

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PENTACHLOROPHENOL IN THE UNITED STATES

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

Humans may be exposed to pentachlorophenol in occupational settings through inhalation of contaminated workplace air and dermal contact with the compound or with wood products treated with the compound. General population exposure may occur through contact with contaminated environmental media, particularly in the vicinity of wood treatment facilities and hazardous waste sites. Important routes of exposure appear to be inhalation of contaminated air, inhalation exposure to pentachlorophenol that has volatilized from treated wood surfaces, ingestion of contaminated groundwater used as a source of drinking water, ingestion of contaminated food, and dermal contact with contaminated soils or wood products treated with the compound. Children are likely to be exposed to pentachlorophenol by the same routes as adults. In addition, small children are generally more likely than adults to have significant contact with soil and have less concern with hygiene than adults. ATSDR believes that the primary route of human exposure to pentachlorophenol at hazardous waste sites is ingestion of contaminated media, and to a lesser extent, inhalation and dermal contact with contaminated media. Pentachlorophenol has been identified in at least 313 of the 1,585 hazardous waste sites that have

2. RELEVANCE TO PUBLIC HEALTH

been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of sites evaluated for pentachlorophenol is not known.

2.2 SUMMARY OF HEALTH EFFECTS

Adverse health effects have been observed in humans and experimental animals following short- and long-term exposure to pentachlorophenol by the inhalation, oral, and dermal exposure routes. Reports of inhalation and/or dermal exposure in humans and oral exposure studies in animals make up the bulk of the available toxicity data. The liver, thyroid, immune system, reproductive system, and the developing organism are the primary targets of pentachlorophenol toxicity. Case reports of individuals acutely exposed to pentachlorophenol via inhalation and dermal contact and longer-term occupational exposure via inhalation and/or dermal contact identify a number of adverse health effects. The observed effects include symptoms associated with uncoupling of oxidative phosphorylation (tachycardia, increased respiratory rate, labored breathing, profuse sweating, fever, metabolic acidosis), liver effects, and impaired immune function. The lack of information on exposure characterization and the possible concomitant exposure to other chemicals in the studies reporting these effects somewhat clouds their interpretation. However, acute and longer-term oral studies in experimental animals provide support for these health effects. Since humans are generally exposed to technical-grade pentachlorophenol, which usually contains such toxic impurities as polychlorinated dibenzo-*p*-dioxins and dibenzofurans, some of the effects observed in humans (or the severity and dose-response characteristics of the effects) may be related, at least in part, to the presence of the impurities. Animal studies with both technical-grade and purified pentachlorophenol have demonstrated that, within the ranges of doses tested, some of the toxic effects attributed to pentachlorophenol were actually due to the impurities. Because human exposure is generally to technical-grade pentachlorophenol, studies on technical-grade pentachlorophenol are considered relevant.

In addition to the liver, thyroid, immune, reproductive, and developmental effects, exposure to pentachlorophenol is also associated with carcinogenic, renal, and neurological effects. The results of several epidemiology studies suggest that pentachlorophenol may be a human carcinogen. This assessment is supported by the findings in chronic oral rodent studies of increased incidences of liver tumors (hemangiosarcomas, adenomas, and carcinomas) and adrenal gland pheochromocytomas in mice and mesotheliomas and nasal squamous cell carcinomas in rats. No increases in gene mutations have been observed in a variety of *in vivo* or *in vitro* studies. Clastogenic effects have been observed in a number of *in vitro* studies. The EPA classifies pentachlorophenol in group B2 (probable human

2. RELEVANCE TO PUBLIC HEALTH

carcinogen) and IARC classifies it in group 2B (possibly carcinogenic to humans). Several studies have reported adverse health effects in children accidentally exposed to pentachlorophenol. The observed effects were symptoms of oxidative phosphorylation uncoupling (high fever, profuse sweating, increased respiratory rate, labored breathing, tachycardia, hepatomegaly, and irritability) and death. Thus, the effects observed in children are similar to those seen in adults. However, the data are inadequate to assess whether children are more susceptible than adults to the toxicity of pentachlorophenol.

Hepatic Effects. A number of case reports describe liver effects in individuals exposed to technical-grade pentachlorophenol either occupationally or in the home via inhalation and/or dermal contact. The types of hepatic effects noted in the case reports include enlarged liver, jaundice, centrilobular degeneration, and elevated serum biliary acid concentrations. Liver enlargement was also observed in newborns exposed for a short time via contaminated diapers and bed linen in a hospital nursery. In addition, elevated urinary porphyrin and delta-amino levulinic acid concentrations and elevated levels of serum alanine aminotransferase and aspartate aminotransferase have been reported in epidemiological studies.

Animal studies have confirmed the identification of the liver as one of the primary targets of pentachlorophenol toxicity. Increased liver weights, increased serum enzymes, and histological alterations (centrilobular hepatocellular hypertrophy and vacuolization, necrosis, degeneration, and periportal fibrosis) have been observed in rats and mice exposed to pure and technical-grade pentachlorophenol.

Thyroid Effects. There are limited data on the effect of pentachlorophenol on thyroid function in humans. An inverse relationship between triiodothyronine levels and blood pentachlorophenol levels was found in women with gynecological and/or endocrinological disorders; who lived in homes with wood ceilings and wood panels treated with a wood preservative containing pentachlorophenol. However, the triiodothyronine levels were frequently within the normal range and it is likely that they were also exposed to other chemicals.

In animal studies, decreases in circulating and free concentrations of triiodothyronine and thyroxine have been observed in rats and sheep orally exposed to pure or technical-grade pentachlorophenol for an intermediate duration and first and second generation mink exposed to pentachlorophenol (purity not reported) in a multigeneration study. The chronic-duration oral MRL is based on alterations in thyroid hormone levels (see Section 2.3).

2. RELEVANCE TO PUBLIC HEALTH

Developmental Effects. Developmental effects (congenital eye cataracts) have been observed in the children of male sawmill workers exposed to a mixture of sodium salts of pentachlorophenol and tetrachlorophenol; however, other chemicals, in particular CDDs, may have contributed to the occurrence of these effects. However, animal studies provide strong evidence that pentachlorophenol is a developmental toxicant following oral exposure. Developmental effects are frequently observed at doses that cause decreases in maternal body weight gain. However, decreases in fetal or pup body weight have been observed at doses that do not result in maternal toxicity. Increases in fetal/neonatal mortality, and soft tissue and skeletal malformations/variation (subcutaneous edema, diaphragmatic hernia, dilation of kidneys, lumbar spurs, and delays in ossification), and decreases in offspring growth have been observed in rats and sheep. Pure pentachlorophenol appears to be slightly more developmentally toxic than technical-grade pentachlorophenol. The maternal dose of technical grade pentachlorophenol that would be lethal to 50% of embryos was over two times higher than for pure pentachlorophenol. The acute-duration oral MRL, see Section 2.3 for details, was based on the increased occurrence of delayed skull ossification in rats.

Reproductive Effects. No studies were found that adequately assessed the reproductive toxicity of pentachlorophenol in humans. A possible association between pentachlorophenol exposure and reproductive effects was found in women exposed to technical-grade pentachlorophenol from outgassing wood panels treated with a wood preservative containing pentachlorophenol; however, study limitations, particularly lack of exposure characterization and possible exposure to other chemicals, preclude using these study to establish a causal relationship. A number of animal studies provide evidence that the reproductive system is a sensitive target of pentachlorophenol toxicity. A decrease in fertility was observed in first generation rats administered pentachlorophenol by gavage in a two-generation study; no alterations in fertility were observed in the parental generation in this study. In contrast, no effects on fertility were observed in another multigeneration study in which mink were exposed to lower doses of pentachlorophenol. Several other studies have reported alterations in reproductive tissues. The observed effects include decreased testes weight and focal/multifocal mononuclear cell infiltrate in the epididymis in first generation rats, focal degeneration of the seminiferous tubules in sheep, and increased severity of uterine and oviduct cysts in sheep and mink. Histological alterations were not observed in rats orally exposed to pure or technical-grade pentachlorophenol for an intermediate or chronic duration.

2. RELEVANCE TO PUBLIC HEALTH

Immunological Effects. Immunological effects have been reported in humans exposed via inhalation and/or dermal contact with pentachlorophenol and in animals following oral exposure. A number of immunological effects (e.g., activated T-cells, autoimmunity, immunosuppression, B-cell dysregulation) have been reported in families living in pentachlorophenol-treated log homes and male factory workers involved in brushing technical-grade pentachlorophenol onto wood strips. A number of animal studies indicate that oral exposure to technical-grade pentachlorophenol affects a wide range of immune functions, such as humoral and cellular immunity, susceptibility to tumor induction, and complement activity. However, studies that tested both technical-grade and pure pentachlorophenol provide strong evidence that the immune effects are related to the level of impurities in the technical-grade product (e.g., CDDs and CDFs). There is some evidence that pure pentachlorophenol is an immunotoxicant in rats. Enhanced mitogen-induced T- and B-lymphocyte blastogenesis and suppression of the antibody response against sheep red blood cells has been observed in rats orally exposed to pure pentachlorophenol (>99% pure with no detectable dioxin impurities) for 28 days. However, studies in mice suggest that pure pentachlorophenol has relatively little immunotoxic activity.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

Inhalation MRLs for acute, intermediate, or chronic exposure have not been derived. While target organs have been identified in humans following inhalation exposure to technical-grade pentachlorophenol, the exposure levels at which these effects occur have not been quantified. No data exist on the toxicity of pentachlorophenol following inhalation exposure in animals from which MRLs could be developed.

Oral MRLs

For acute oral exposure, an MRL of 0.005 mg/kg/day has been derived for pentachlorophenol.

This MRL is based on a developmental toxicity study in which groups of pregnant rats were administered pure or technical-grade pentachlorophenol in corn oil by gavage on gestational days 6–15. At the lowest pure pentachlorophenol dose tested (5 mg/kg/day), a significant increase in the occurrence of delayed ossification of the skull was observed. At higher doses (15 mg/kg/day), significant increases in the occurrence of subcutaneous edema, lumbar spurs, and skeletal anomalies in the ribs, sternbrae, and vertebrae were observed. Increased fetal resorptions and decreased fetal body weight were observed at

2. RELEVANCE TO PUBLIC HEALTH

\$30 mg/kg/day. Decreases in maternal body weight gain were observed at \$30 mg/kg/day. Similar results were found in rats exposed to technical-grade pentachlorophenol. However, increased fetal resorptions and skeletal anomalies were observed at \$15 mg/kg/day. The MRL was derived by dividing the lowest-observed-adverse-effect level (LOAEL) of 5 mg/kg/day pure pentachlorophenol by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for interspecies extrapolation, and 10 for human variability). Similar developmental effects have been observed in another rat developmental toxicity study. In this study, significant increases in the occurrence of resorptions, and soft tissue and skeletal malformations and variations, and decreases in fetal body weight were observed in the offspring of rats that were administered by gavage 80 mg/kg/day technical-grade (89% pure) pentachlorophenol on gestational days 6–15. This study identified a no-observed-adverse-effect level (NOAEL) of 30 mg/kg/day. Intermediate-duration oral developmental toxicity studies in rats have also reported increased fetal/neonatal mortality, malformations and/or variations, and decreased growth.

C An intermediate-duration oral MRL of 0.001 mg/kg/day has been derived for pentachlorophenol.

This MRL is based on a LOAEL of 1 mg/kg/day for reproductive effects in mink exposed to pentachlorophenol (purity not reported) in the diet for 3 weeks prior to mating and throughout gestation and lactation. At the only dose tested, 1 mg/kg/day, decreases in the proportion of mated females accepting a second mating and mink that whelped were observed. No effect on the proportion of mink accepting the first mating or the proportion of mink with visible implantation sites were found. An increase in the severity cystic uterine glands was also observed in the pentachlorophenol-exposed mink. The MRL was derived by dividing a LOAEL of 1 by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for interspecies extrapolation, and 10 for human variability).

As discussed in the previous section, reproductive effects have also been observed in rats and sheep orally exposed to pentachlorophenol for intermediate or chronic durations, but the results have been inconsistent. Significant decreases in the number of rats mated and in the ratio of pregnant rats to number of rats in cohabitation were observed in a two-generation rat study. The effects were observed in the first generation of rats exposed to 60 mg/kg/day, but not in the parental generation. In contrast, no effects on fertility were observed in a multi-generation study in mink exposed to 1 mg/kg/day pentachlorophenol in the diet or in sheep or sheep offspring (only females were exposed) exposed to 1 mg/kg/day pentachlorophenol in the diet. Histological alterations in female reproductive tissues have also been observed in sheep; increased severity of oviductal intraepithelial cysts in sheep exposed to 2 mg/kg/day pentachlorophenol by gavage twice weekly for 43 days and lymphocyte infiltration into the endometrium

2. RELEVANCE TO PUBLIC HEALTH

were observed in sheep exposed to 1 mg/kg/day pentachlorophenol in the diet for 5 weeks prior to mating and during pregnancy and lactation. However, no histological alterations were observed in female mink exposed to 1 mg/kg/day pentachlorophenol in the diet in a multi-generation study.

Liver and developmental effects also appear to be sensitive end points of pentachlorophenol following intermediate-duration oral exposure; the lowest adverse effect levels for these effects are 10-fold higher than the reproductive effects reported in mink. Significant increases in relative liver weight and the occurrence of centrilobular hepatocellular hypertrophy have been reported in rats and mice exposed to <10 mg/kg/day pure or technical-grade pentachlorophenol. At higher doses, hepatocyte degeneration and necrosis have been observed. Developmental effects (decreased pup body weight) have also been observed in rat offspring at 10–15 mg/kg/day.

For chronic oral exposure, an MRL of 0.001 mg/kg/day has been derived for pentachlorophenol.

This MRL was based on a LOAEL of 1 mg/kg/day (only dose tested) for significantly decreased serum thyroxine concentrations first generation males and both males and females of the second generation, and decreased relative thyroid weight second generation females when mink were administered pentachlorophenol of unspecified purity continuously in the diet in a multigeneration reproduction study. Several studies support the identification of the thyroid gland as a sensitive target of pentachlorophenol toxicity. Oral gavage administration of pure pentachlorophenol to young adult female rats over a 28-day period at doses of 3 or 30 mg/kg produced decreases in circulating and free concentrations of the thyroid hormones triiodothyronine and thyroxine in serum, a decrease in serum thyroid stimulating hormone, decreases in intrathyroidal levels of triiodothyronine and thyroxine, a decrease in the thyroxine:triiodothyronine ratio in serum, and a reduction in thyroidal hormone stores. Technical-grade pentachlorophenol, tested only at a dose of 3 mg/kg, produced the same effects, except for the reduction in free triiodothyronine in serum (data for free serum thyroxine were not reported). A decrease in maternal serum thyroxine concentration throughout pregnancy and lactation and a significant increase in maternal thyroid gland follicle size were found in female sheep administered 1 mg/kg/day pentachlorophenol (purity not indicated) in the diet 5 weeks prior to mating and throughout pregnancy and lactation until 2 weeks after weaning of the lambs. Additionally, increased thyroxine levels were observed in their ewe and ram lambs that also received postnatal exposure to pentachlorophenol. The chronic-duration MRL was derived by dividing the LOAEL of 1 mg/kg/day by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for interspecies extrapolation, and 10 for human variability).

Dermal MRLs

2. RELEVANCE TO PUBLIC HEALTH

Appropriate methodology does not currently exist to develop MRLs for dermal exposure. This is most often because of the difficulty in identifying reliable, absorbed doses from most dermal studies. The paucity of dermal studies is in part due to the difficulty in constructing animal models which limit exposure exclusively to the dermal route. An approach to deriving dermal MRLs from oral or inhalation data through route-to-route extrapolation is currently being evaluated for potential use by the agency.