the 1-degree multistage model was considered questionable because the BMDL was 10 times lower than the lowest non-zero dose. BMDLs for the viable models were not sufficiently close (differed by >3-fold). Therefore, the model with the lowest BMDL was selected. The polynomial multistage 2-,3-, 4-, and 5-degree models all provided the same BMDL; the 2-degree model was the most parsimonious and 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 = not determined, goodness-of-fit criteria, p<0.10

Figure A-9. Fit of Multistage (2-Degree) Model to Data on Hepatocellular Hypertrophy (Centrilobular and Diffuse) in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol for 13 Weeks



A comparison of the BMDs and BMDLs for the selected models is shown in Table A-28. The lowest BMDL for the remaining two datasets was the $BMDL_{10}$ of 1.02 mg/kg/day for centrilobular or diffuse hypertrophy; this value was selected as the POD.

Table A-28. Benchmark Dose Modeling Results for Hepatic Endpoints in 13-Week Rat Study by Dodd et al. (2012)

Endpoint[a]	Selected model	BMD (mg/kg/day)	BMDL (mg/kg/day)
Absolute liver weight (g)	Hill	7.43	4.47
Hypertrophy (centrilobular or diffuse):	Multistage (3 degree)	3.15	1.02

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The $BMDL_{1SD}$ of 1.02 mg/kg/day was divided by a total uncertainty factor (UF) of 100:

- 10 UF for extrapolation from animals to humans
- 10 UF for human variability

Provisional MRL = $BMDL_{1SD}$ ÷ (UF)
1.02 mg/kg/day ÷ (10 x 10) = 0.01 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The liver is a well-established target of chlorophenol toxicity in laboratory animals. Hepatic effects including clinical chemistry changes, increased liver weight, hepatocellular hypertrophy, and necrosis have been observed in rats or mice after oral exposure to 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, and 2,4,6-TCP (Aydin et al. 2009;

Bercz et al. 1990; BSRC 2011; Exon and Koller 1985; Exon et al. 1984; Hasegawa et al. 2005; Kobayashi et al. 1972; McCollister et al. 1961; NCI 1979; NTP 1989).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,6-Tetrachlorophenol
CAS Numbers: 58-90-2
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 2,3,4,6-TeCP due to the lack of chronic studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. No chronic-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,5,6-Tetrachlorophenol
CAS Numbers: 935-95-5
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 2,3,5,6-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No acute-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,5,6-Tetrachlorophenol
CAS Numbers: 935-95-5
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 2,3,5,6-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,5,6-Tetrachlorophenol
CAS Numbers: 935-95-5
Date: July 2021
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for 2,3,5,6-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No chronic-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,5,6-Tetrachlorophenol
CAS Numbers: 935-95-5
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for 2,3,5,6-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. The only information on the health effects of 2,3,5,6-TeCP following oral exposure in animals was acute lethality data following a single exposure (Ahlborg and Larsson 1978).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,5,6-Tetrachlorophenol
CAS Numbers: 935-95-5
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for 2,3,5,6-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,5,6-Tetrachlorophenol
CAS Numbers: 935-95-5
Date: July 2021
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 2,3,5,6-TeCP because there are no relevant studies.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. No chronic-duration oral data were located for experimental animals.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CHLOROPHENOLS

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 chlorophenols.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for chlorophenols. 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 chlorophenols 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 chlorophenols 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 1999 toxicological profile for chlorophenols; thus, the literature search was restricted to studies published between 1997 and 2019. The following main databases were searched in 2019:

- PubMed
- National Library of Medicine's TOXLINE
- 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 chlorophenols. 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 chlorophenols 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	
02/2019	((Chlorophenols[mh:noexp] AND 1997:3000[mhda]) AND (chlorophenols/to[mh] OR chlorophenols/ae[mh] OR chlorophenols/po[mh] OR chlorophenols/pk[mh] OR chlorophenols/bl[mh] OR chlorophenols/cf[mh] OR chlorophenols/ur[mh] OR chlorophenols/ai[mh] OR ("chlorophenols"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("chlorophenols"[mh] AND toxicokinetics[mh:noexp]) OR ("chlorophenols"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("chlorophenols"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("chlorophenols/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("chlorophenols"[majr] AND cancer[sb]))) OR ((("1,3,5-Trichloro-2-hydroxybenzene"[tw] OR "1,3-Dichloro-4-hydroxybenzene"[tw] OR "1-Chloro-2-hydroxybenzene"[tw] OR "1-Hydroxy-2,3,4,6-tetrachlorobenzene"[tw] OR "1-Hydroxy-2,4-dichlorobenzene"[tw] OR "2,3,4,5-Tetrachlorophenate"[tw] OR "2,3,4,5-Tetrachlorophenol"[tw] OR "2,3,4,6-Tetrachlorophenate"[tw] OR "2,3,4,6-Tetrachlorophenol"[tw] OR "2,3,4,6-Tetrachlorphenol"[tw] OR "2,3,4,6-tetraclorofenol"[tw] OR "2,3,5,6-Tetrachlorophenate"[tw] OR "2,3,5,6-Tetrachlorophenol"[tw] OR "2,4,-Dichlorophenol"[tw] OR "2,4,5,6-Tetrachlorophenol"[tw] OR "2,4,5-Trichlorophenol"[tw] OR "2,4,5-Trichlorphenol"[tw] OR "2,4,5-triclorofenol"[tw] OR "2,4,6-Trichlorfenol"[tw] OR "2,4,6-Trichlorophenol"[tw] OR "2,4,6-Trichlorphenol"[tw] OR "2,4,6-triclorofenol"[tw] OR "2,4-Dichlorohydroxybenzene"[tw] OR "2,4-Dichlorophenic acid"[tw] OR "2,4-Dichlorophenol"[tw] OR "2,4-Dichlorphenol"[tw] OR "2,4-diclorofenol"[tw] OR "2-Chloro-1-hydroxybenzene"[tw] OR "2-Chlorophenol"[tw] OR "2-Chlorphenol"[tw] OR "2-clorofenol"[tw] OR "2-Hydroxychlorobenzene"[tw] OR "2-Monochlorophenol"[tw] OR "2.4,5-Trichlorophenic acid"[tw] OR "4,6-Dichlorophenol"[tw] OR "4-Chloro-1-hydroxybenzene"[tw] OR "4-Chlorophenol"[tw] OR "4-Chlorphenol"[tw] OR "4-clorofenol"[tw] OR "4-Hydroxychlorobenzene"[tw] OR "4-Monochlorophenol"[tw] OR "Chlorophenol"[tw] OR "Chlorophenol, 2-"[tw] OR "Chlorophenol, 4-"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Chlorophenol, o-"[tw] OR "Chlorophenol, p-"[tw] OR "Chlorophenols"[tw] OR "Chlorophenols, liquid"[tw] OR "Chlorophenols, solid"[tw] OR "Collunosol"[tw] OR "Dichlorophenol (2,4-)"[tw] OR "Dichlorophenol, 2,4-"[tw] OR "Monochlorophenol (mixed isomers)"[tw] OR "Monochlorophenols (all isomers)"[tw] OR "Monochlorophenols (total)"[tw] OR "o,p-Dichlorophenol"[tw] OR "o-Chlorophenic acid"[tw] OR "o-Chlorophenol"[tw] OR "o-Chlorphenol"[tw] OR "ortho,para-Dichlorophenol"[tw] OR "ortho-Chlorophenol"[tw] OR "p-Chlorophenic acid"[tw] OR "p-Chlorophenol"[tw] OR "Parachlorophenol"[tw] OR "Phenachlor"[tw] OR "Phenaclor"[tw] OR "Phenol, 2,3,4,5-tetrachloro-"[tw] OR "Phenol, 2,3,4,6-tetrachloro-"[tw] OR "Phenol, 2,3,5,6-tetrachloro-"[tw] OR "Phenol, 2,4,5-trichloro-"[tw] OR "Phenol, 2,4,6-trichloro-"[tw] OR "Phenol, 2,4-dichloro-"[tw] OR "Phenol, 2-chloro-"[tw] OR "Phenol, 4-chloro-"[tw] OR "Phenol, chloro-"[tw] OR "Phenol, o-chloro-"[tw] OR "Phenol, p-chloro-"[tw] OR "Phenol, tetrachloro-"[tw] OR "Pine-O Disinfectant"[tw] OR "Tetrachlorophenol"[tw] OR "Tetrachlorophenol, 2,3,4,5-"[tw] OR "Tetrachlorophenol, 2,3,4,6-"[tw] OR "Tetrachlorophenol, 2,3,5,6-"[tw] OR "Tetrachlorophenol, isomer"[tw] OR "Tetrachlorophenols"[tw] OR "Trichlorophenol (2,4,5-)"[tw] OR "Trichlorophenol, 2,4,5-"[tw] OR "Trichlorophenol, 2,4,6-"[tw] OR "2,4,5-TCP"[tw] OR "2,4,6-T"[tw] OR "2,4,6-TCP"[tw] OR "2,4-DCP"[tw] OR "Applied 3-78"[tw] OR "BTS 45186"[tw] OR "Dowicide 2"[tw] OR "Dowicide 2S"[tw] OR "Dowicide 6"[tw] OR "Preventol I"[tw] OR "Septi-Kleen"[tw]) NOT medline[sb]) AND (1997:3000[crdt] OR 1997:3000[edat]))
10/2019	(576-24-9[rn] OR 583-78-8[rn] OR 95-77-2[rn] OR "3,5-dichlorophenol"[nm] OR "2,3,4-trichlorophenol"[nm]) OR (("2,3-Dichlorophenol"[tw] OR "2,3-Dichlorphenol"[tw] OR "Dichlorophenol, 2,3-"[tw] OR "Phenol, 2,3-dichloro-"[tw] OR "1-Hydroxy-2,5-dichlorobenzene"[tw] OR "2,5-Dichlorophenol"[tw] OR "2,5-Dichlorphenol"[tw] OR "Dichlorophenol, 2,5-"[tw] OR "PHENOL, 1,4-DICHLORO-"[tw] OR "Phenol, 2,5-dichloro-"[tw] OR "1,4-DICHLOROPHENOL"[tw] OR "3,4-Dichlorophenol"[tw] OR "3,4-Dichlorphenol"[tw] OR "4,5-Dichlorophenol"[tw] OR "Dichlorophenol, 3,4-"[tw] OR "Phenol, 3,4-dichloro-"[tw] OR "1-Hydroxy-3,5-dichlorobenzene"[tw] OR "3,5-Dichlorophenol"[tw] OR "3,5-Dichlorphenol"[tw] OR "Dichlorophenol, 3,5-"[tw] OR "Phenol, 3,5-dichloro-"[tw] OR "2,3,4-Trichlorophenol"[tw] OR "Phenol, 2,3,4-trichloro-"[tw] OR "Trichlorophenol, 2,3,4-"[tw]) NOT medline[sb])
Toxline	
02/2019	(88-06-2[rn] OR 120-83-2[rn] OR 95-95-4[rn] OR 95-57-8[rn] OR 4901-51-3[rn] OR 935-95-5[rn] OR 58-90-2[rn] OR 106-48-9[rn] OR 25167-80-0[rn] OR 25167-83-3[rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication: 1997 through 2019 ("1,3,5-Trichloro-2-hydroxybenzene" OR "1,3-Dichloro-4-hydroxybenzene" OR "1-Chloro-2-hydroxybenzene" OR "1-Hydroxy-2,3,4,6-tetrachlorobenzene" OR "1-Hydroxy-2,4-dichlorobenzene" OR "2,3,4,5-Tetrachlorophenate" OR "2,3,4,5-Tetrachlorophenol" OR "2,3,4,6-Tetrachlorophenate" OR "2,3,4,6-Tetrachlorophenol" OR "2,3,4,6-Tetrachlorphenol" OR "2,3,4,6-tetraclorofenol" OR "2,3,5,6-Tetrachlorophenate" OR "2,3,5,6-Tetrachlorophenol" OR "2,4,-Dichlorophenol" OR "2,4,5,6-Tetrachlorophenol") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication: 1997 through 2019

Table B-2. Database Query Strings

Database search date	Query string
	("2,4,5-Trichlorophenol" OR "2,4,5-Trichlorphenol" OR "2,4,5-triclorofenol" OR "2,4,6-Trichlorfenol" OR "2,4,6-Trichlorophenol" OR "2,4,6-Trichlorphenol" OR "2,4,6-triclorofenol" OR "2,4-Dichlorohydroxybenzene" OR "2,4-Dichlorophenic acid" OR "2,4-Dichlorophenol" OR "2,4-Dichlorphenol" OR "2,4-diclorofenol" OR "2-Chloro-1-hydroxybenzene" OR "2-Chlorophenol" OR "2-Chlorphenol" OR "2-clorofenol" OR "2-Hydroxychlorobenzene" OR "2-Monochlorophenol" OR "2.4,5-Trichlorophenic acid") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication: 1997 through 2019
	("4,6-Dichlorophenol" OR "4-Chloro-1-hydroxybenzene" OR "4-Chlorophenol" OR "4-Chlorphenol" OR "4-clorofenol" OR "4-Hydroxychlorobenzene" OR "4-Monochlorophenol" OR "Chlorophenol" OR "Chlorophenol, 2-" OR "Chlorophenol, 4-" OR "Chlorophenol, o-" OR "Chlorophenol, p-" OR "Chlorophenols" OR "Chlorophenols, liquid" OR "Chlorophenols, solid" OR "Collunosol" OR "Dichlorophenol (2,4-)" OR "Dichlorophenol, 2,4-" OR "Monochlorophenol (mixed isomers)") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication: 1997 through 2019
	("Monochlorophenols (all isomers)" OR "Monochlorophenols (total)" OR "o,p-Dichlorophenol" OR "o-Chlorophenic acid" OR "o-Chlorophenol" OR "o-Chlorphenol" OR "ortho,para-Dichlorophenol" OR "ortho-Chlorophenol" OR "p-Chlorophenic acid" OR "p-Chlorophenol" OR "Parachlorophenol" OR "Phenachlor" OR "Phenaclor" OR "Phenol, 2,3,4,5-tetrachloro-" OR "Phenol, 2,3,4,6-tetrachloro-" OR "Phenol, 2,3,5,6-tetrachloro-" OR "Phenol, 2,4,5-trichloro-" OR "Phenol, 2,4,6-trichloro-" OR "Phenol, 2,4-dichloro-") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication: 1997 through 2019
	("Phenol, 2-chloro-" OR "Phenol, 4-chloro-" OR "Phenol, chloro-" OR "Phenol, o-chloro-" OR "Phenol, p-chloro-" OR "Phenol, tetrachloro-" OR "Pine-O Disinfectant" OR "Tetrachlorophenol" OR "Tetrachlorophenol, 2,3,4,5-" OR "Tetrachlorophenol, 2,3,4,6-" OR "Tetrachlorophenol, 2,3,5,6-" OR "Tetrachlorophenol, isomer" OR "Tetrachlorophenols" OR "Trichlorophenol (2,4,5-)" OR "Trichlorophenol, 2,4,5-" OR "Trichlorophenol, 2,4,6-" OR "2,4,5-TCP" OR "2,4,6-T" OR "2,4,6-TCP" OR "2,4-DCP" OR "BTS 45186" OR "Dowicide 2" OR "Dowicide 2S" OR "Dowicide 6" OR "Preventol I" OR "Septi-Kleen") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication: 1997 through 2019

Table B-2. Database Query Strings

Database search date	Query string
10/2019	(576-24-9[rn] OR 583-78-8[rn] OR 95-77-2[rn] OR 591-35-5[rn] OR 15950-66-0[rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] ("2,3-Dichlorophenol" OR "2,3-Dichlorphenol" OR "Dichlorophenol, 2,3-" OR "Phenol, 2,3-dichloro-" OR "1-Hydroxy-2,5-dichlorobenzene" OR "2,5-Dichlorophenol" OR "2,5-Dichlorphenol" OR "Dichlorophenol, 2,5-" OR "PHENOL, 1,4-DICHLORO-" OR "Phenol, 2,5-dichloro-" OR "1,4-DICHLOROPHENOL" OR "3,4-Dichlorophenol" OR "3,4-Dichlorphenol") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] ("4,5-Dichlorophenol" OR "Dichlorophenol, 3,4-" OR "Phenol, 3,4-dichloro-" OR "1-Hydroxy-3,5-dichlorobenzene" OR "3,5-Dichlorophenol" OR "3,5-Dichlorphenol" OR "Dichlorophenol, 3,5-" OR "Phenol, 3,5-dichloro-" OR "2,3,4-Trichlorophenol" OR "Phenol, 2,3,4-trichloro-" OR "Trichlorophenol, 2,3,4-") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
02/2019	FILE 'TOXCENTER' ENTERED AT 11:03:07 ON 14 FEB 2019 CHARGED TO COST=EH038.02.01.LB.01 L1 17425 SEA FILE=TOXCENTER 88-06-2 OR 120-83-2 OR 95-95-4 OR 95-57-8 OR 4901-51-3 OR 935-95-5 OR 58-90-2 OR 106-48-9 OR 25167-80-0 OR 25167-83-3 L2 15210 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 15122 SEA FILE=TOXCENTER L2 NOT TSCATS/FS L4 10203 SEA FILE=TOXCENTER L3 AND PY>=1997 ACT TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)

Table B-2. Database Query Strings

Database search date	Query string
	L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR 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
	L31 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?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L35 QUE L33 OR L34

	L36 3357 SEA FILE=TOXCENTER L4 AND L35
	L37 416 SEA FILE=TOXCENTER L36 AND MEDLINE/FS
	L38 374 SEA FILE=TOXCENTER L36 AND BIOSIS/FS
	L39 2559 SEA FILE=TOXCENTER L36 AND CAPLUS/FS

Table B-2. Database Query Strings

Database search date	Query string
	L40 8 SEA FILE=TOXCENTER L36 NOT (L37 OR L38 OR L39) L41 2973 DUP REM L37 L38 L40 L39 (384 DUPLICATES REMOVED) ANSWERS '1-2973' FROM FILE TOXCENTER L*** DEL 416 S L36 AND MEDLINE/FS L*** DEL 416 S L36 AND MEDLINE/FS L42 416 SEA FILE=TOXCENTER L41 L*** DEL 374 S L36 AND BIOSIS/FS L*** DEL 374 S L36 AND BIOSIS/FS L43 302 SEA FILE=TOXCENTER L41 L*** DEL 2559 S L36 AND CAPLUS/FS L*** DEL 2559 S L36 AND CAPLUS/FS L44 2249 SEA FILE=TOXCENTER L41 L*** DEL 8 S L36 NOT (L37 OR L38 OR L39) L*** DEL 8 S L36 NOT (L37 OR L38 OR L39) L45 6 SEA FILE=TOXCENTER L41 L46 2557 SEA FILE=TOXCENTER (L42 OR L43 OR L44 OR L45) NOT MEDLINE/FS D SCAN L46
10/2019	FILE 'TOXCENTER' ENTERED AT 13:18:44 ON 11 OCT 2019 CHARGED TO COST=EH038.02.01.LB.01 L1 2567 SEA FILE=TOXCENTER 576-24-9 OR 583-78-8 OR 95-77-2 OR 591-35-5 OR 15950-66-0 L2 2025 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 2023 SEA FILE=TOXCENTER L2 NOT TSCATS/FS ACT TOXQUERY/Q --------- L4 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L5 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L6 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L7 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L8 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L9 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L10 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L11 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L12 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L13 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L14 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L15 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L16 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR

Table B-2. Database Query Strings

Database search date	Query string
	SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L17 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR
	SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L18 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L19 QUE (ENDOCRIN? AND DISRUPT?)
	L20 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L21 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L22 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L23 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR
	NEOPLAS?)
	L24 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L25 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L26 QUE (NEPHROTOX? OR HEPATOTOX?)
	L27 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L28 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L29 QUE L4 OR L5 OR L6 OR 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
	L30 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?)
	L31 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L32 QUE L29 OR L30 OR L31
	L33 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L34 QUE L32 OR L33

	L35 1074 SEA FILE=TOXCENTER L3 AND L34
	L37 68 SEA FILE=TOXCENTER L35 AND MEDLINE/FS
	L38 1006 SEA FILE=TOXCENTER L35 NOT MEDLINE/FS
	L39 984 DUP REM L37 L38 (90 DUPLICATES REMOVED)
	ANSWERS '1-984' FROM FILE TOXCENTER
	L*** DEL 68 S L35 AND MEDLINE/FS
	L*** DEL 68 S L35 AND MEDLINE/FS
	L40 68 SEA FILE=TOXCENTER L39
	L*** DEL 1006 S L35 NOT MEDLINE/FS
	L*** DEL 1006 S L35 NOT MEDLINE/FS
	L41 916 SEA FILE=TOXCENTER L39
	L42 916 SEA FILE=TOXCENTER (L40 OR L41) NOT MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	SAVE TEMP L42 CPLS/A D SCAN L42

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
02/2019	Compounds searched: 88-06-2; 120-83-2; 95-95-4; 95-57-8; 4901-51-3; 935-95-5; 58-90-2; 106-48-9; 25167-80-0; 25167-83-3
10/2019	Compounds searched: 576-24-9; 583-78-8; 95-77-2; 591-35-5; 15950-66-0
NTP	
02/2019	88-06-2 120-83-2 95-95-4 95-57-8 4901-51-3 935-95-5 58-90-2 106-48-9 25167-80-0 25167-83-3 chlorophenol dichlorophenol trichlorophenol tetrachlorophenol
10/2019	"576-24-9" "583-78-8" "95-77-2" "591-35-5" "15950-66-0" "1-Hydroxy-3,5-dichlorobenzene" "1-Hydroxy-2,5-dichlorobenzene"
Regulations.gov	
02/2019	Compounds searched: 88-06-2; 120-83-2; 95-95-4; 95-57-8; 4901-51-3; 935-95-5; 58-90-2; 106-48-9; 25167-80-0; 25167-83-3
10/2019	Compounds searched: 576-24-9; 583-78-8; 95-77-2; 591-35-5; 15950-66-0
NIH RePORTER	
12/2019	Text Search: "1,3,5-Trichloro-2-hydroxybenzene" OR "1,3-Dichloro-4-hydroxybenzene" OR "1-Chloro-2-hydroxybenzene" OR "1-Hydroxy-2,3,4,6-tetrachlorobenzene" OR "1-Hydroxy-2,4-dichlorobenzene" OR "2,3,4,5-Tetrachlorophenate" OR "2,3,4,5-Tetrachlorophenol" OR "2,3,4,6-Tetrachlorophenate" OR "2,3,4,6-Tetrachlorophenol" OR "2,3,4,6-Tetrachlorphenol" OR "2,3,4,6-tetraclorofenol" OR "2,3,5,6-Tetrachlorophenate" OR "2,3,5,6-Tetrachlorophenol" OR "2,4,-Dichlorophenol" OR "2,4,5,6-Tetrachlorophenol" OR "2,4,5-Trichlorophenol" OR "2,4,5-Trichlorphenol" OR "2,4,5-triclorofenol" OR "2,4,6-Trichlorfenol" OR "2,4,6-Trichlorophenol" OR "2,4,6-Trichlorphenol" OR "2,4,6-triclorofenol" OR "2,4-Dichlorohydroxybenzene" OR "2,4-Dichlorophenic acid" OR "2,4-Dichlorophenol" OR "2,4-Dichlorphenol" OR "2,4-diclorofenol" OR "2-Chloro-1-hydroxybenzene" OR "2-Chlorophenol" OR "2-Chlorphenol" OR "2-clorofenol" OR "2-Hydroxychlorobenzene" OR "2-Monochlorophenol" OR "2.4,5-Trichlorophenic acid" OR "4,6-Dichlorophenol" OR "4-Chloro-1-hydroxybenzene" OR "4-Chlorophenol" OR "4-Chlorphenol" OR "4-

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	clorofenol" OR "4-Hydroxychlorobenzene" OR "4-Monochlorophenol" OR "Chlorophenol" OR "Chlorophenol, 2-" OR "Chlorophenol, 4-" OR "Chlorophenol, o-" OR "Chlorophenol, p-" OR "Chlorophenols" OR "Chlorophenols, liquid" OR "Chlorophenols, solid" OR "Collunosol" OR "Dichlorophenol (2,4-)" OR "Dichlorophenol, 2,4-" OR "Monochlorophenol (mixed isomers)" OR "Monochlorophenols (all isomers)" OR "Monochlorophenols (total)" OR "o,p-Dichlorophenol" OR "o-Chlorophenic acid" OR "o-Chlorophenol" OR "o-Chlorphenol" OR "ortho,para-Dichlorophenol" OR "ortho-Chlorophenol" OR "p-Chlorophenic acid" OR "p-Chlorophenol" OR "Parachlorophenol" OR "Phenachlor" OR "Phenaclor" OR "Phenol, 2,3,4,5-tetrachloro-" OR "Phenol, 2,3,4,6-tetrachloro-" OR "Phenol, 2,3,5,6-tetrachloro-" OR "Phenol, 2,4,5-trichloro-" OR "Phenol, 2,4,6-trichloro-" OR "Phenol, 2,4-dichloro-" OR "Phenol, 2-chloro-" OR "Phenol, 4-chloro-" OR "Phenol, chloro-" OR "Phenol, o-chloro-" OR "Phenol, p-chloro-" OR "Phenol, tetrachloro-" OR "Pine-O Disinfectant" OR "Tetrachlorophenol" OR "Tetrachlorophenol, 2,3,4,5-" OR "Tetrachlorophenol, 2,3,4,6-" OR "Tetrachlorophenol, 2,3,5,6-" OR "Tetrachlorophenol, isomer" OR "Tetrachlorophenols" OR "Trichlorophenol (2,4,5-)" OR "Trichlorophenol, 2,4,5-" OR "Trichlorophenol, 2,4,6-" OR "2,4,5-TCP" OR "2,4,6-TCP" OR "2,4-DCP" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects "2,3-Dichlorophenol" OR "2,3-Dichlorphenol" OR "Dichlorophenol, 2,3-" OR "Phenol, 2,3-dichloro-" OR "1-Hydroxy-2,5-dichlorobenzene" OR "2,5-Dichlorophenol" OR "2,5-Dichlorphenol" OR "Dichlorophenol, 2,5-" OR "PHENOL, 1,4-DICHLORO-" OR "Phenol, 2,5-dichloro-" OR "1,4-DICHLOROPHENOL" OR "3,4-Dichlorophenol" OR "3,4-Dichlorphenol" OR "4,5-Dichlorophenol" OR "Dichlorophenol, 3,4-" OR "Phenol, 3,4-dichloro-" OR "1-Hydroxy-3,5-dichlorobenzene" OR "3,5-Dichlorophenol" OR "3,5-Dichlorphenol" OR "Dichlorophenol, 3,5-" OR "Phenol, 3,5-dichloro-" OR "2,3,4-Trichlorophenol" OR "Phenol, 2,3,4-trichloro-" OR "Trichlorophenol, 2,3,4-" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects "Applied 3-78" OR "BTS 45186" OR "Dowicide 2" OR "Dowicide 2S" OR "Dowicide 6" OR "Preventol I" OR "Septi-Kleen" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2019 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 5,101
- Number of records identified from other strategies: 70
- Total number of records to undergo literature screening: 5,171

B.1.2 Literature Screening

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

- 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.

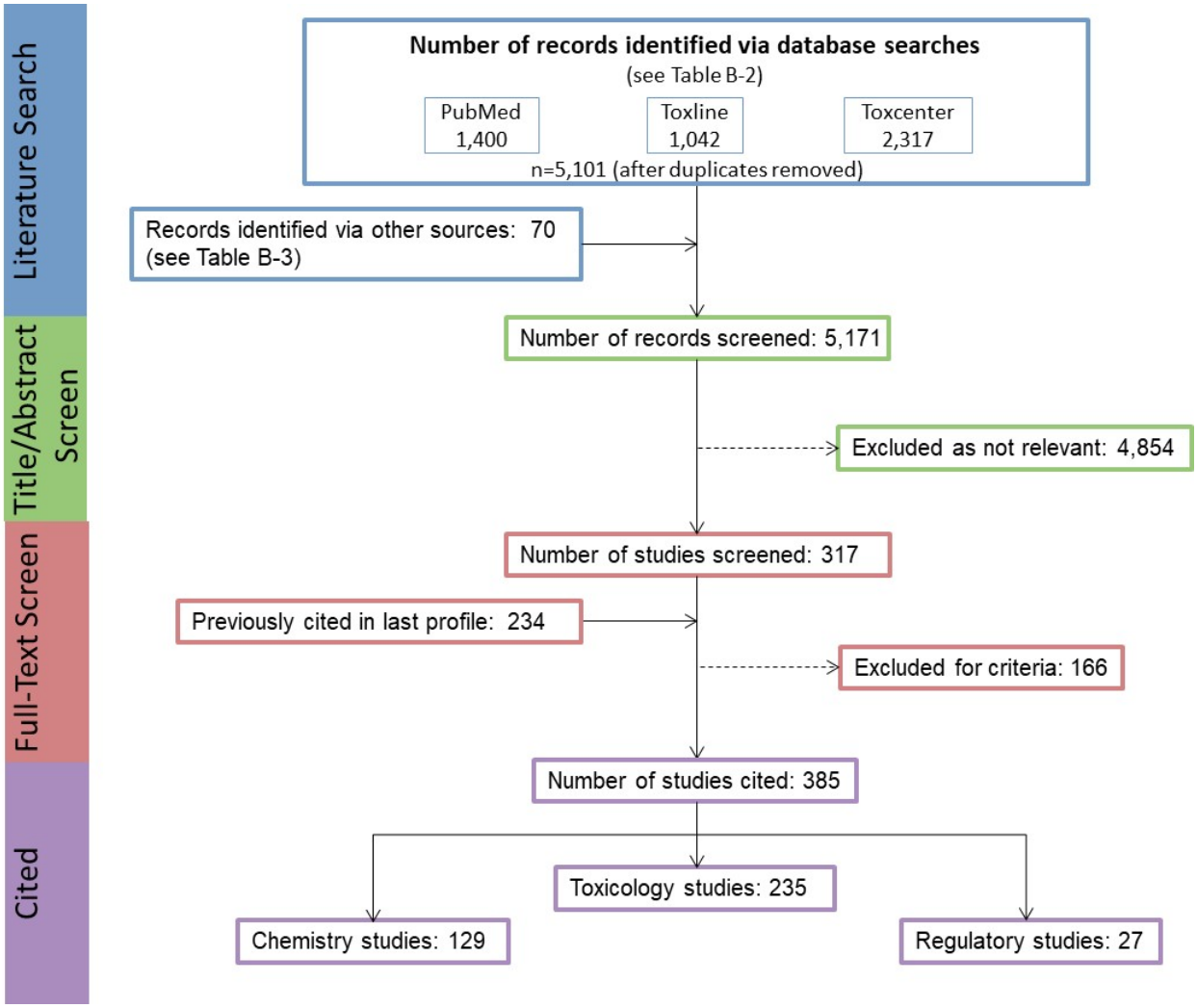
- Number of titles and abstracts screened: 5,171
- Number of studies considered relevant and moved to the next step: 317

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: 317
- Number of studies cited in the pre-public draft of the toxicological profile: 234
- Total number of studies cited in the profile: 385

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

Figure B-1. 2019 Literature Search Results and Screen for Chlorophenols



APPENDIX C. 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 C-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 C-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.

(13) 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.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) 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.

(16) 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).

(17) 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.

(18) 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 (1)

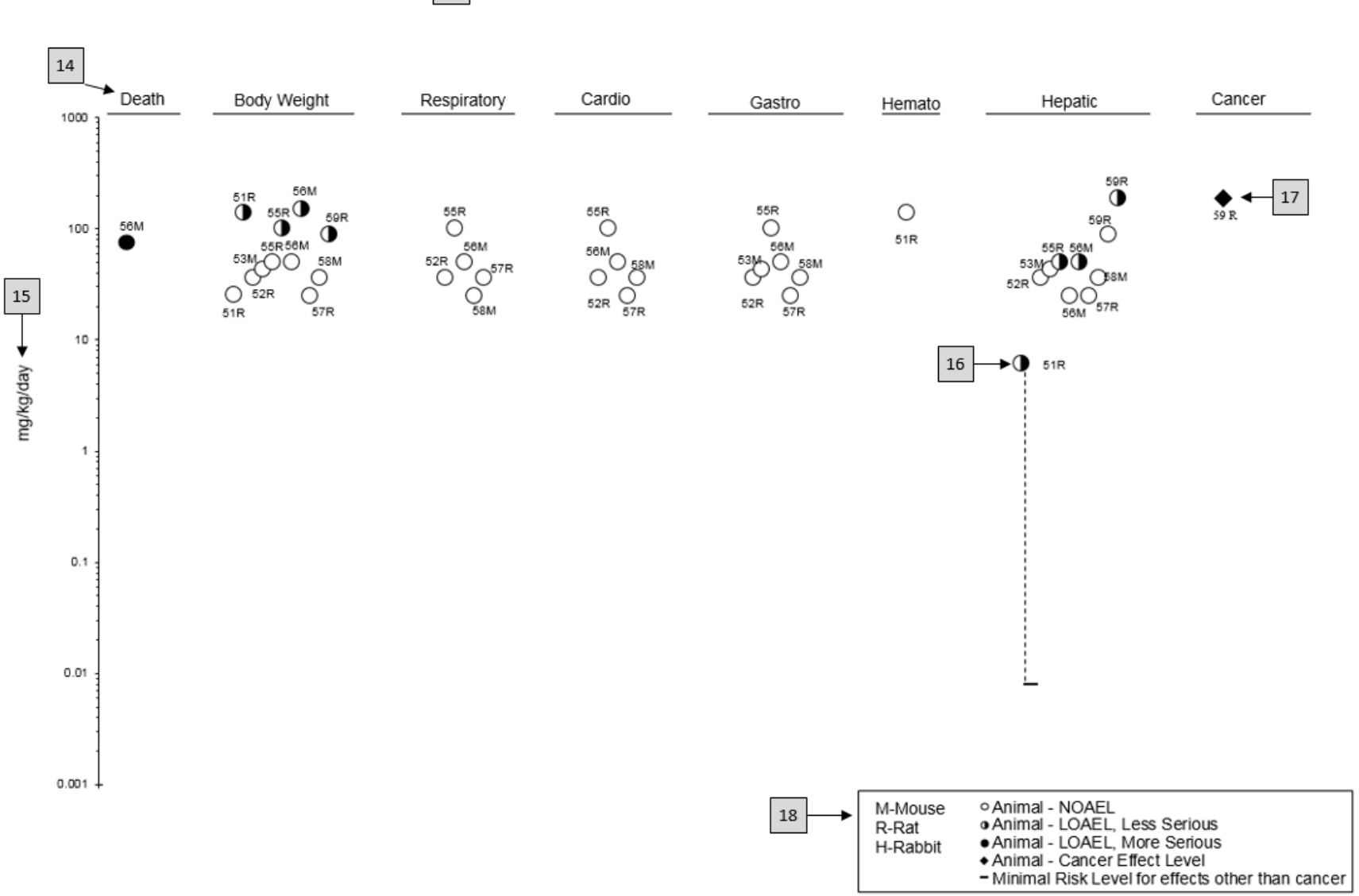
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

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

(11) [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 D. 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

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.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.asp).

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 E. 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 F. 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
DHHS	Department of Health and Human Services
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
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