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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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Chlorophenol
CAS Numbers: 95-57-8
Date: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.08 mg/kg/day
Critical Effect: Decreased litter size
References: Exon and Koller 1982, 1983a, 1983b, 1985
Point of Departure: NOAEL of 7.6 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 5
Species: Rats

MRL Summary: An intermediate-duration oral MRL of 0.08 mg/kg/day was derived 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, 1983a, 1983b, 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, 1983a, 1983b, 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, 1983a, 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 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

MRL = NOAEL ÷ (UF)
7.6 mg/kg/day ÷ (10 x 10) = 0.076 mg/kg/day ≈ 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

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Chlorophenol
CAS Numbers: 95-57-8
Date: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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 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 (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: June 2022
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.9 mg/kg/day
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: An intermediate-duration oral MRL of 0.9 mg/kg/day was derived for 4-CP based on a $BMDL_{1SD}$ of 85.77 mg/kg/day for 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 and 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)

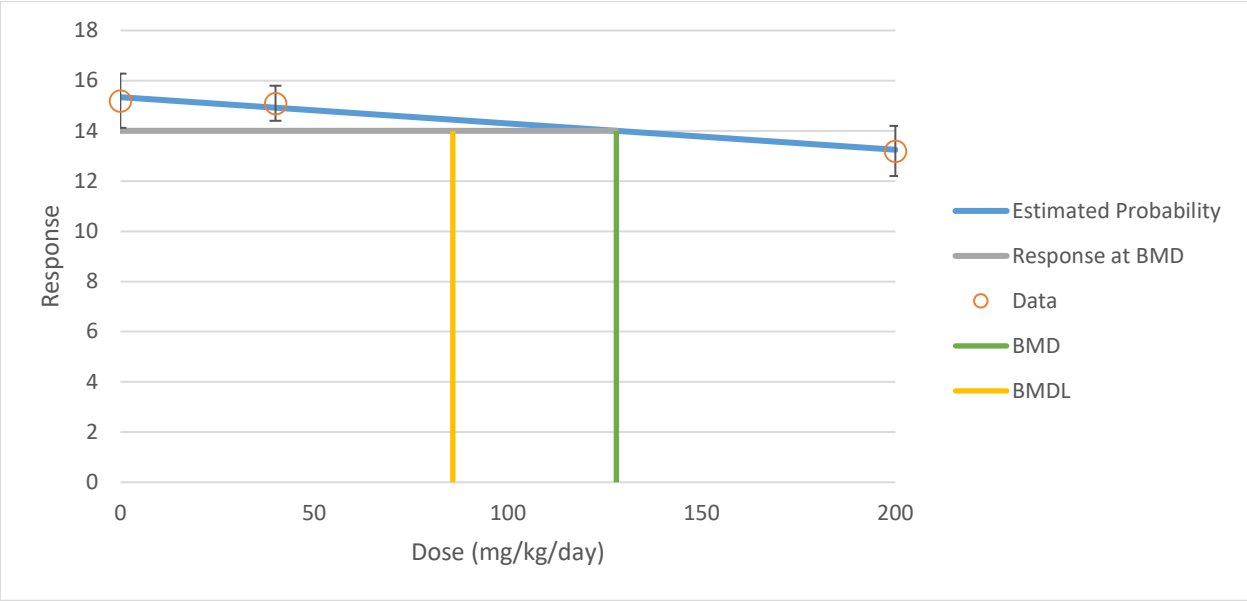
Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Exponential (model 2)[e]	0.01	0.31	0.52	0.50	-0.13	0.50	119.03	124.81	80.81
Exponential (model 3)[e]	0.01	0.31	NA	-1.1×10^{-5}	-5.7×10^{-5}	-9.12×10^{-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	-2.01×10^{-6}	-9.98×10^{-6}	-5.0×10^{-5}	122.61	158.91	40.92
Hill[e]	0.01	0.31	<0.0001	-0.0003	8.05×10^{-5}	-0.0003	122.61	54.43	41.50
Polynomial (2-degree)[e]	0.01	0.31	NA	1.85×10^{-6}	-1.92×10^{-8}	-1.88×10^{-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

MRL = $BMDL_{1SD}$ ÷ (UF)
85.77 mg/kg/day ÷ (10 x 10) = 0.8577 mg/kg/day ≈ 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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.02 mg/kg/day
Critical Effect: Decreased delayed-type immunological 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: An intermediate-duration oral MRL of 0.02 mg/kg/day was derived 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 the 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	4.6	Decreased delayed-type immunological hypersensitivity response	Exon and Koller 1985; Exon et al. 1984

Table A-9. Summary of Candidate Critical Effects for the 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

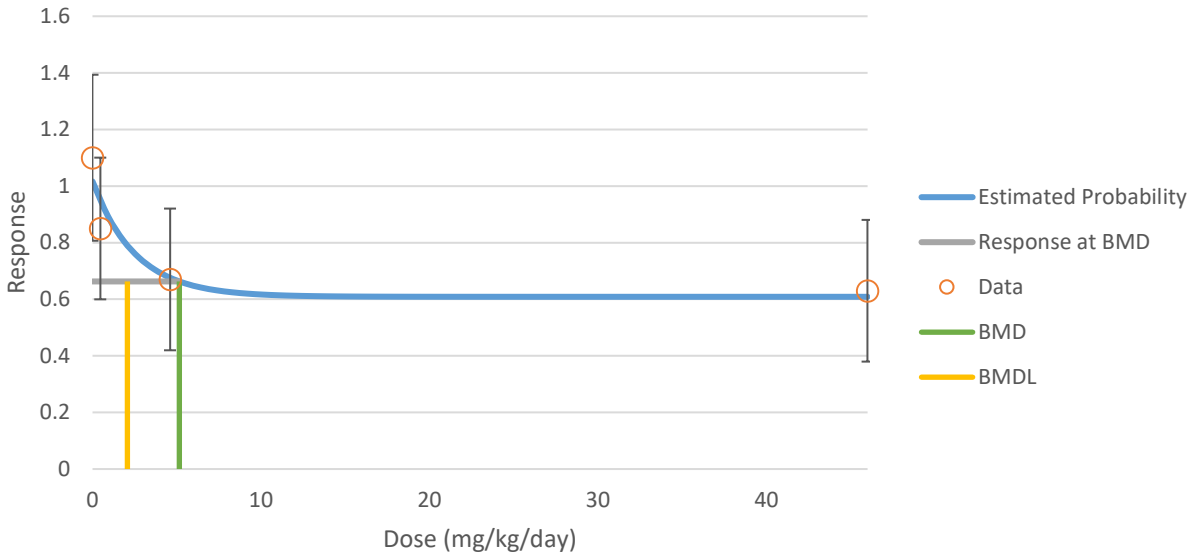
Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Exponential (model 2)[e]	0.11	0.94	0.05	0.23	ND	1.73	41.07	63.11	27.59
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 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

$MRL = BMDL_{1SD} \div (UF)$
$2.07 \text{ mg/kg/day} \div (10 \times 10) = 0.0207 \text{ mg/kg/day} \approx 0.02 \text{ mg/kg/day}$

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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 3,5-Dichlorophenol
CAS Numbers: 591-35-5
Date: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,5-Trichlorophenol
CAS Numbers: 95-95-4
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 1 mg/kg/day
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: An intermediate-duration oral MRL of 1 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 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

MRL = NOAEL ÷ (UF x MF)
100 mg/kg/day ÷ (10 x 10) = 1 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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.005 mg/kg/day (5 μg/kg/day)
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: An intermediate-duration oral MRL of 0.005 mg/kg/day (5 μg/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 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.

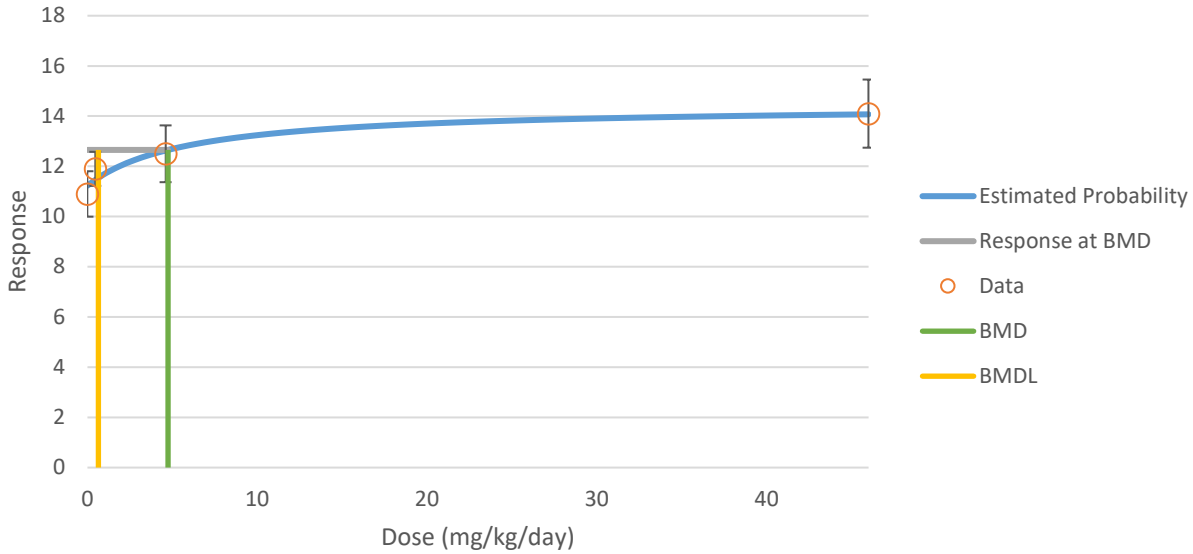
Table A-15. Results from BMD Analysis (Constant Variance) of Absolute Liver Weights in Male and Female Sprague-Dawley Rats Exposed to 2,4,6-Trichlorophenol

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 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

MRL = NOAEL ÷ (UF)
0.46 mg/kg/day ÷ (10 x 10) = 0.0046 mg/kg/day ≈ 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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,4,6-Trichlorophenol
CAS Numbers: 88-06-2
Date: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,5-Tetrachlorophenol
CAS Numbers: 4901-51-3
Date: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,5-Tetrachlorophenol
CAS Numbers: 4901-51-3
Date: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,5-Tetrachlorophenol
CAS Numbers: 4901-51-3
Date: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.08 mg/kg/day
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: An 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

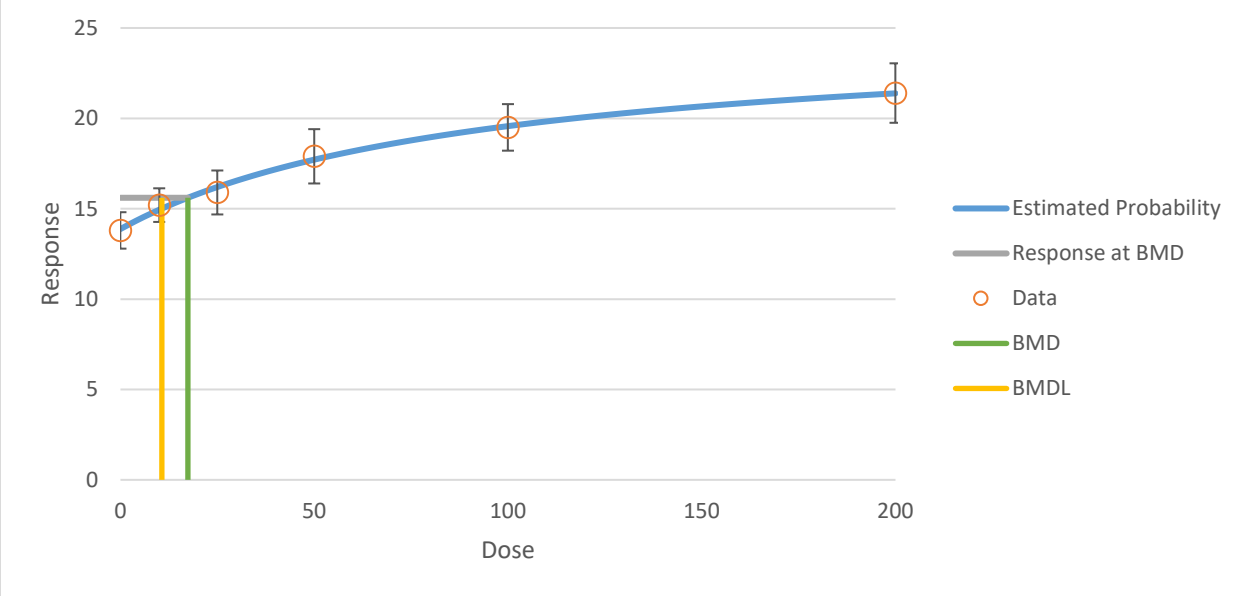


Table A-20. Results from BMD Analysis (Constant Variance) of Relative Liver Weights in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol for 2 Weeks (Dodd et al. 2012)

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

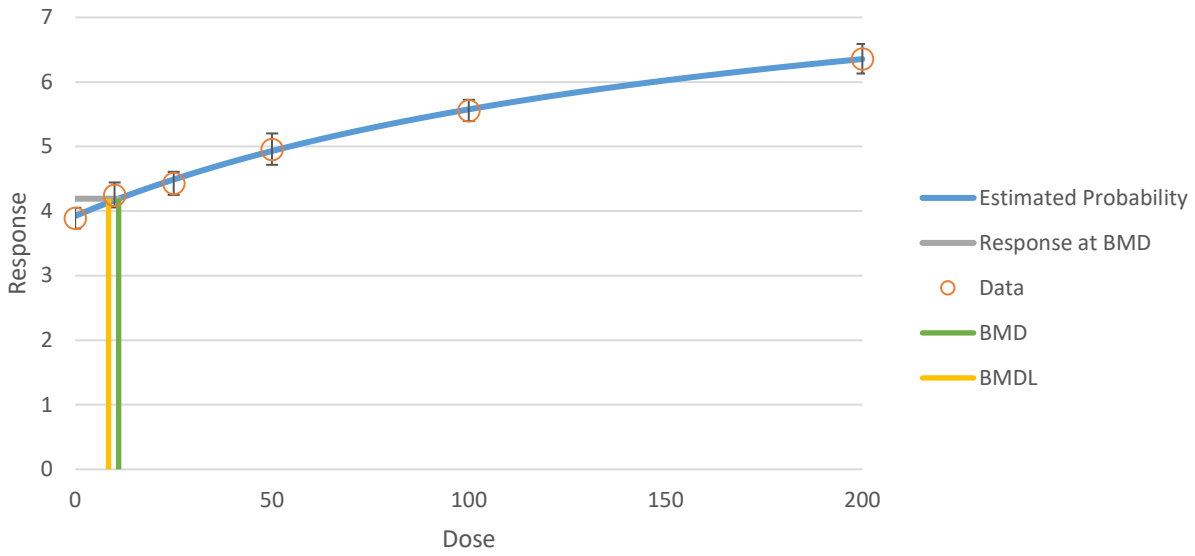


Table A-21. Model Predictions for Vacuolation (Centrilobular) in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol (Dodd et al. 2012)

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

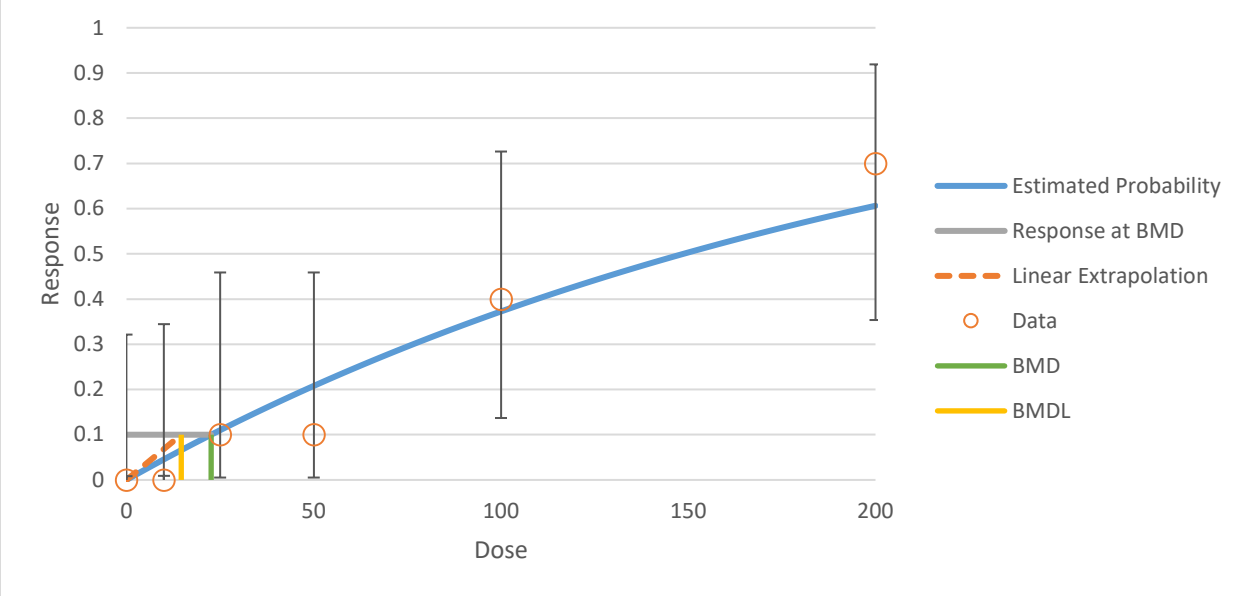


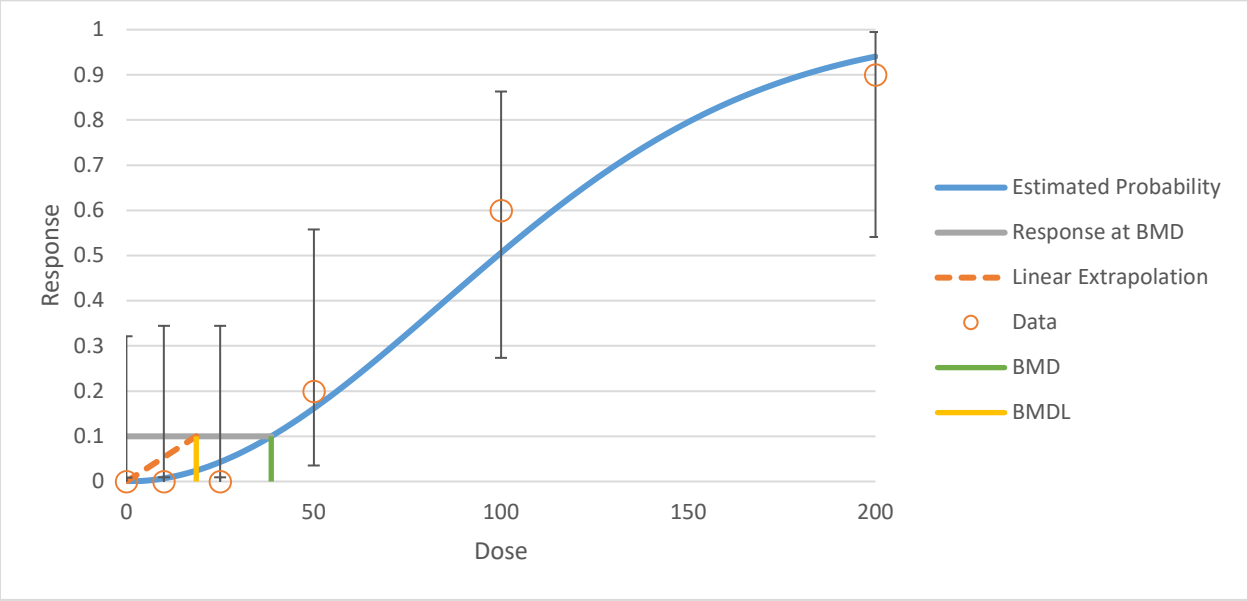
Table A-22. Model Predictions for Necrosis (Centrilobular) in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol (Dodd et al. 2012)

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

$MRL = BMDL_{1SD} \div (UF)$
$8.45 \text{ mg/kg/day} \div (10 \times 10) = 0.0845 \text{ mg/kg/day} \approx 0.08 \text{ mg/kg/day}$

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,6-Tetrachlorophenol
CAS Numbers: 58-90-2
Date: June 2022
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.01 mg/kg/day
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: An 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 $BMDL_{10}$ 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

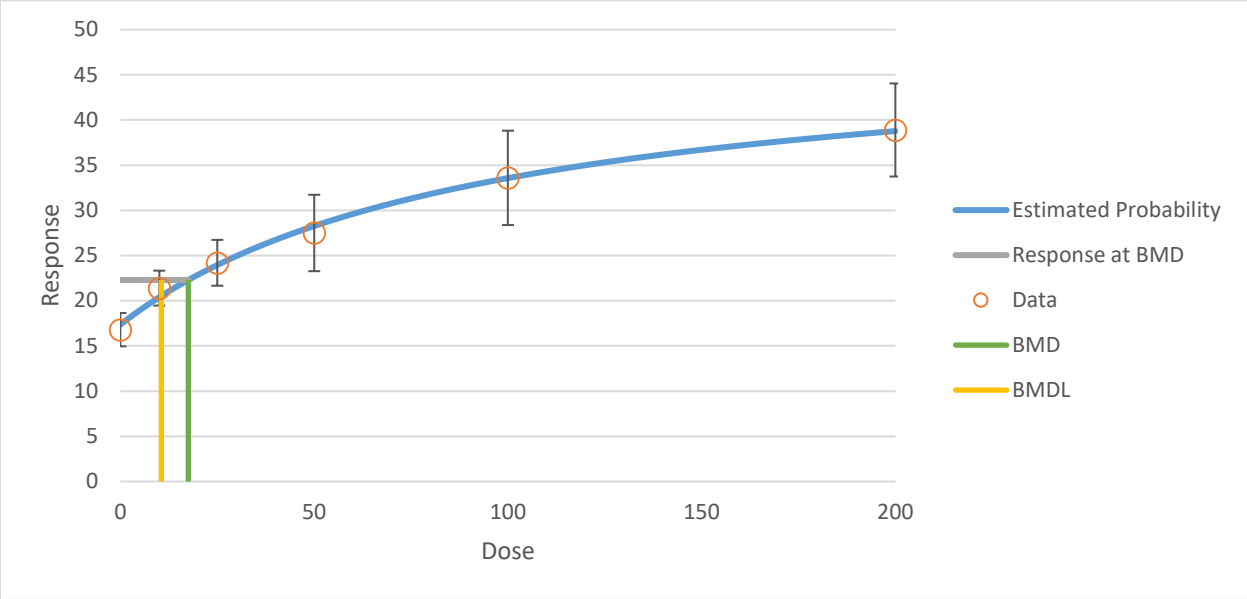


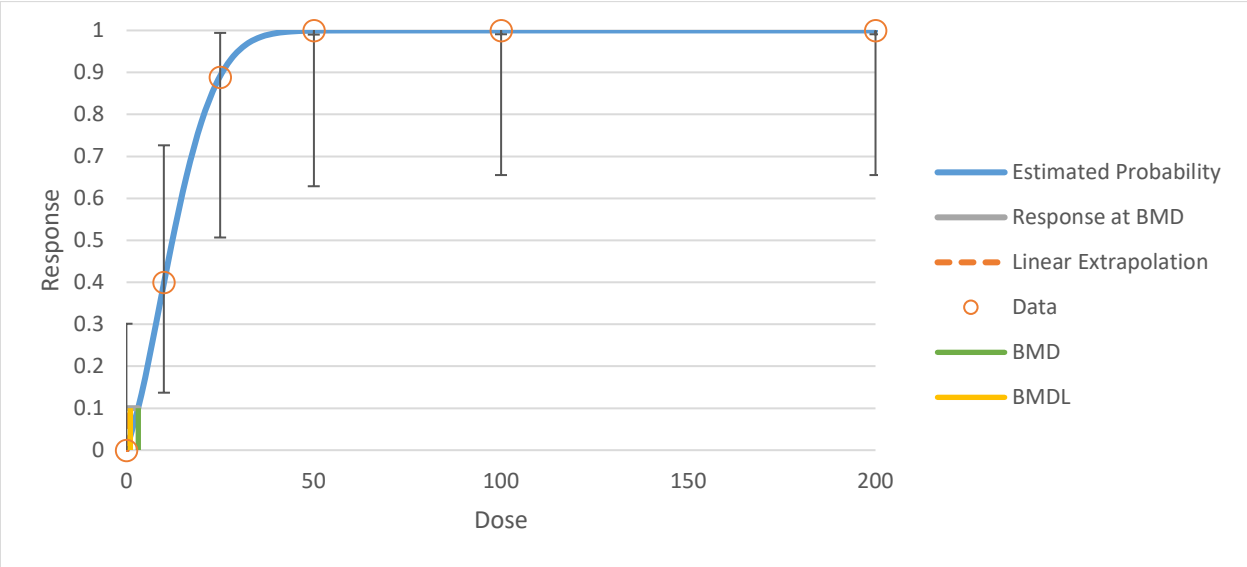
Table A-27. Model Predictions for Hypertrophy (Centrilobular and Diffuse) in Male Rats Exposed to 2,3,4,6-Tetrachlorophenol for 13 Weeks (Dodd et al. 2012)

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 $BMDL_{10}$ 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

$MRL = BMDL_{10} \div (UF)$
$1.02 \text{ mg/kg/day} \div (10 \times 10) = 0.0102 \text{ mg/kg/day} \approx 0.01 \text{ mg/kg/day}$

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,6-Tetrachlorophenol
CAS Numbers: 58-90-2
Date: June 2022
Profile Status: Final
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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,5,6-Tetrachlorophenol
CAS Numbers: 935-95-5
Date: June 2022
Profile Status: Final
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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,5,6-Tetrachlorophenol
CAS Numbers: 935-95-5
Date: June 2022
Profile Status: Final
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: June 2022
Profile Status: Final
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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,5,6-Tetrachlorophenol
CAS Numbers: 935-95-5
Date: June 2022
Profile Status: Final
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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,5,6-Tetrachlorophenol
CAS Numbers: 935-95-5
Date: June 2022
Profile Status: Final
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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,5,6-Tetrachlorophenol
CAS Numbers: 935-95-5
Date: June 2022
Profile Status: Final
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 was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 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 draft toxicological profile for chlorophenols released for public comment in 2021; thus, the literature search was restricted to studies published between January 2018 and November 2021. The following main databases were searched in November 2021:

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for 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	
11/2021	((Chlorophenols[mh:noexp] 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] 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])) AND (2018:3000[dp] OR 2019/02/01:3000[edat] OR 2019/02/01:3000[crdt] OR 2019/02/01:3000[mhda])
NTRL	
11/2021	"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-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-

Table B-2. Database Query Strings

Database search date	Query string
	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-T" OR "2,4,6-TCP" OR "2,4-DCP" OR "Applied 3-78" OR "BTS 45186" OR "Dowicide 2" OR "Dowicide 2S" OR "Dowicide 6" OR "Preventol I" OR "Septi-Kleen" OR "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-"
Toxcenter	
11/2021	FILE 'TOXCENTER' ENTERED AT 15:14:31 ON 01 NOV 2021 CHARGED TO COST=EH038.12.03.LB.04 L1 20852 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 OR 576-24-9 OR 583-78-8 OR 95-77-2 OR 591-35-5 OR 15950-66-0 L2 17979 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 17891 SEA FILE=TOXCENTER L2 NOT TSCATS/FS L4 1829 SEA FILE=TOXCENTER L3 AND ED>=20190201 DIS TOXQUERY/Q 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 598 SEA FILE=TOXCENTER L4 AND L35
	L37 47 SEA FILE=TOXCENTER L36 AND MEDLINE/FS
	L38 551 SEA FILE=TOXCENTER L36 NOT MEDLINE/FS
	L39 559 DUP REM L37 L38 (39 DUPLICATES REMOVED)

Table B-2. Database Query Strings

Database search date	Query string
	ANSWERS '1-559' FROM FILE TOXCENTER
	L*** DEL 47 S L36 AND MEDLINE/FS
	L*** DEL 47 S L36 AND MEDLINE/FS
	L40 47 SEA FILE=TOXCENTER L39
	L*** DEL 551 S L36 NOT MEDLINE/FS
	L*** DEL 551 S L36 NOT MEDLINE/FS
	L41 512 SEA FILE=TOXCENTER L39
	L42 512 SEA FILE=TOXCENTER (L40 OR L41) NOT MEDLINE/FS
	D SCAN L42

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
11/2021	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, 576-24-9, 583-78-8, 95-77-2, 591-35-5, 15950-66-0
NTP	
11/2021	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 25167-83-3 576-24-9 583-78-8 95-77-2 591-35-5 15950-66-0 chlorophenol dichlorophenol trichlorophenol tetrachlorophenol "1-Hydroxy-3,5-dichlorobenzene" "1-Hydroxy-2,5-dichlorobenzene"
Regulations.gov	
11/2021	88-06-2 120-83-2 95-95-4 95-57-8 4901-51-3 935-95-5 58-90-2

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	106-48-9 25167-80-0 25167-83-3 576-24-9 583-78-8 95-77-2 591-35-5 15950-66-0 chlorophenol dichlorophenol trichlorophenol tetrachlorophenol "1-Hydroxy-3,5-dichlorobenzene" "1-Hydroxy-2,5-dichlorobenzene"
NIH RePORTER	
01/2022	Search Criteria Fiscal Year: Active Projects 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-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-T" OR "2,4,6-TCP" OR "2,4-DCP" OR "Applied 3-78" OR "BTS 45186" OR "Dowicide 2" OR "Dowicide 2S" OR "Dowicide 6" OR "Preventol I" (advanced)Limit to: Project Title, Project Terms, Project Abstracts

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	Search Criteria Fiscal Year: Active Projects Text Search: "Septi-Kleen" OR "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)Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2021 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 930
- Number of records identified from other strategies: 44
- Total number of records to undergo literature screening: 974

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.

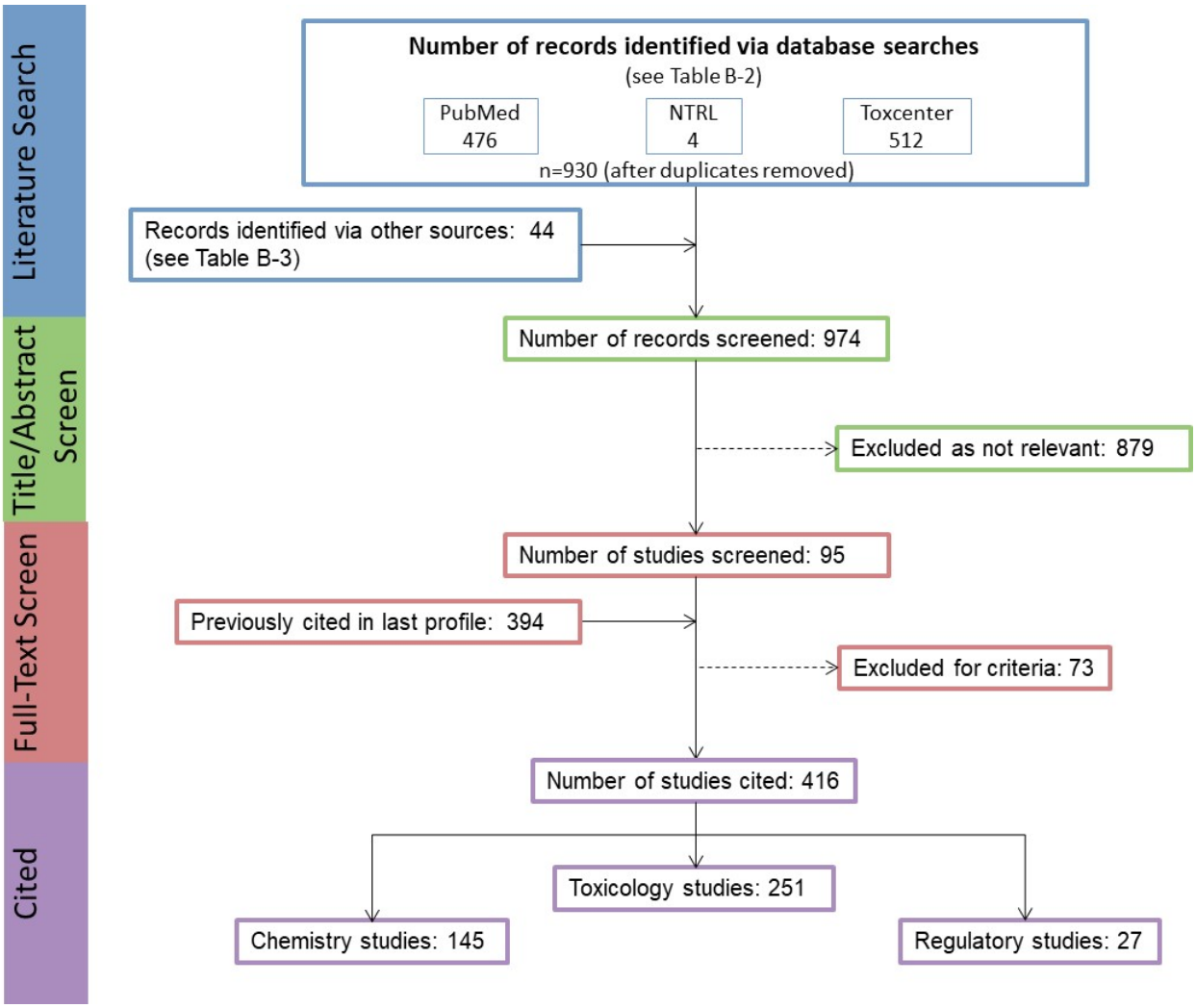
- Number of titles and abstracts screened: 974
- Number of studies considered relevant and moved to the next step: 95

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: 95
- Number of studies cited in the pre-public draft of the toxicological profile: 394
- Total number of studies cited in the profile: 416

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

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

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

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

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

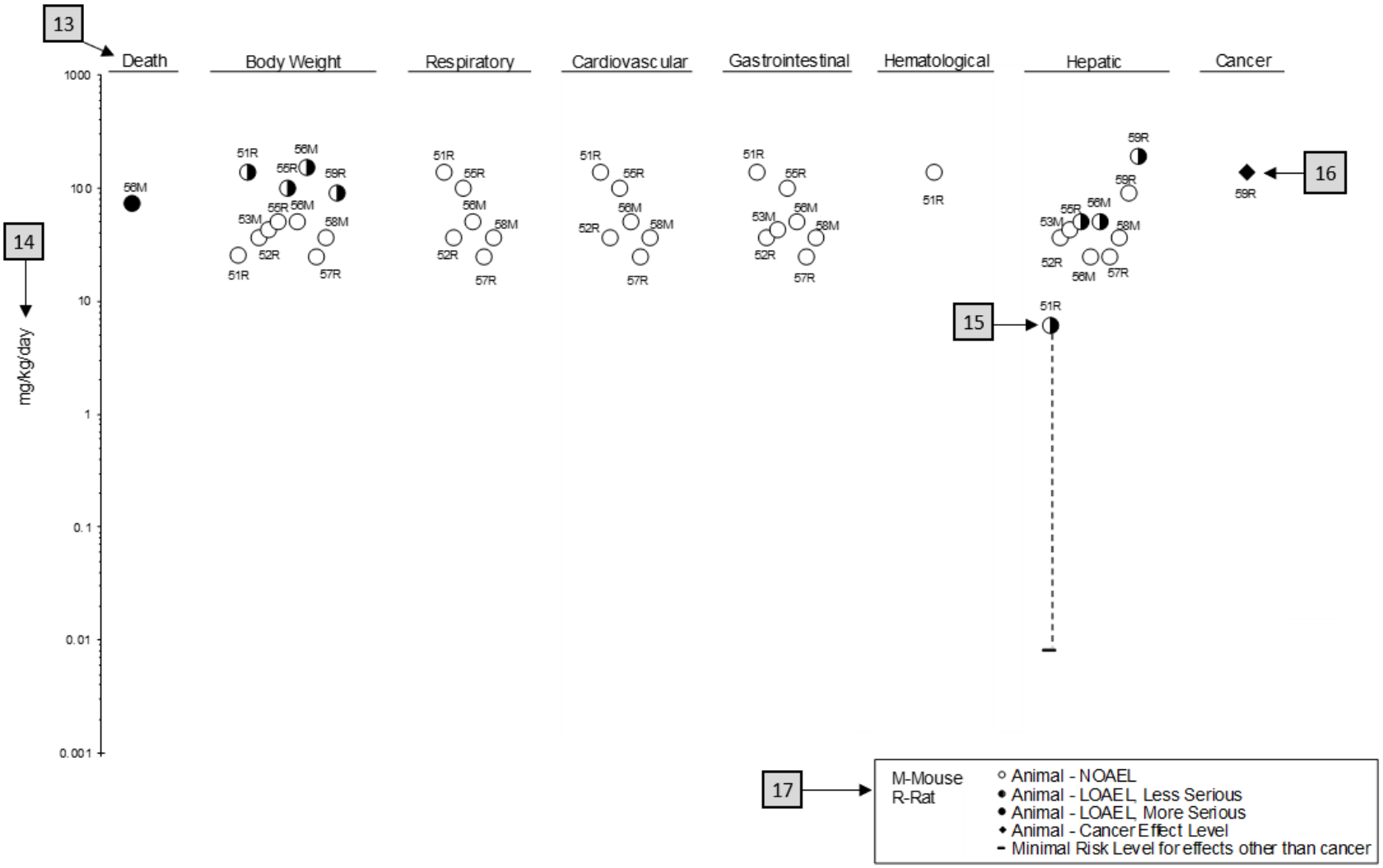
[a]The number corresponds to entries in Figure 2-x.

(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).

APPENDIX C

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

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

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

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX 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
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture

USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result