# 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.

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Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

***Agency Contacts (Chemical Managers):*** Obaid Faroon

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# MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

***Agency Contacts (Chemical Managers):*** Obaid Faroon

# MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

***Agency Contacts (Chemical Managers):*** Obaid Faroon

# MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

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

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

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

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

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

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

***Summary of the Principal Study:***

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

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

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

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

***Uncertainty Factor:***

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

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

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

***Agency Contacts (Chemical Managers):*** Obaid Faroon

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Source: Welsh et al. 1987

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

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

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

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

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

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

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

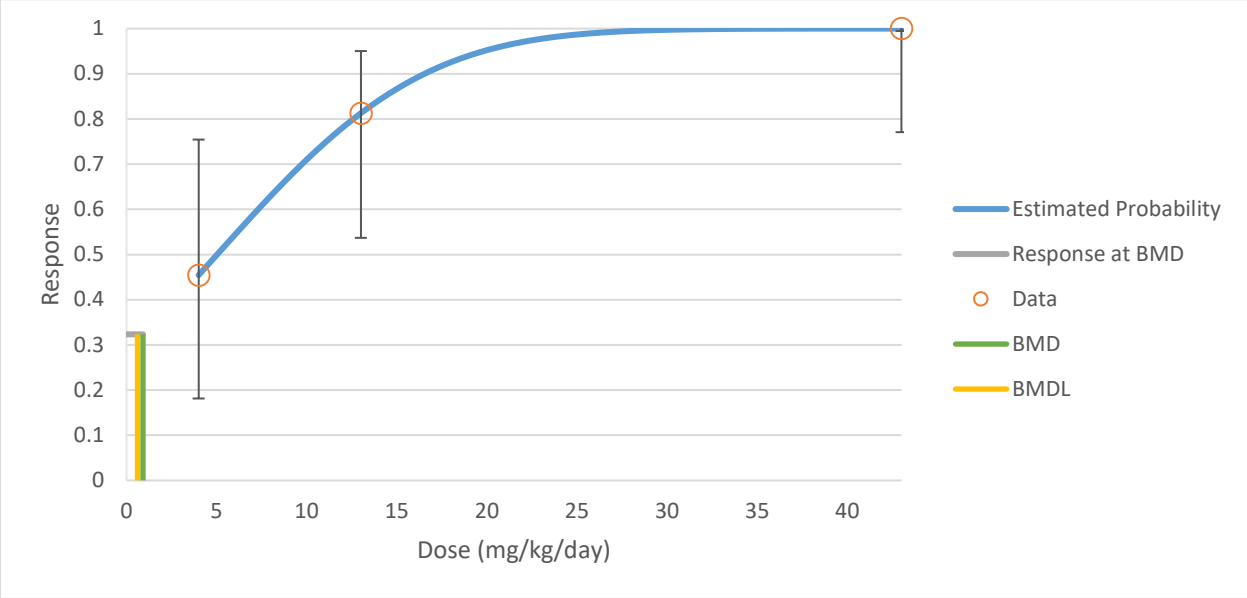


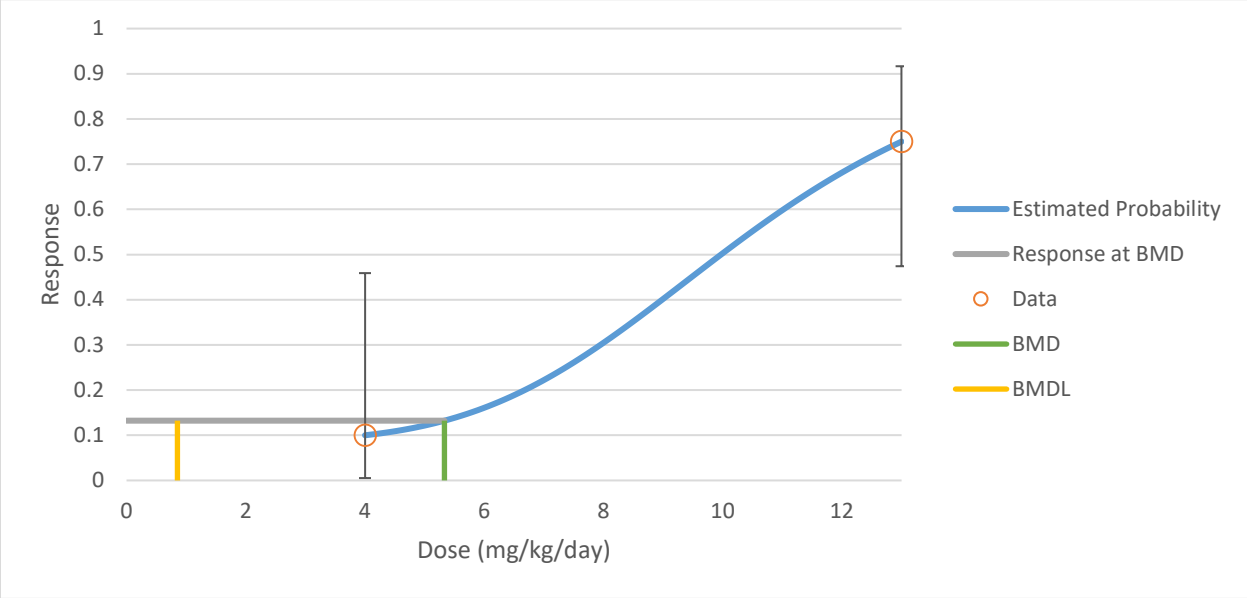

**Table A-5. Model Predictions for Litters with Two or More Skeletal Variations in the Offspring of Rats Exposed to Pure Pentachlorophenol (Welsh et al. 1987)**

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

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

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

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




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

***Agency Contacts (Chemical Managers):*** Obaid Faroon

# MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

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

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

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

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

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

***Summary of the Principal Study:***

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

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

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

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

***Uncertainty Factor:***

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

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

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

***Agency Contacts (Chemical Managers):*** Obaid Faroon

# APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR PENTACHLOROPHENOL

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

## B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for pentachlorophenol. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of pentachlorophenol have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of pentachlorophenol are presented in Table B-1.

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

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

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

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

### B.1.1 Literature Search

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

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

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

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

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

## Table B-2. Database Query Strings

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

## Table B-2. Database Query Strings

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

## Table B-2. Database Query Strings

| Database search date | Query string |
|---|---|
| | L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) |
| | L22 QUE (ENDOCRIN? AND DISRUPT?) |
| | L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) |
| | L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) |
| | L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) |
| | L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) |
| | L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) |
| | L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) |
| | L29 QUE (NEPHROTOX? OR HEPATOTOX?) |
| | L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) |
| | L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) |
| | L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 |
| | L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) |
| | L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) |
| | L35 QUE L32 OR L33 OR L34 |
| | L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) |
| | L37 QUE L35 OR L36 |
| | --- |
| | L41 503 SEA L3 AND ED>=20190101 |
| | L42 281 SEA L41 AND L37 |
| | L43 45 SEA L42 AND MEDLINE/FS |
| | L44 236 SEA L42 NOT MEDLINE/FS |
| | L45 234 DUP REM L43 L44 (47 DUPLICATES REMOVED) ANSWERS '1-234' FROM FILE TOXCENTER |
| | L*** DEL 45 S L42 AND MEDLINE/FS |
| | L*** DEL 45 S L42 AND MEDLINE/FS |
| | L46 45 SEA L45 |
| | L*** DEL 236 S L42 NOT MEDLINE/FS |
| | L*** DEL 236 S L42 NOT MEDLINE/FS |
| | L47 189 SEA L45 |
| | L48 189 SEA (L46 OR L47) NOT MEDLINE/FS |
| | D SCAN L48 |

## Table B-3. Strategies to Augment the Literature Search

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

**Table B-3. Strategies to Augment the Literature Search**

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

The 2021 results were:

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

### B.1.2 Literature Screening

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

- Title and abstract screen
- Full text screen

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

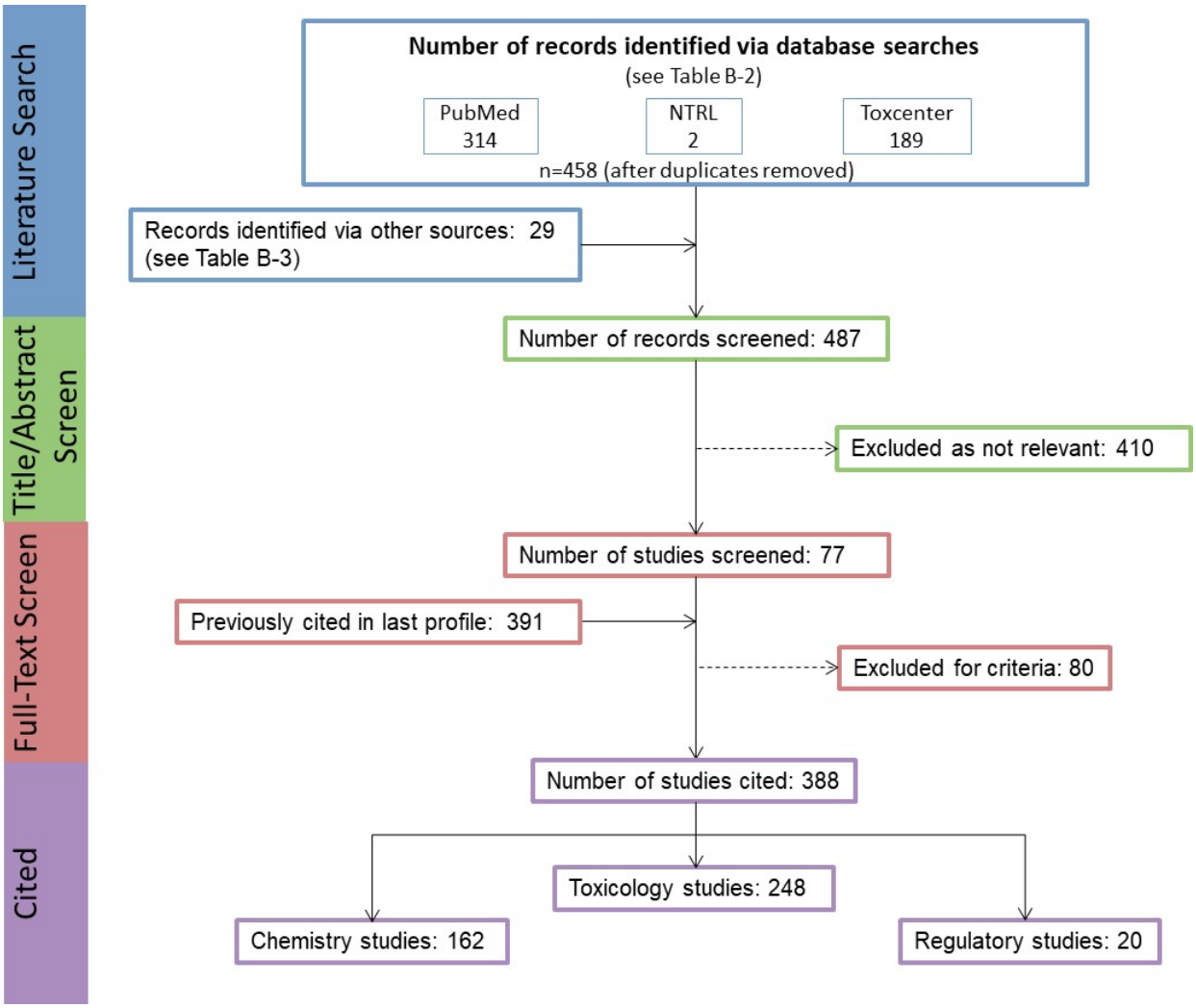
- Number of titles and abstracts screened: 487
- Number of studies considered relevant and moved to the next step: 77

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

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

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

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



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

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

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

## C.1 PROBLEM FORMULATION

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

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

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

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

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

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

## C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

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

### C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the draft toxicological profile for pentachlorophenol released for public comment in 2021. See Appendix B for the databases searched and the search strategy.

A total of 3,182 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

### C.2.2 Literature Screening

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

***Title and Abstract Screen.*** In the Title and Abstract Screen step, 487 records were reviewed; 4 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

***Full Text Screen.*** In the second step in the literature screening process for the systematic review, a full text review of 89 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 89 documents, 117 studies were included in the qualitative review.

## C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

**Table C-2. Data Extracted From Individual Studies**

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

A summary of the extracted data for each study is presented in the Supplemental Document for pentachlorophenol and overviews of the results of the oral exposure studies (no inhalation or dermal exposure laboratory animal studies were identified) are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures table in Section 2.1 of the profile (**Error! Reference source not found.**).

## C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

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

Some of these findings were attributed to the contaminants present in technical-grade pentachlorophenol. Of the consistently observed effects attributed to pentachlorophenol, hepatic and developmental effects were considered sensitive outcomes (i.e., effects were observed at low concentrations or doses). Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. There were 117 studies (published in 89 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

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

| | Body weight | Respiratory | Cardiovascular | Gastrointestinal | Hematological | Musculoskeletal | Hepatic | Renal | Dermal | Ocular | Endocrine | Immunological | Neurological | Reproductive | Developmental | Other Noncancer | Caner |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inhalation studies | | | | | | | | | | | | | | | | | |
| Cohort | 1 | 3 | 0 | 0 | 1 | 0 | 4 | 0 | 5 | 1 | 0 | 2 | 3 | 0 | 0 | 1 | 4 |
| | 1 | 3 | 0 | 0 | 1 | 0 | 4 | 0 | 5 | 1 | 0 | 2 | 2 | 0 | 0 | 1 | 4 |
| Case control | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 8 |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 6 |
| Cross sectional | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 2 | 1 | 2 | 0 | 0 | 0 |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 2 | 1 | 1 | 0 | 0 | 0 |
| Case report | 0 | 0 | 0 | 0 | 5 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| | 0 | 0 | 0 | 0 | 5 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Oral studies | | | | | | | | | | | | | | | | | |
| Cohort | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Case control | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Case report | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Dermal studies | | | | | | | | | | | | | | | | | |
| Cohort | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Case report | 0 | 1 | 0 | 0 | 0 | 0 | 4 | 4 | 2 | 0 | 0 | 1 | 3 | 0 | 0 | 0 | 0 |
| | 0 | 1 | 0 | 0 | 0 | 0 | 4 | 4 | 2 | 0 | 0 | 1 | 3 | 0 | 0 | 0 | 0 |

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

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

| | Body weight | Respiratory | Cardiovascular | Gastrointestinal | Hematological | Musculoskeletal | Hepatic | Renal | Dermal | Ocular | Endocrine | Immunological[a] | Neurological[a] | Reproductive[a] | Developmental | Other Noncancer | Caner |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inhalation studies | | | | | | | | | | | | | | | | | |
| Acute-duration | | | | | | | | | | | | | | | | | |
| Intermediate-duration | | | | | | | | | | | | | | | | | |
| Chronic-duration | | | | | | | | | | | | | | | | | |
| Acute-duration | 9 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 8 | 0 | 0 |
| | 6 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 7 | 0 | 0 |
| Intermediate-duration | 16 | 8 | 8 | 7 | 6 | 5 | 15 | 9 | 0 | 0 | 9 | 10 | 2 | 6 | 4 | 3 | 4 |
| | 8 | 1 | 0 | 0 | 1 | 0 | 15 | 1 | 0 | 0 | 0 | 7 | 0 | 2 | 4 | 3 | 4 |
| Chronic-duration | 7 | 5 | 5 | 5 | 3 | 4 | 6 | 6 | 0 | 1 | 6 | 0 | 1 | 2 | 0 | 2 | 5 |
| | 6 | 1 | 0 | 1 | 2 | 0 | 6 | 1 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 2 | 3 |
| Dermal studies | | | | | | | | | | | | | | | | | |
| Acute-duration | | | | | | | | | | | | | | | | | |
| Intermediate-duration | | | | | | | | | | | | | | | | | 1 |
| | | | | | | | | | | | | | | | | | 1 |
| Chronic-duration | | | | | | | | | | | | | | | | | |

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

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

## C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

### C.5.1 Risk of Bias Assessment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

*Key question used to assign risk of bias tier

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

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

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

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

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

| Reference | Risk of bias criteria and ratings: Selection bias: Administered dose or exposure level adequately randomized? | Selection bias: Allocation to study groups adequately concealed? | Performance bias: Experimental conditions identical across study groups? | Performance bias: Research personnel blinded to the study group during the study? | Attrition/ exclusion bias: Outcome data complete without attrition or exclusion from analysis? | Detection bias: Confidence in the exposure characterization? | Detection bias: **Confidence in the outcome assessment?*** | Selective reporting bias: All measured outcomes reported? | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|
| Schwetz et al. 1974 (technical, GDs 8–11) | – | + | + | + | + | + | + | + | First |
| Schwetz et al. 1974 (technical, GDs 12–15) | – | + | + | + | + | + | + | + | First |
| Bernard et al. 2001 | ++ | + | + | + | + | ++ | + | ++ | First |
| *Oral intermediate exposure* | | | | | | | | | |
| Bernard et al. 2002 | ++ | + | + | + | + | ++ | + | ++ | First |
| Exon and Koller 1982 | – | + | + | + | + | – – | + | ++ | First |
| Schwetz et al. 1978 | + | + | + | + | + | ++ | + | ++ | First |
| Welsh et al. 1987 | – | + | + | + | + | ++ | + | ++ | First |

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable
*Key question used to assign risk of bias tier

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

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

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

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

### C.6.1 Initial Confidence Rating

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

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

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

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

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

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

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

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

The presence or absence of the key features and the initial confidence levels for studies examining hepatic effects and developmental effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-13 and C-14, respectively.

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

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

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

| Reference | Key feature | | | | |
|---|---|---|---|---|---|
| | Concurrent control group | Sufficient number of animals per group | Appropriate parameters to assess potential effect | Adequate data for statistical analysis | Initial study confidence |
| ***Outcome: Hepatic Effects*** | | | | | |
| *Oral acute exposure* | | | | | |
| Umemura et al. 1996 | Yes | Yes | Yes | No | Moderate |
| Bekhouche et al. 2019 | Yes | Yes | Yes | No | Moderate |
| *Oral intermediate exposure* | | | | | |
| Bernard et al. 2002 | Yes | Yes | Yes | Yes | High |
| Kerkvliet et al. 1982 (technical) | Yes | Yes | Yes | Yes | High |
| Kerkvliet et al. 1982 (pure) | Yes | Yes | Yes | Yes | High |
| Kimbrough and Linder 1978 (technical) | Yes | Yes | Yes | Yes | High |
| Kimbrough and Linder 1978 (pure) | Yes | Yes | Yes | Yes | High |
| Knudsen et al. 1974 | Yes | Yes | Yes | Yes | High |
| NTP 1989 (technical, 30 days) | Yes | Yes | Yes | No | Moderate |
| NTP 1989 (EC-7, 30 days) | Yes | Yes | Yes | No | Moderate |
| NTP 1989 (pure, 30 days) | Yes | Yes | Yes | No | Moderate |
| NTP 1989 (technical, 6 months) | Yes | Yes | Yes | Yes | High |
| NTP 1989 (EC-7, 6 months) | Yes | Yes | Yes | Yes | High |
| NTP 1989 (DP-2, 6 months) | Yes | Yes | Yes | Yes | High |
| NTP 1989 (pure, 6 months) | Yes | Yes | Yes | Yes | High |
| NTP 1999 | Yes | Yes | Yes | Yes | High |
| Umemura et al. 1996 | Yes | Yes | Yes | No | Moderate |
| Umemura et al. 2006 | Yes | Yes | No | Yes | Moderate |
| *Oral chronic exposure* | | | | | |
| EPA 1997 | Yes | Yes | Yes | Yes | High |
| NTP 1999 (2 years) | Yes | Yes | Yes | Yes | High |
| NTP 1999 (1 year) | Yes | Yes | Yes | Yes | High |
| Schwetz et al. 1978 | Yes | Yes | Yes | Yes | High |
| NTP 1989 (technical) | Yes | Yes | Yes | Yes | High |

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

| Reference | Key feature: Concurrent control group | Key feature: Sufficient number of animals per group | Key feature: Appropriate parameters to assess potential effect | Key feature: Adequate data for statistical analysis | Initial study confidence |
|---|---|---|---|---|---|
| NTP 1989 (pure) | Yes | Yes | Yes | Yes | High |
| ***Outcome: Developmental Effects*** | | | | | |
| *Oral acute studies* | | | | | |
| Bernard and Hoberman 2001 | Yes | Yes | Yes | Yes | High |
| Schwetz et al. 1974 (pure, GDs 6–15) | Yes | Yes | Yes | Yes | High |
| Schwetz et al. 1974 (pure, GDs 8–11) | Yes | Yes | Yes | Yes | High |
| Schwetz et al. 1974 (technical, GDs 12–15) | Yes | Yes | Yes | Yes | High |
| Schwetz et al. 1974 (technical, GDs 6–15) | Yes | Yes | Yes | Yes | High |
| Schwetz et al. 1974 (technical, GDs 8–11) | Yes | Yes | Yes | Yes | High |
| Schwetz et al. 1974 (technical, GDs 12–15) | Yes | Yes | Yes | Yes | High |
| Bernard et al. 2001 | Yes | Yes | Yes | Yes | High |
| *Oral intermediate exposure* | | | | | |
| Bernard et al. 2002 | Yes | Yes | Yes | Yes | High |
| Exon and Koller 1982 | Yes | Yes | Yes | Yes | High |
| Schwetz et al. 1978 | Yes | Yes | Yes | Yes | High |
| Welsh et al. 1987 | Yes | Yes | Yes | Yes | High |

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

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

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

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

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

## C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for hepatic effects and developmental effects are presented in Table C-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with pentachlorophenol exposure is presented in Table C-17.

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

| | Initial confidence | Adjustments to the initial confidence rating | Final confidence |
|---|---|---|---|
| **Outcome: Hepatic effects** | | | |
| Human studies | Low | -1 risk of bias | Very Low |
| Animal studies | High | | High |
| **Outcome: Developmental effects** | | | |
| Human studies | Moderate | -1 risk of bias, -1 inconsistency | Very Low |
| Animal studies | High | +1 consistency | High |

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

| | Confidence in body of evidence | |
|---|---|---|
| Outcome | Human studies | Animal studies |
| Hepatic effects | Very Low | High |
| Developmental effects | Very Low | High |

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

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

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

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

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

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

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

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

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

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

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

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

- Upgrade one confidence level if there is a high degree of consistency in the database

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

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

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

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

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

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

## C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

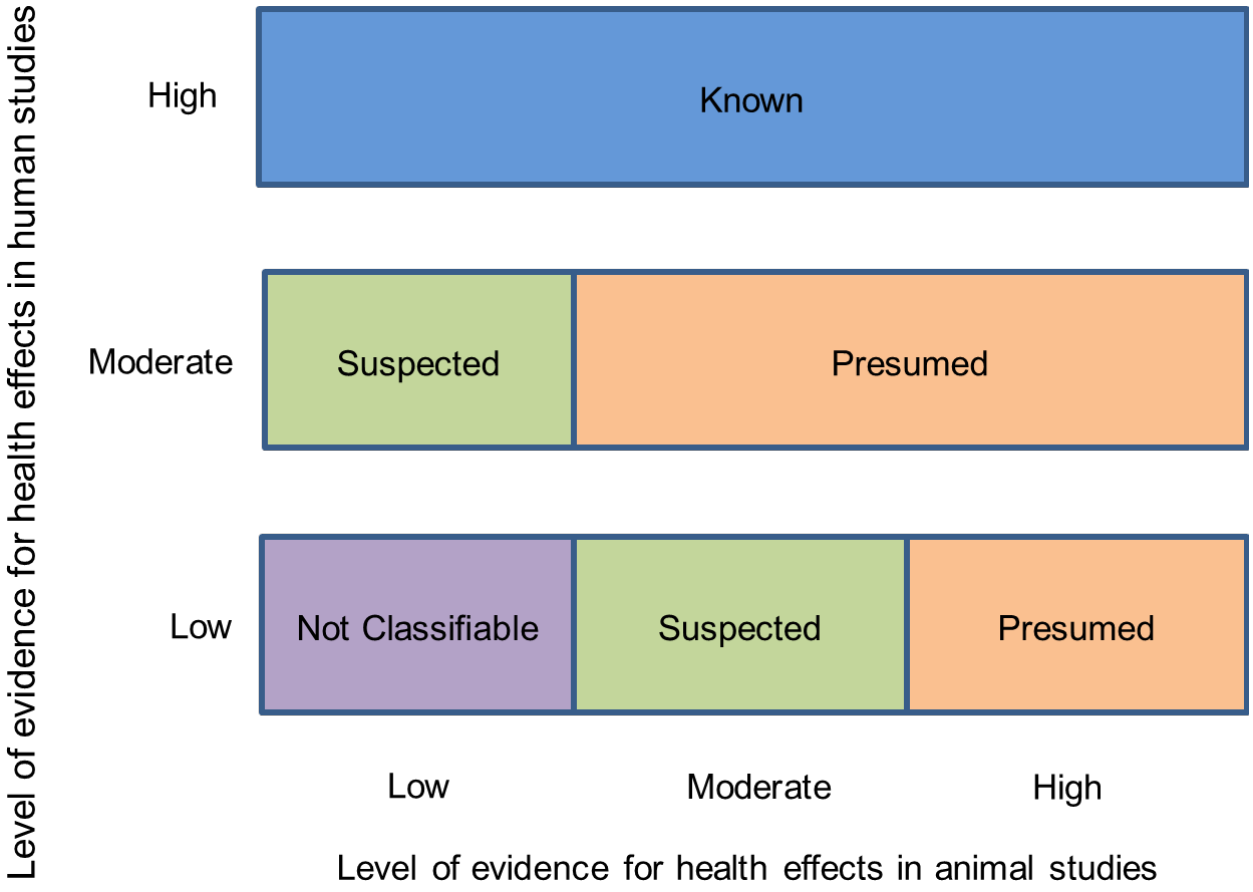
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

**Figure C-1. Hazard Identification Scheme**



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for pentachlorophenol are listed below and summarized in Table C-19.

**Presumed Health Effects**

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

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

## Table C-19. Hazard Identification Conclusions for Pentachlorophenol

| Outcome | Hazard identification |
|---|---|
| Hepatic effects | Presumed health effect |
| Developmental effects | Presumed health effect |

# APPENDIX D. USER'S GUIDE

## Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

### Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

**Chapter 2. Health Effects**

**Tables and Figures for Levels of Significant Exposure (LSE)**

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

**TABLE LEGEND**

**See Sample LSE Table (page D-5)**

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

**FIGURE LEGEND**

**See Sample LSE Figure (page D-6)**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

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

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

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

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

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

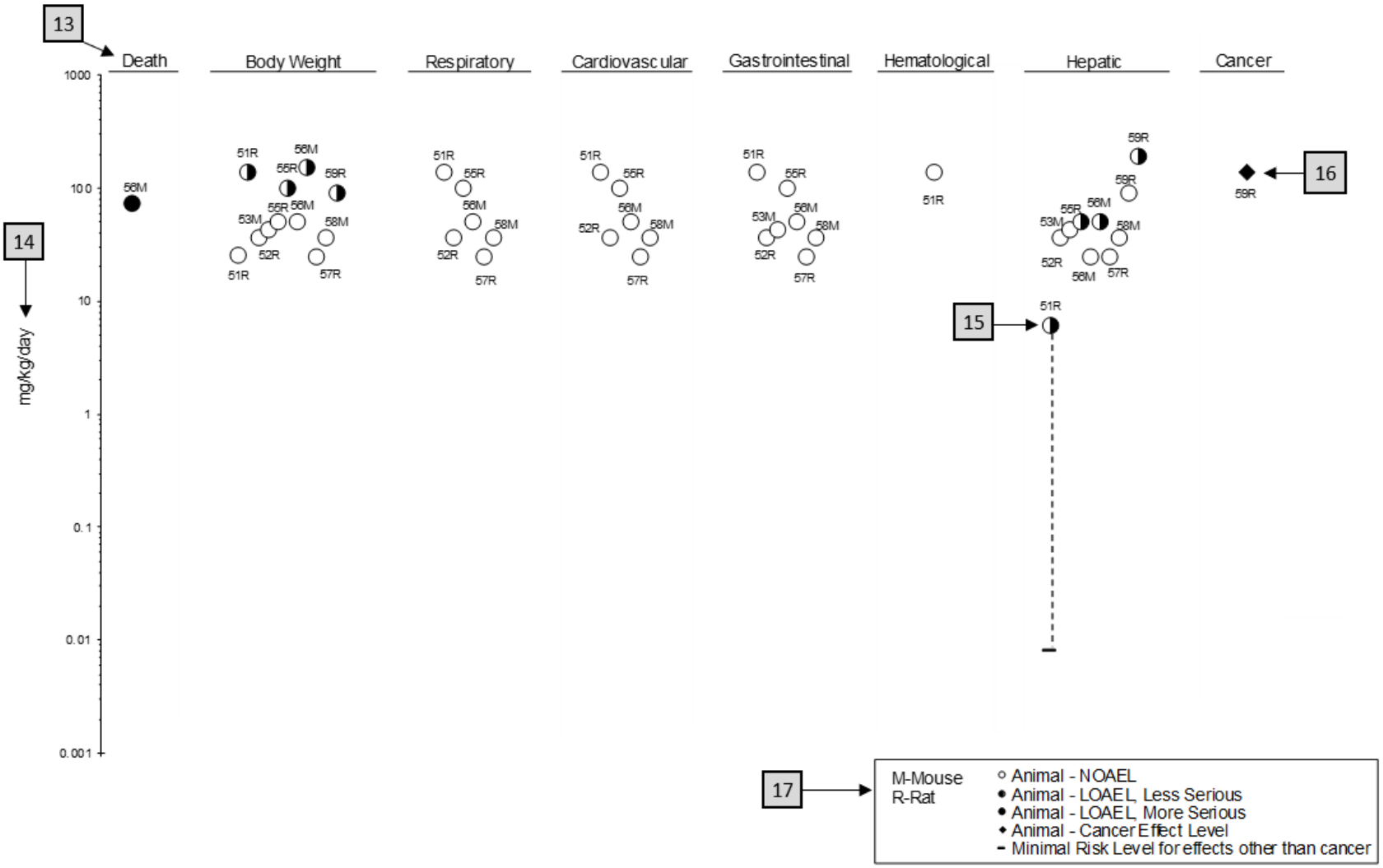
(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effect |
|---|---|---|---|---|---|---|---|---|---|
| **CHRONIC EXPOSURE** | | | | | | | | | |
| 51 | Rat (Wistar) 40 M, 40 F | 2 years (F) | M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4 | CS, WI, BW, OW, HE, BC, HP | Bd wt | 25.5 | 138.0 | | Decreased body weight gain in males (23–25%) and females (31–39%) |
| | | | | | Hemato | 138.0 | | | |
| | | | | | Hepatic | | 6.1[c] | | Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure |
| **Aida et al. 1992** | | | | | | | | | |
| 52 | Rat (F344) 78 M | 104 weeks (W) | 0, 3.9, 20.6, 36.3 | CS, BW, FI, BC, OW, HP | Hepatic | 36.3 | | | |
| | | | | | Renal | 20.6 | 36.3 | | Increased incidence of renal tubular cell hyperplasia |
| | | | | | Endocr | 36.3 | | | |
| **George et al. 2002** | | | | | | | | | |
| 59 | Rat (Wistar) 58M, 58F | Lifetime (W) | M: 0, 90 F: 0, 190 | BW, HP | Cancer | | 190 F | | Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided |
| **Tumasonis et al. 1985** | | | | | | | | | |

[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

**Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral**



# APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

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***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**

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***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).

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***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/.

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***Clinical Resources (Publicly Available Information)***

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

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

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

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

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

# APPENDIX F. GLOSSARY

**Absorption—**The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

**Acute Exposure—**Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

**Adsorption—**The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

**Adsorption Coefficient ($K_{oc}$)—**The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

**Adsorption Ratio (Kd)—**The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

**Benchmark Dose (BMD) or Benchmark Concentration (BMC)—**is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a $BMD_{10}$ would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

**Bioconcentration Factor (BCF)—**The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

**Biomarkers—**Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

**Cancer Effect Level (CEL)—**The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

**Carcinogen—**A chemical capable of inducing cancer.

**Case-Control Study—**A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

**Case Report—**A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

**Case Series—**Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

**Ceiling Value—**A concentration that must not be exceeded.

**Chronic Exposure—**Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

**Clastogen—**A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

**Cohort Study—**A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

**Cross-sectional Study—**A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

**Data Needs—**Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

**Developmental Toxicity—**The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

**Dose-Response Relationship—**The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

**Embryotoxicity and Fetotoxicity—**Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

**Epidemiology—**The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

**Excretion—**The process by which metabolic waste products are removed from the body.

**Genotoxicity—**A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

**Half-life—**A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

**Health Advisory—**An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

**Immediately Dangerous to Life or Health (IDLH)—**A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

**Immunotoxicity—**Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

**Incidence—**The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

**Intermediate Exposure—**Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

**Lethal Concentration$_{(LO)}$ ($LC_{LO}$)—**The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

**Lethal Concentration$_{(50)}$ ($LC_{50}$)—**A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose$_{(LO)}$ ($LD_{Lo}$)—**The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

**Lethal Dose$_{(50)}$ ($LD_{50}$)—**The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time$_{(50)}$ ($LT_{50}$)—**A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

**Lowest-Observed-Adverse-Effect Level (LOAEL)—**The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

**Lymphoreticular Effects—**Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

**Malformations—**Permanent structural changes that may adversely affect survival, development, or function.

**Metabolism—**Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

**Minimal Risk Level (MRL)—**An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

**Modifying Factor (MF)—**A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

**Morbidity—**The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

**Mortality—**Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

**Mutagen—**A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

**Necropsy—**The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

**Neurotoxicity—**The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

**No-Observed-Adverse-Effect Level (NOAEL)—**The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

**Octanol-Water Partition Coefficient ($K_{ow}$)—**The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

**Odds Ratio (OR)—**A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

**Permissible Exposure Limit (PEL)—**An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

**Pesticide—**General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

**Pharmacokinetics—**The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

**Pharmacokinetic Model—**A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

**Physiologically Based Pharmacodynamic (PBPD) Model—**A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

**Physiologically Based Pharmacokinetic (PBPK) Model—**A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

**Prevalence—**The number of cases of a disease or condition in a population at one point in time.

**Prospective Study—**A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

**Recommended Exposure Limit (REL)—**A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

**Reference Concentration (RfC)—**An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of $mg/m^3$ or ppm.

**Reference Dose (RfD)—**An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

**Reportable Quantity (RQ)—**The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

**Reproductive Toxicity—**The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

**Retrospective Study—**A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

**Risk—**The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

**Risk Factor—**An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

**Risk Ratio/Relative Risk—**The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

**Short-Term Exposure Limit (STEL)—**A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

**Standardized Mortality Ratio (SMR)—**A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

**Target Organ Toxicity—**This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

**Teratogen—**A chemical that causes structural defects that affect the development of an organism.

**Threshold Limit Value (TLV)—**An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

**Time-Weighted Average (TWA)—**An average exposure within a given time period.

**Toxicokinetic—**The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

**Toxics Release Inventory (TRI)—**The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

**Uncertainty Factor (UF)—**A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

**Xenobiotic—**Any substance that is foreign to the biological system.

# APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

| | |
|---|---|
| AAPCC | American Association of Poison Control Centers |
| ACGIH | American Conference of Governmental Industrial Hygienists |
| ACOEM | American College of Occupational and Environmental Medicine |
| ACMT | American College of Medical Toxicology |
| ADI | acceptable daily intake |
| ADME | absorption, distribution, metabolism, and excretion |
| AEGL | Acute Exposure Guideline Level |
| AIC | Akaike's information criterion |
| AIHA | American Industrial Hygiene Association |
| ALT | alanine aminotransferase |
| AOEC | Association of Occupational and Environmental Clinics |
| AP | alkaline phosphatase |
| AST | aspartate aminotransferase |
| atm | atmosphere |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| AWQC | Ambient Water Quality Criteria |
| BCF | bioconcentration factor |
| BMD/C | benchmark dose or benchmark concentration |
| $BMD_X$ | dose that produces a X% change in response rate of an adverse effect |
| $BMDL_X$ | 95% lower confidence limit on the $BMD_X$ |
| BMDS | Benchmark Dose Software |
| BMR | benchmark response |
| BUN | blood urea nitrogen |
| C | centigrade |
| CAA | Clean Air Act |
| CAS | Chemical Abstract Services |
| CDC | Centers for Disease Control and Prevention |
| CEL | cancer effect level |
| CERCLA | Comprehensive Environmental Response, Compensation, and Liability Act |
| CFR | Code of Federal Regulations |
| Ci | curie |
| CI | confidence interval |
| cm | centimeter |
| CPSC | Consumer Products Safety Commission |
| CWA | Clean Water Act |
| DNA | deoxyribonucleic acid |
| DOD | Department of Defense |
| DOE | Department of Energy |
| DWEL | drinking water exposure level |
| EAFUS | Everything Added to Food in the United States |
| ECG/EKG | electrocardiogram |
| EEG | electroencephalogram |
| EPA | Environmental Protection Agency |
| ERPG | emergency response planning guidelines |
| F | Fahrenheit |
| F1 | first-filial generation |
| FDA | Food and Drug Administration |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| FR | Federal Register |

| | |
|---|---|
| FSH | follicle stimulating hormone |
| g | gram |
| GC | gas chromatography |
| gd | gestational day |
| GGT | γ-glutamyl transferase |
| GRAS | generally recognized as safe |
| HEC | human equivalent concentration |
| HED | human equivalent dose |
| HHS | Department of Health and Human Services |
| HPLC | high-performance liquid chromatography |
| HSDB | Hazardous Substance Data Bank |
| IARC | International Agency for Research on Cancer |
| IDLH | immediately dangerous to life and health |
| IRIS | Integrated Risk Information System |
| Kd | adsorption ratio |
| kg | kilogram |
| kkg | kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton |
| $K_{oc}$ | organic carbon partition coefficient |
| $K_{ow}$ | octanol-water partition coefficient |
| L | liter |
| LC | liquid chromatography |
| $LC_{50}$ | lethal concentration, 50% kill |
| $LC_{Lo}$ | lethal concentration, low |
| $LD_{50}$ | lethal dose, 50% kill |
| $LD_{Lo}$ | lethal dose, low |
| LDH | lactic dehydrogenase |
| LH | luteinizing hormone |
| LOAEL | lowest-observed-adverse-effect level |
| LSE | Level of Significant Exposure |
| $LT_{50}$ | lethal time, 50% kill |
| m | meter |
| mCi | millicurie |
| MCL | maximum contaminant level |
| MCLG | maximum contaminant level goal |
| MF | modifying factor |
| mg | milligram |
| mL | milliliter |
| mm | millimeter |
| mmHg | millimeters of mercury |
| mmol | millimole |
| MRL | Minimal Risk Level |
| MS | mass spectrometry |
| MSHA | Mine Safety and Health Administration |
| Mt | metric ton |
| NAAQS | National Ambient Air Quality Standard |
| NAS | National Academy of Science |
| NCEH | National Center for Environmental Health |
| ND | not detected |
| ng | nanogram |
| NHANES | National Health and Nutrition Examination Survey |
| NIEHS | National Institute of Environmental Health Sciences |

| | |
|---|---|
| NIOSH | National Institute for Occupational Safety and Health |
| NLM | National Library of Medicine |
| nm | nanometer |
| nmol | nanomole |
| NOAEL | no-observed-adverse-effect level |
| NPL | National Priorities List |
| NR | not reported |
| NRC | National Research Council |
| NS | not specified |
| NTP | National Toxicology Program |
| OR | odds ratio |
| OSHA | Occupational Safety and Health Administration |
| PAC | Protective Action Criteria |
| PAH | polycyclic aromatic hydrocarbon |
| PBPD | physiologically based pharmacodynamic |
| PBPK | physiologically based pharmacokinetic |
| PEHSU | Pediatric Environmental Health Specialty Unit |
| PEL | permissible exposure limit |
| PEL-C | permissible exposure limit-ceiling value |
| pg | picogram |
| PND | postnatal day |
| POD | point of departure |
| ppb | parts per billion |
| ppbv | parts per billion by volume |
| ppm | parts per million |
| ppt | parts per trillion |
| REL | recommended exposure level/limit |
| REL-C | recommended exposure level-ceiling value |
| RfC | reference concentration |
| RfD | reference dose |
| RNA | ribonucleic acid |
| SARA | Superfund Amendments and Reauthorization Act |
| SCE | sister chromatid exchange |
| SD | standard deviation |
| SE | standard error |
| SGOT | serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST) |
| SGPT | serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT) |
| SIC | standard industrial classification |
| SLOAEL | serious lowest-observed-adverse-effect level |
| SMR | standardized mortality ratio |
| sRBC | sheep red blood cell |
| STEL | short term exposure limit |
| TLV | threshold limit value |
| TLV-C | threshold limit value-ceiling value |
| TRI | Toxics Release Inventory |
| TSCA | Toxic Substances Control Act |
| TWA | time-weighted average |
| UF | uncertainty factor |
| U.S. | United States |
| USDA | United States Department of Agriculture |
| USGS | United States Geological Survey |

| | |
|---|---|
| USNRC | U.S. Nuclear Regulatory Commission |
| VOC | volatile organic compound |
| WBC | white blood cell |
| WHO | World Health Organization |

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