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, there is a decrease in volatilization from water and moist soils and an increase in mobility in soils. 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 contaminated 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

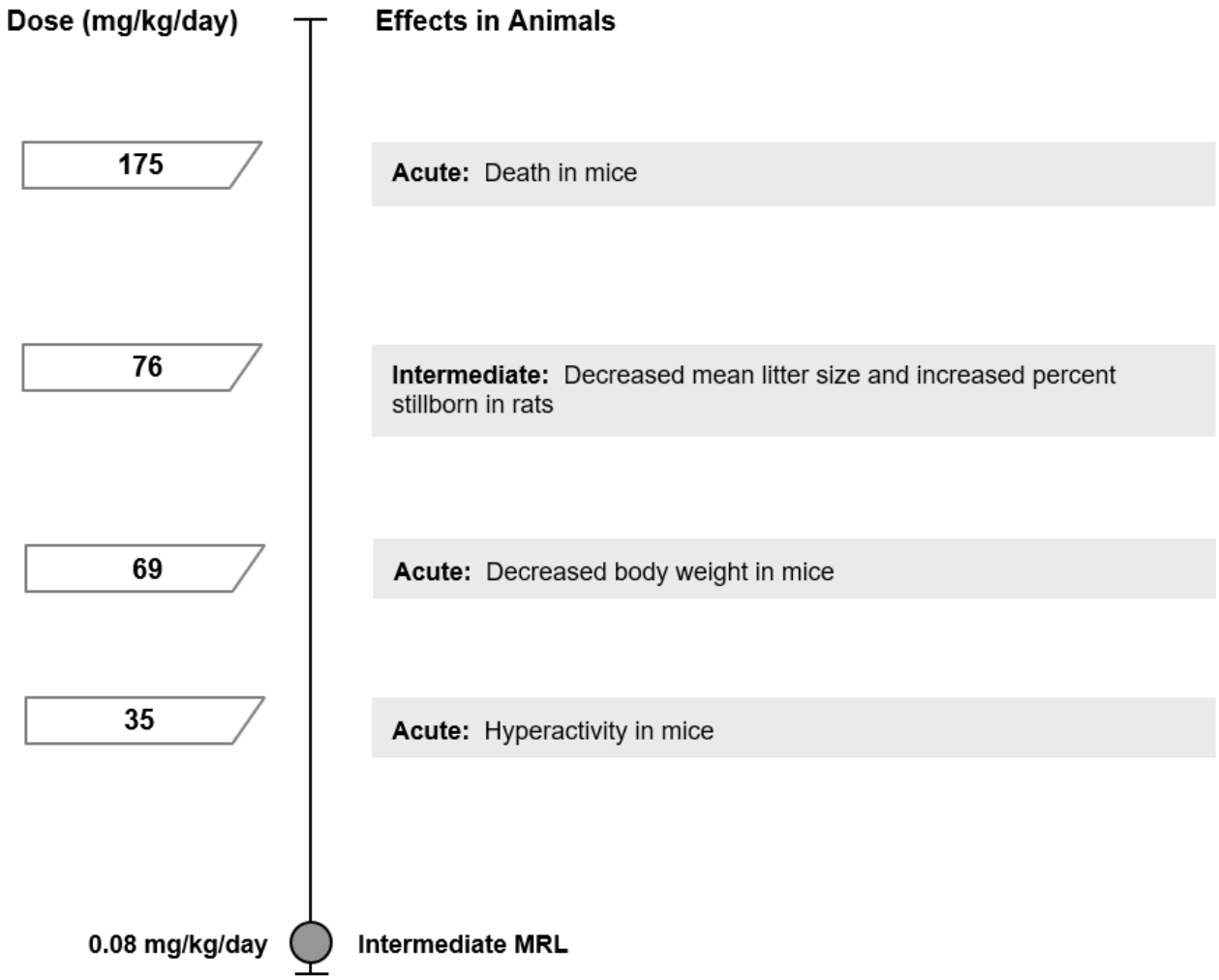


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 4-Chlorophenol

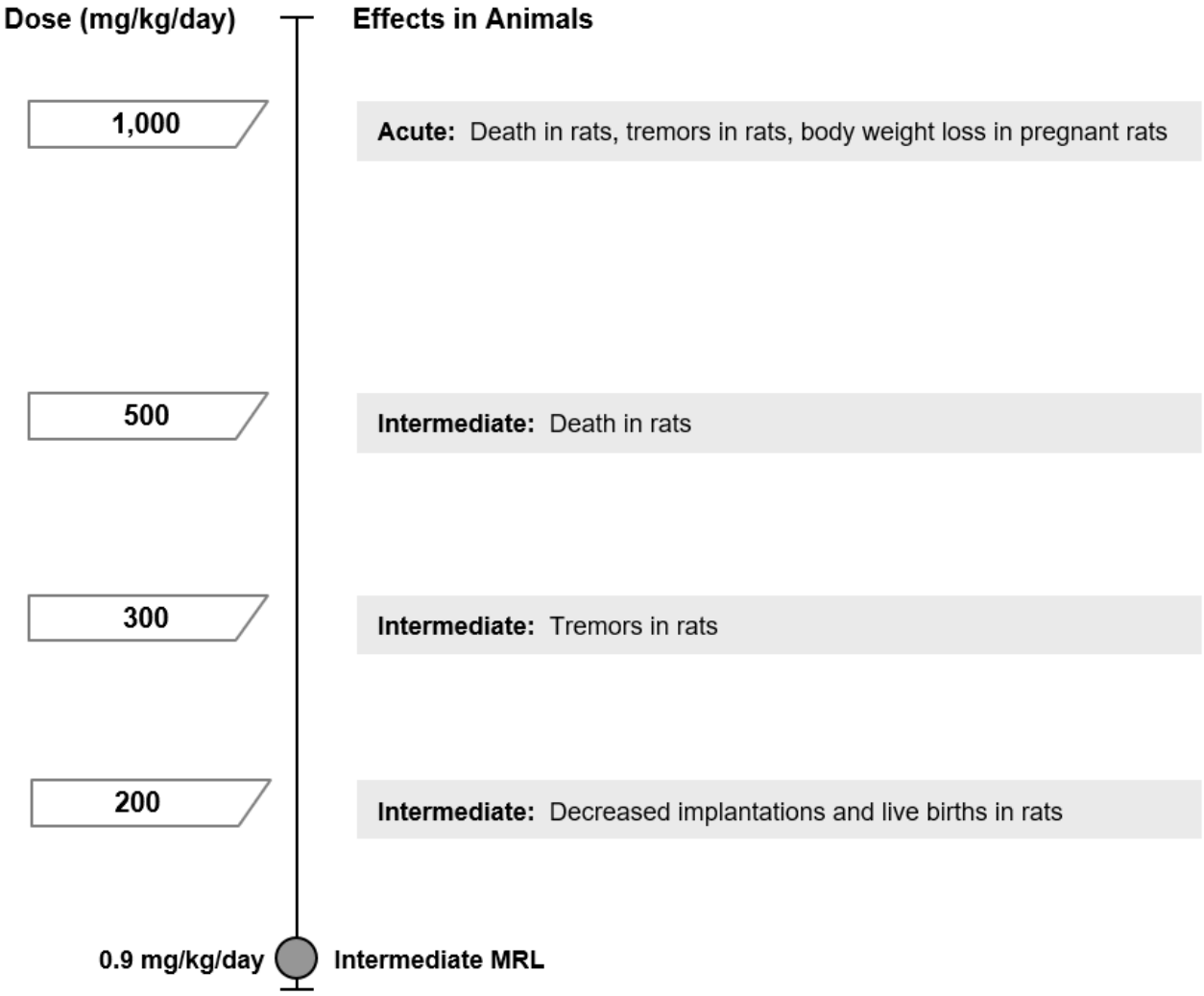


Figure 1-3. Health Effects Found in Animals Following Oral Exposure to 2,4-Dichlorophenol

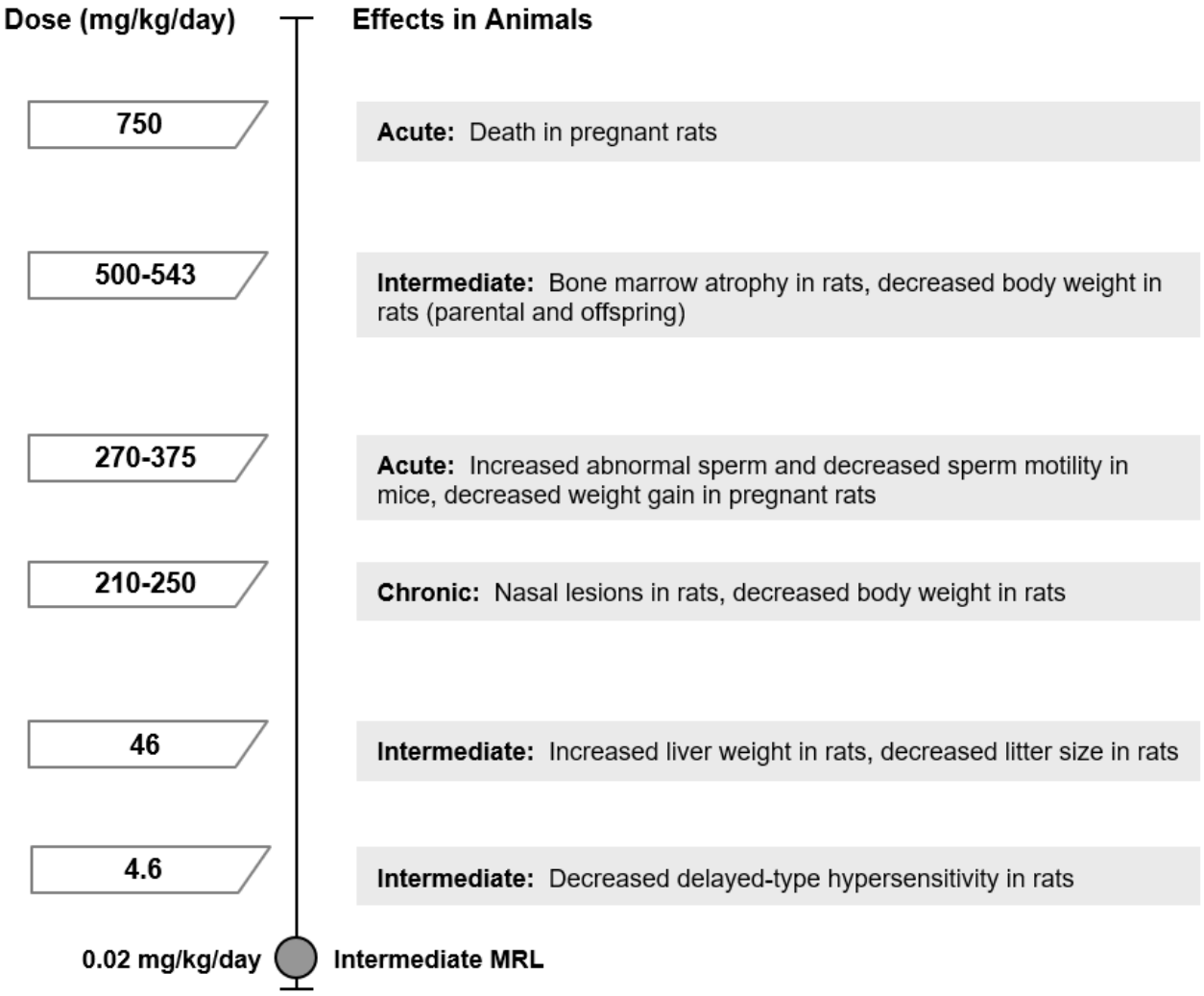


Figure 1-4. Health Effects Found in Animals Following Oral Exposure to 2,4,5-Trichlorophenol

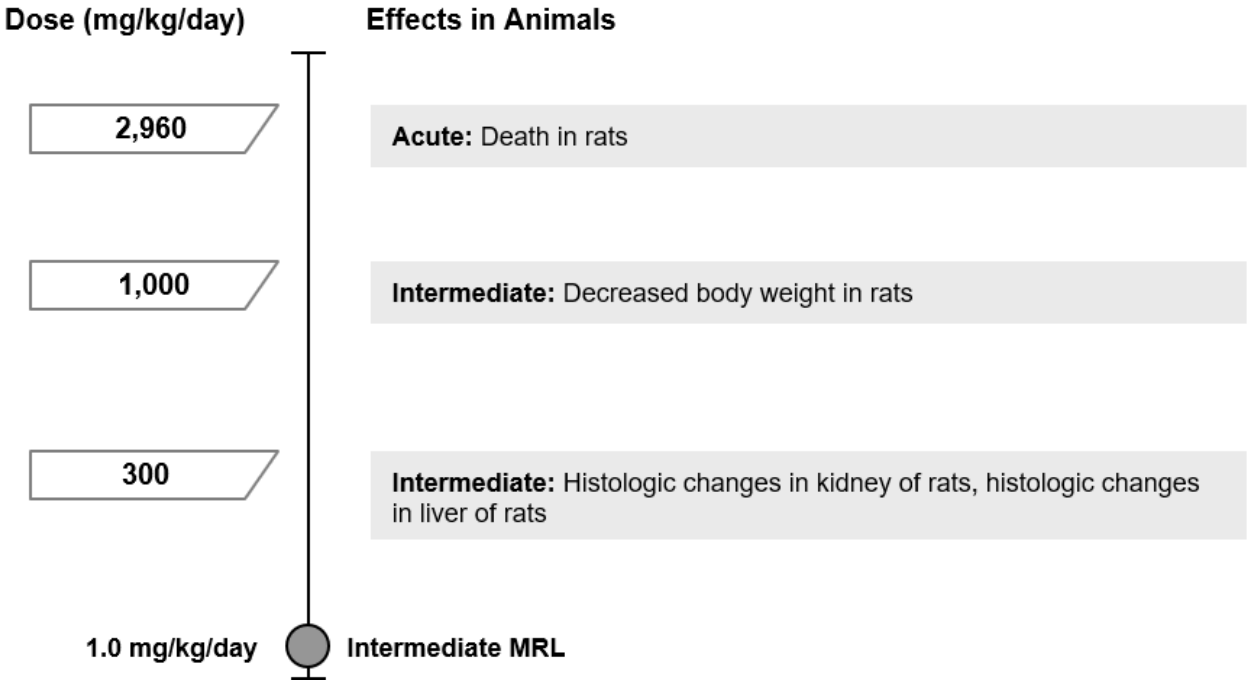


Figure 1-5. Health Effects Found in Animals Following Oral Exposure to 2,4,6-Trichlorophenol

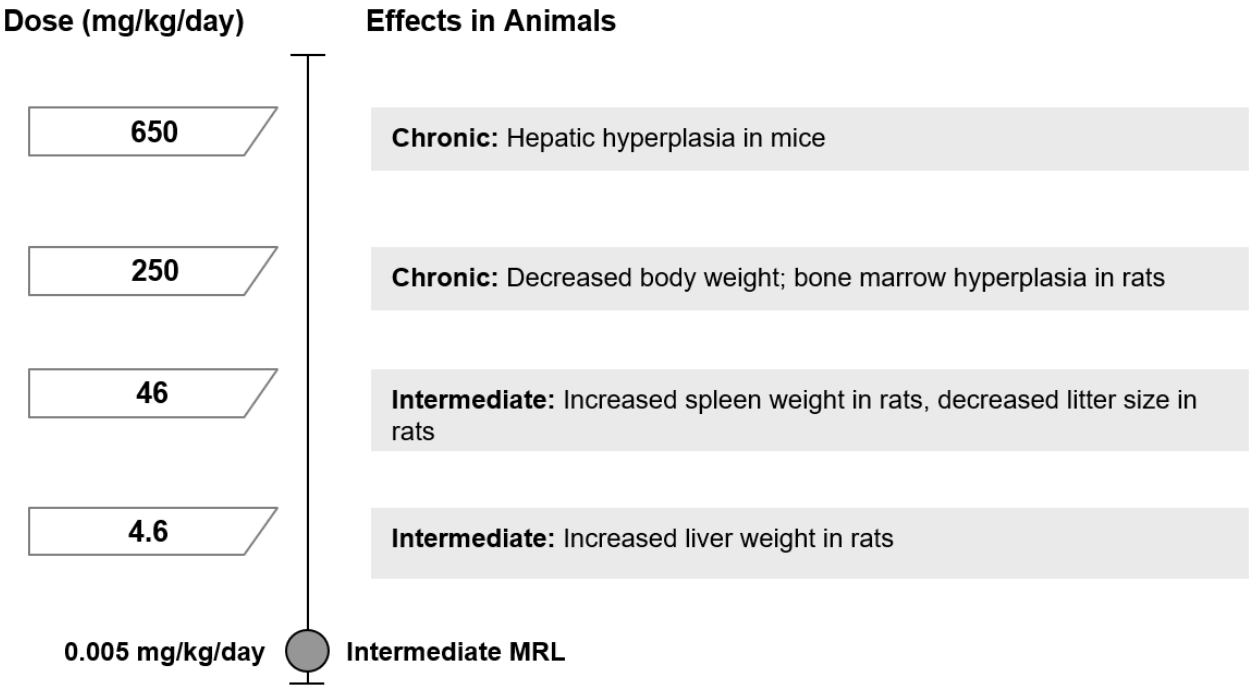


Figure 1-6. Health Effects Found in Animals Following Oral Exposure to 2,3,4,6-Tetrachlorophenol

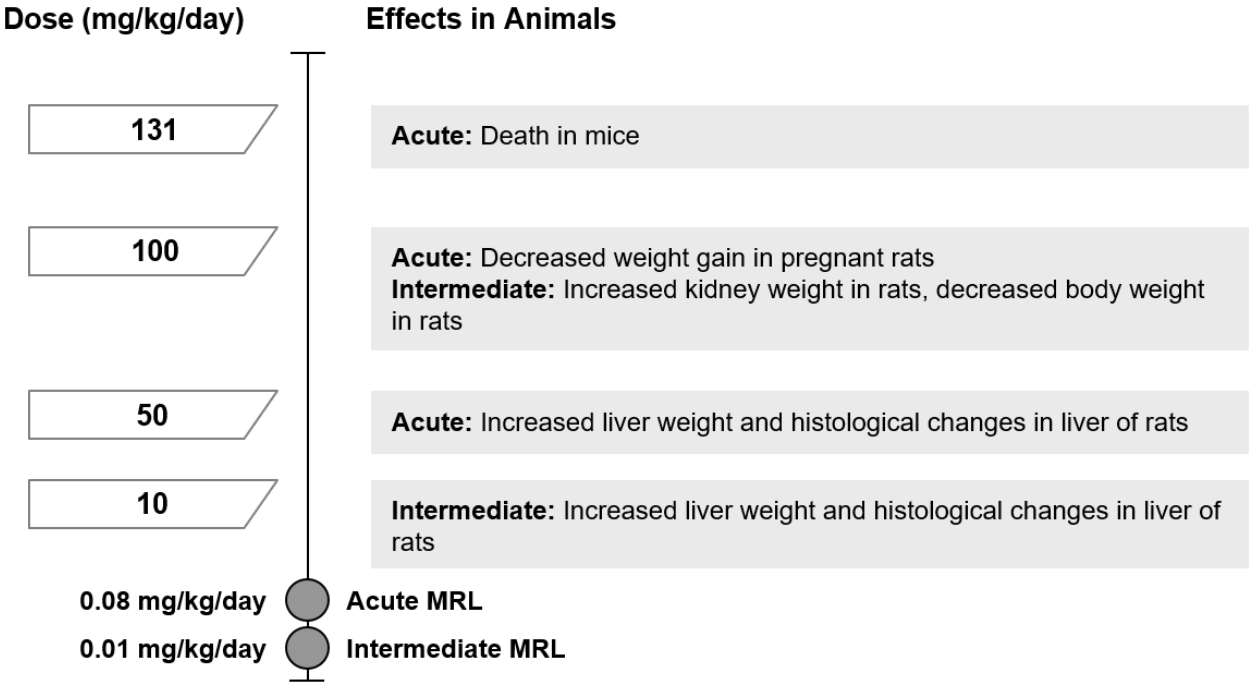
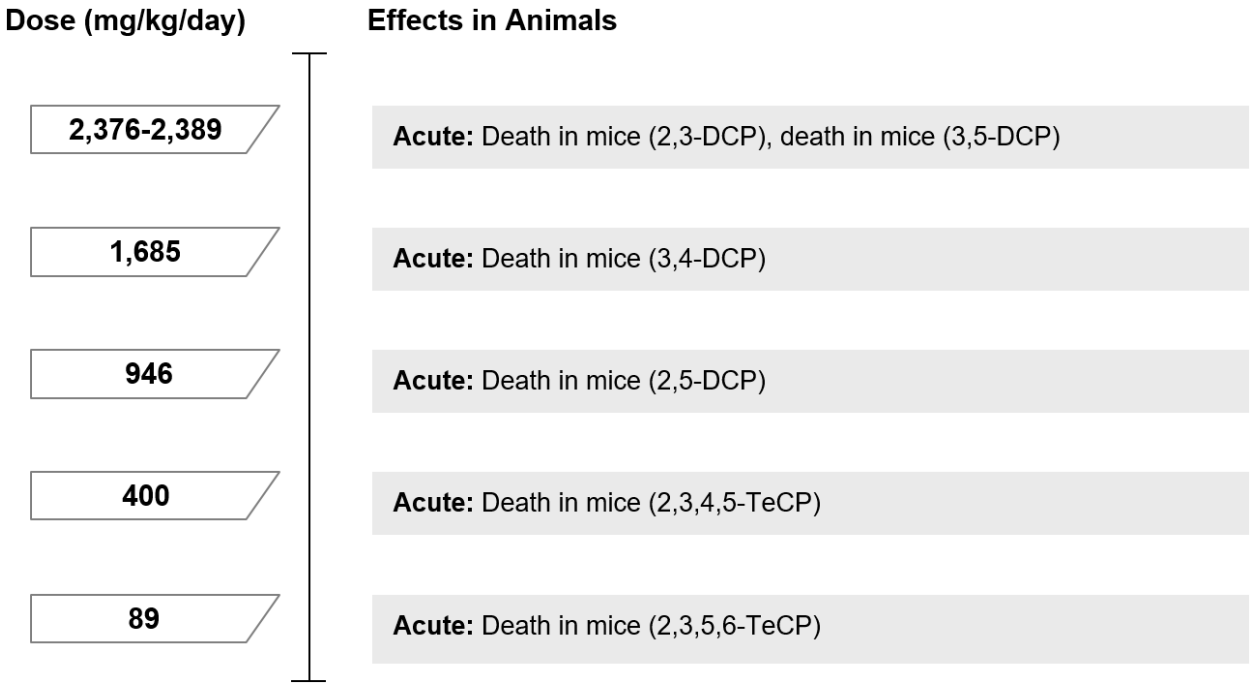


Figure 1-7. Health Effects Found in Animals Following Oral Exposure to Other Chlorophenols



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; EPA 1987a, 1987b). 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 acute-duration oral MRLs for 2,3,4,6-TeCP and 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 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.

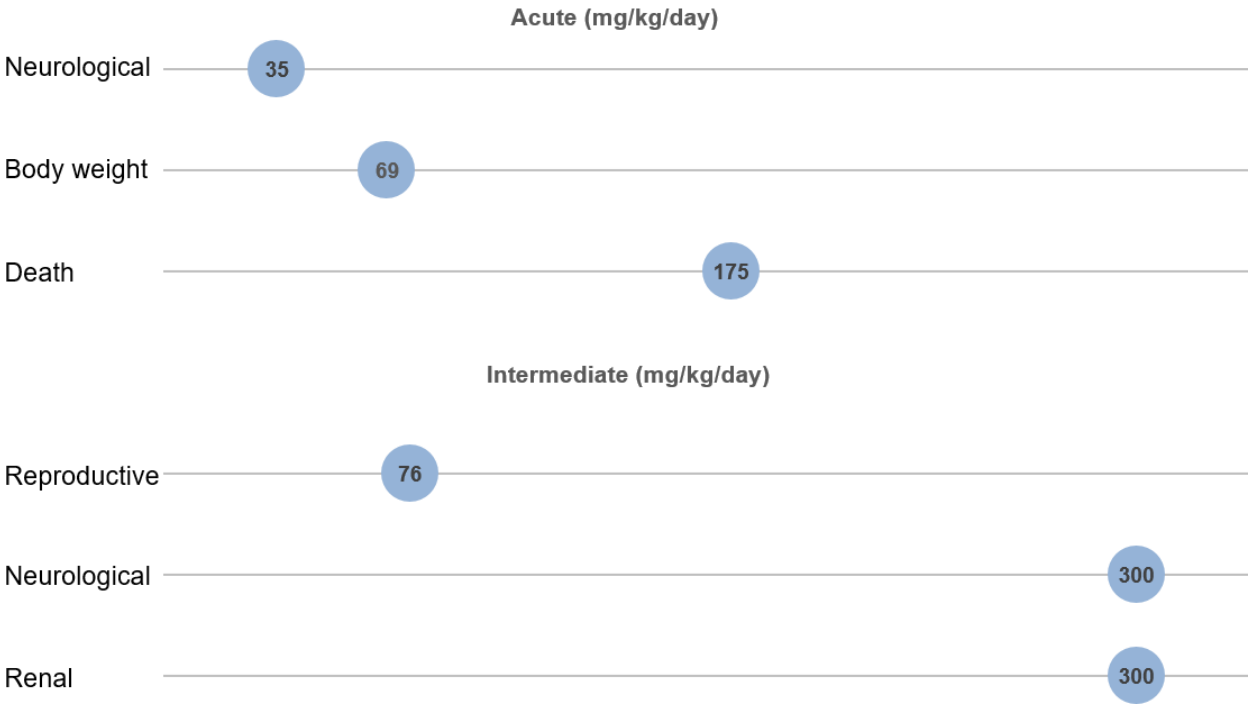


Figure 1-9. Summary of Sensitive Targets of 4-Chlorophenol – Oral

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.

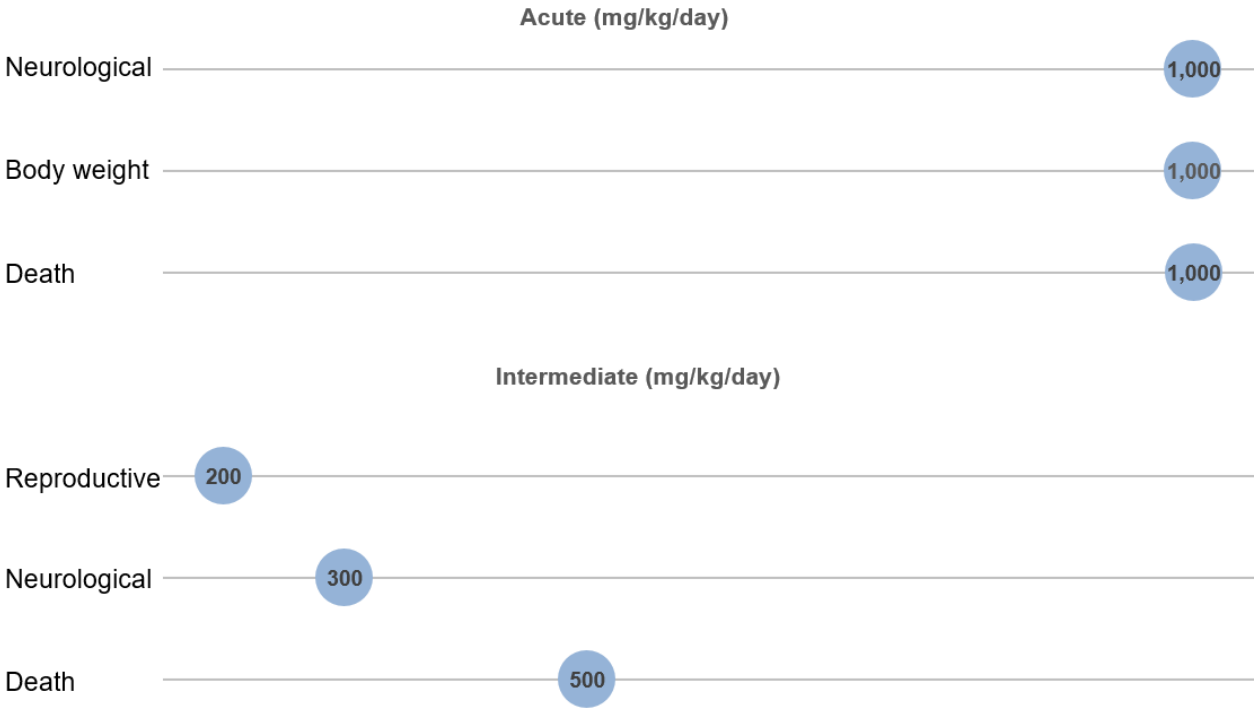


Figure 1-10. Summary of Sensitive Targets of 2,4-Dichlorophenol – Oral

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.

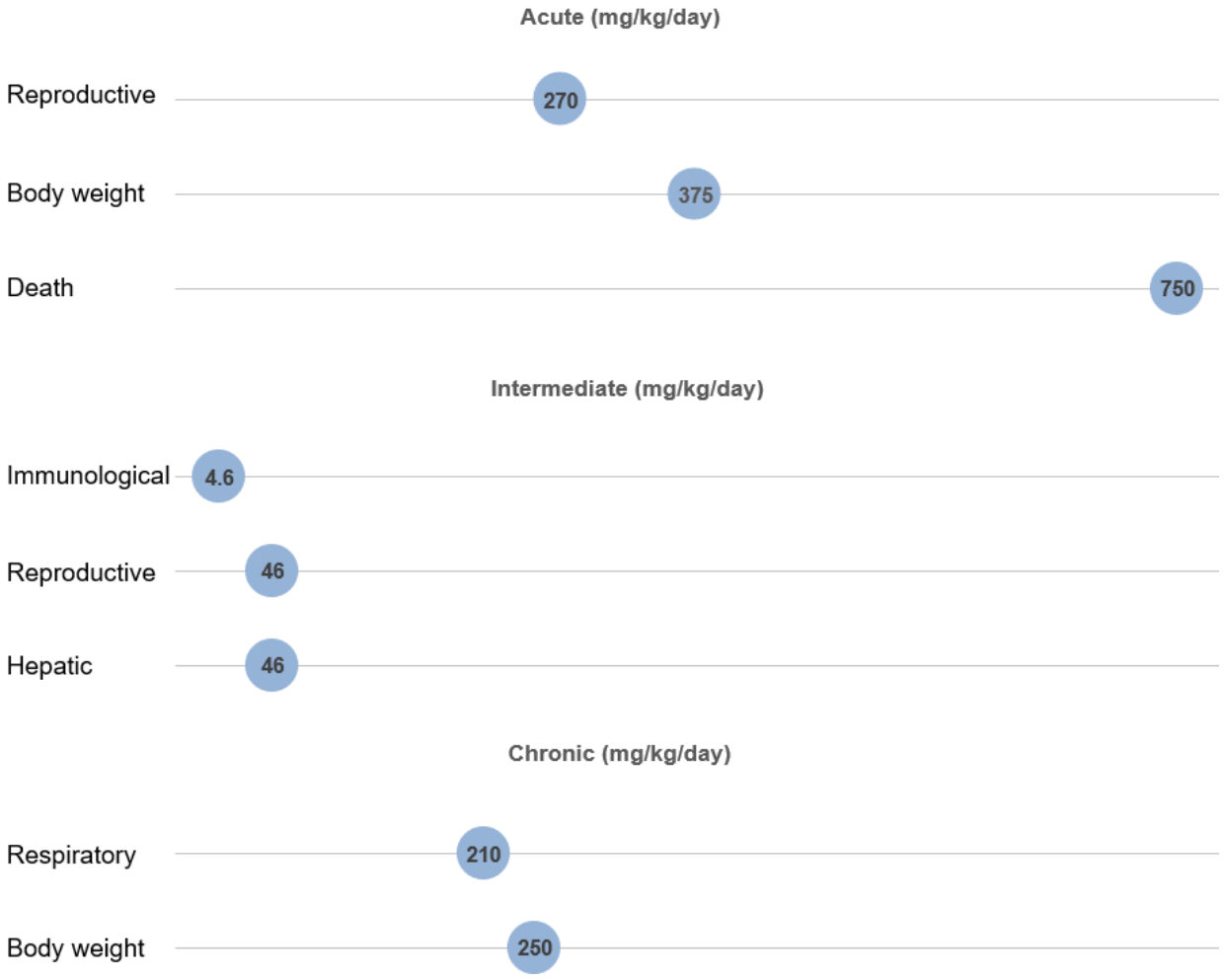


Figure 1-11. Summary of Sensitive Targets of 2,4,5-Trichlorophenol – Oral

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.

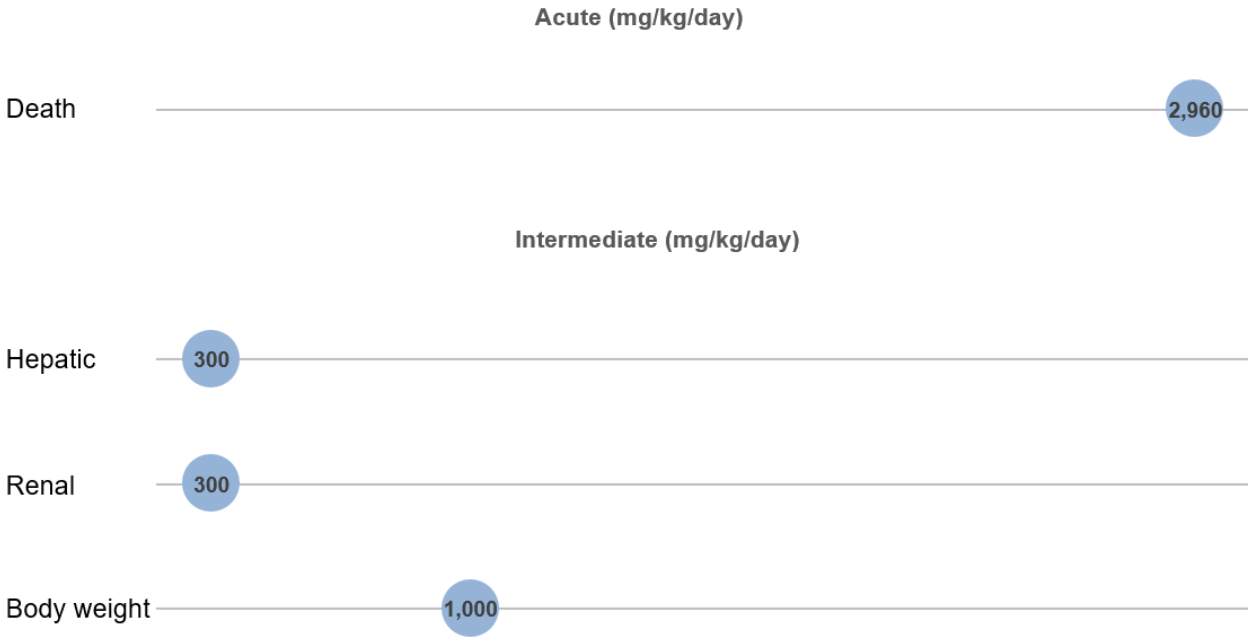


Figure 1-12. Summary of Sensitive Targets of 2,4,6-Trichlorophenol – Oral

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.

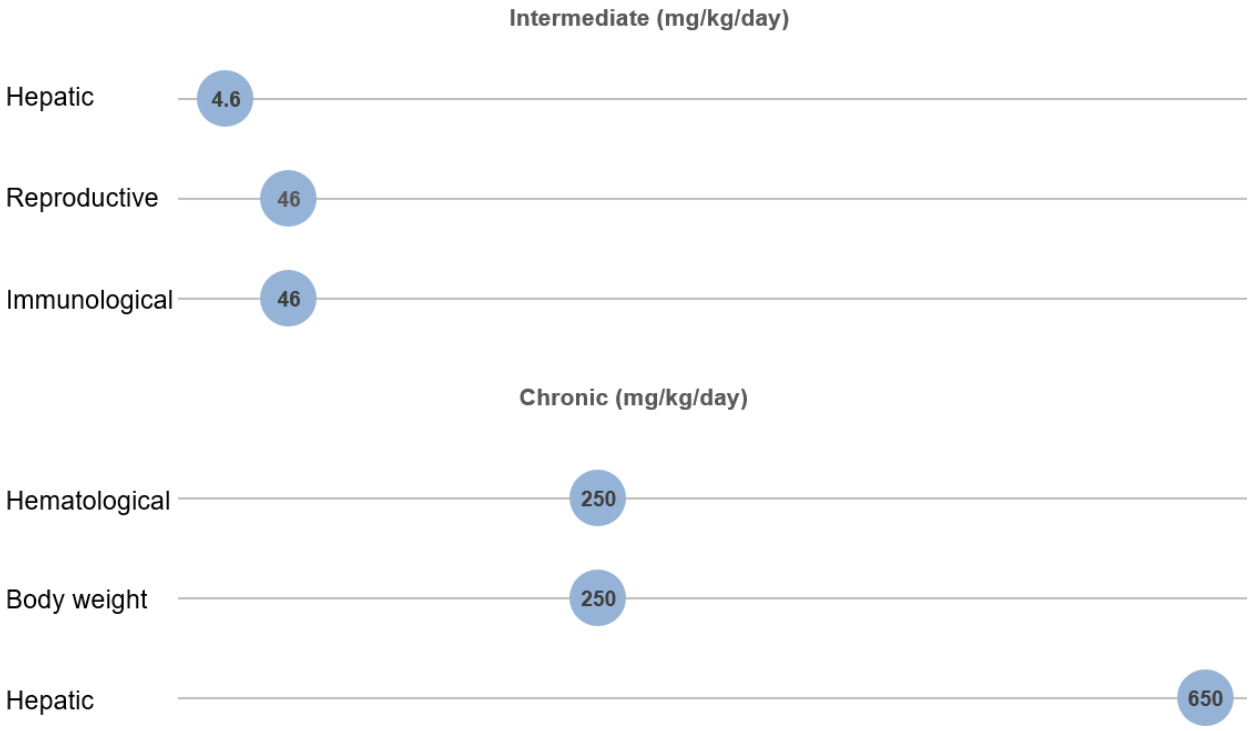


Figure 1-13. Summary of Sensitive Targets of 2,3,4,6-Tetrachlorophenol – Oral

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.

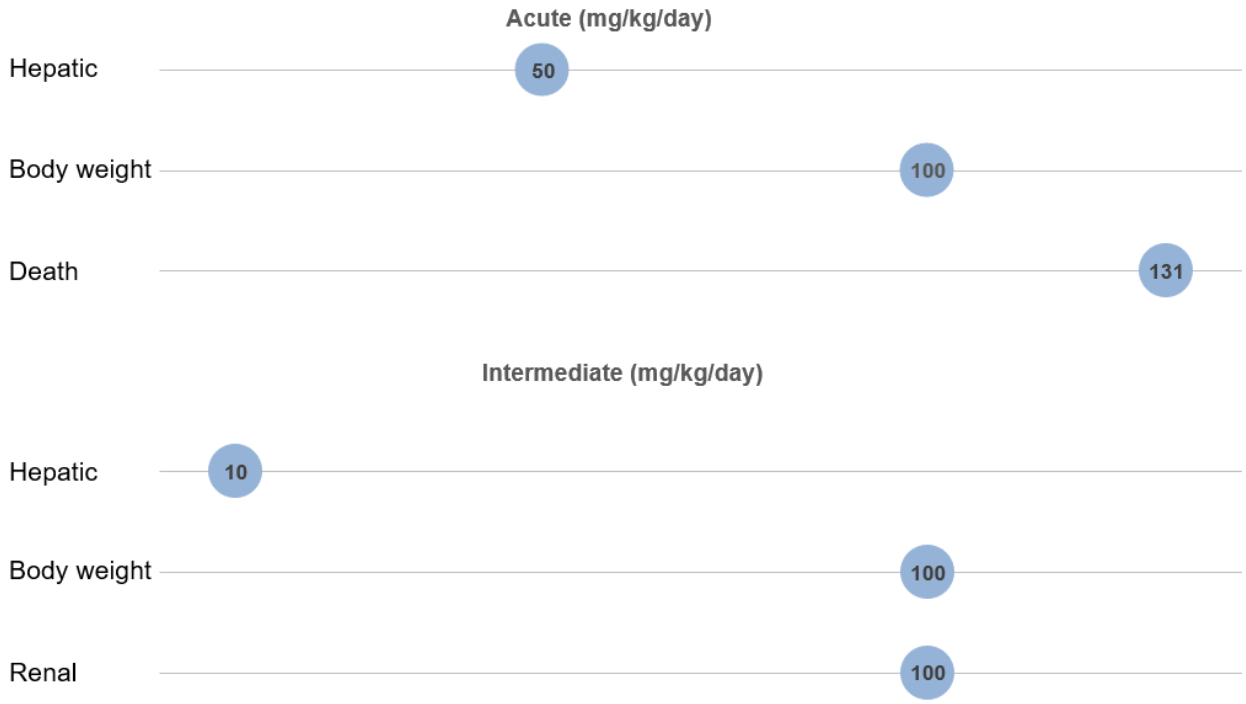


Table 1-1. Minimal Risk Levels (MRLs) for Chlorophenols[a]

Exposure duration	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 immunological 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	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 (5 µg/kg/day)	Increased liver weight	NOAEL: 0.46	UF: 100	Exon and Koller 1985
Chronic	Insufficient data for MRL derivation				

Table 1-1. 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