Pentachlorophenol; CASRN 87-86-5

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR PENTACHLOROPHENOL

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/30/2010
Inhalation RfC (I.B.)	qualitative discussion	9/30/2010
Carcinogenicity Assessment (II.)	yes	9/30/2010

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Substance Name – Pentachlorophenol
CASRN − 87-86-5
Section I.A. Last Revised − 09/30/2010

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information

concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

The previous oral RfD for pentachlorophenol (PCP), posted to the IRIS database in January 1987, was 0.03 mg/kg-day, based on a chronic oral rat study (Schwetz et al., 1978). The no-observed-adverse-effect-level (NOAEL) was identified as 3 mg/kg-day and the lowest-observed-adverse-effect-level (LOAEL) was identified as 10 mg/kg-day for liver and kidney pathology, evidenced by pigmentation of the liver and kidneys in female rats. The RfD of 0.03 mg/kg-day was calculated by applying an uncertainty factor (UF) of 100 (two factors of 10 to account for interspecies and interhuman variability) to the NOAEL of 3 mg/kg-day.

I.A.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD
Hepatotoxicity **1-Year beagle dog study** **Mecler, 1996**	LOAEL: 1.5 mg/kg-day	300	0.005 mg/kg-day

*Conversion Factors and Assumptions − none.

I.A.2. PRINCIPAL AND SUPPORTING STUDIES

In a chronic toxicity study by Mecler (1996), technical-grade PCP (tPCP; 90.9% purity) was fed by gelatin capsules to four beagle dogs/sex/dose at 0, 1.5, 3.5, or 6.5 mg/kg-day for 52 weeks. At 6.5 mg/kg-day, one male and one female dog were sacrificed in extremis on days 247 and 305, respectively, due to significant clinical toxicity (significant weight loss, lethargy, marked dehydration, vomiting, icterus). The morbidity was presumed due to hepatic insufficiency based on profuse toxicity in the liver that consisted of histologic lesions; multifocal, moderate hepatocellular swelling and degeneration of hepatocytes; fibrosis; bile duct hyperplasia; foci of hepatocellular hypertrophy; and hyperplasia consistent with cirrhosis. The mean body weight in surviving males in the 6.5 mg/kg-day dose group was decreased 18% when compared with controls. The decrease in body weight was not considered statistically significant as calculated by the study authors. Absolute body weight was only slightly decreased at the lower doses (4 and 6% at 1.5 and 3.5 mg/kg-day, respectively). Female dogs in the 6.5 mg/kg-day dose group exhibited a 20% decrease in absolute body weight that was statistically significantly less than controls at week 13 and for the remainder of the study. At the lower doses of 1.5 and 3.5 mg/kg-day, the absolute body

weights of females were decreased 9 and 13%, respectively. In contrast to males, the decrease in absolute body weight in treated females was dose-related. Only group means were reported; individual animal data and standard deviations were not included.

There were dose-related, mild-to-moderate decreases in three hematological parameters measured in male dogs for all dose groups, although not all changes were considered statistically significant (in calculations performed by study authors). Statistically significant decreases (15%) in red cell counts were observed in males at the 3.5 mg/kg-day dose, while the 1.5 mg/kg-day group showed only a 3% decrease. In males at the 6.5 mg/kg-day dose, red blood cell (RBC) counts and hemoglobin levels were statistically significantly reduced by 21 and 16%, respectively, compared with controls. In females, statistically significant decreases of 10–17% in these hematological parameters were observed at 6.5 mg/kg-day from week 26 until study termination. In contrast to males, the hematological effects in females were not dose-related.

Activities of alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were elevated for both sexes throughout the study. At study termination, ALP activity was increased, compared with controls, in the serum of males (1.9-, 2.3-, and 4.9-fold) and females (1.9-, 2.6-, and 6.8-fold) at all three doses (1.5, 3.5, and 6.5 mg/kg-day, respectively). AST activity increased slightly at doses ≥3.5 mg/kg-day, although never more than 1.7-fold greater than in controls. The serum activity of ALT was similar to the control at 1.5 mg/kg-day, although ALT activity was observed at levels 2.8- and 3.1-fold greater than the controls for males and females, respectively, in the 3.5 mg/kg-day dose group. Exposure to 6.5 mg/kg-day of tPCP resulted in ALT levels 3.9- and 8.8-fold greater than in controls for males and females, respectively.

Male dogs exhibited increases of 10, 31, and 32% over controls in measurements of absolute liver weight at the 1.5, 3.5, and 6.5 mg/kg-day dose levels, respectively; these were not considered statistically significant by the study authors. However, increases of 14, 39, and 66% in relative liver weights of males were significantly greater than in controls in the 1.5, 3.5, and 6.5 mg/kg-day dose groups, respectively. Absolute and relative liver weights were significantly elevated at 1.5, 3.5, and 6.5 mg/kg-day doses in females by 24, 22, and 49% (absolute liver weights) and 37, 40, and 94% (relative liver weights), respectively. Thyroid weight measurements in males were increased when compared with controls, but did not show a linear dose-response relationship. Absolute and relative thyroid weights were statistically significantly increased in females at the 6.5 mg/kg-day dose by 78 and 138%, respectively. Relative thyroid weight was also increased at the 1.5 (72%) and 3.5 mg/kg-day (64%) doses.

An increased incidence of gross stomach lesions consisting of multiple, raised mucosal foci were observed in all treated groups of male and female dogs. Male and female dogs in all

treatment groups exhibited an increased incidence of dark, discolored livers. Microscopically, liver lesions associated with tPCP treatment consisted of pigmentation, cytoplasmic vacuolization, minimal necrosis, and chronic inflammation; incidence and severity generally increased with dose.

The study authors determined that the LOAEL was 6.5 mg/kg-day tPCP, based on morphologic effects in the liver. The NOAEL was 3.5 mg/kg-day. However, considering the progression of lesions observed with increasing dose and the morbidity observed in both sexes at the 6.5 mg/kg-day dose, EPA identified the LOAEL as 1.5 mg/kg-day (lowest dose tested), based on liver pathology consisting of dose-related increases in incidence and severity of hepatocellular pigmentation, cytoplasmic vacuolation, and chronic inflammation, and significant increases in relative liver weight and increases in absolute liver weight (significant in females), and increased serum enzyme activity. The NOAEL could not be established.

I.A.3. UNCERTAINTY FACTORS

UF = 300

A default 10-fold UF for intraspecies differences (UF_H) was applied to account for variability in susceptibility among members of the human population in the absence of quantitative information on the variability of human response to PCP. Current information is unavailable to assess human-to-human variability in PCP toxicokinetics and toxicodynamics; therefore, to account for these uncertainties, a factor of 10 was applied for individual variability.

A default 10-fold UF for interspecies extrapolation (UF_A) was applied to account for the potential pharmacokinetic and pharmacodynamic differences between dogs and humans. Although toxicokinetic data are available in some animals, a description of toxicokinetics in either dogs or humans is limited or not available. In the absence of data to quantify specific interspecies differences, a factor of 10 was applied.

A LOAEL to NOAEL uncertainty factor (UF_L) of 3 was applied to account for the extrapolation from a LOAEL to a NOAEL. The 1.5 mg/kg-day dose level was selected as the LOAEL based on histopathological changes in the liver, consisting of increased incidence of pigmentation in both males and females; minimal chronic inflammation in males; and increased relative liver weights in males and absolute and relative liver weight in females. These effects were accompanied by small changes (less than twofold) in serum enzymes (ALT in males and ALP in males and females), indicating an effect of minimal toxicological significance. Therefore, a factor 3 was applied to account for the use of a LOAEL that is characterized by effects that can be considered mild.

An UF to account for extrapolation from subchronic to chronic (UF_S) exposure duration was not applied because the RfD was derived from a study using a chronic exposure protocol.

An UF to account for database deficiencies (UF_D) was not applied because the database for PCP contains human studies; chronic studies in rats, mice, and dogs; subchronic studies in various animal species; neurological, reproductive, endocrine, and developmental and reproductive toxicity studies; and a two-generation reproductive toxicity study.

I.A.4. ADDITIONAL STUDIES/COMMENTS

The liver is the primary target for noncancer effects of oral exposure to PCP. Numerous short- and long-term oral studies show that PCP is toxic to the liver of rats, mice, and dogs. Liver toxicity is generally manifested by increased absolute and relative weights and a wide spectrum of microscopic lesions. Liver toxicity in long-term studies in rats was primarily characterized by pigment accumulation (Schwetz et al., 1978), chronic inflammation at high doses, and cystic degeneration at lower doses in males (NTP, 1999); female rats were not as sensitive as males in the National Toxicology Program (NTP) study. Liver toxicity in mice exposed orally to PCP was manifested primarily by necrosis, cytomegaly, chronic active inflammation, and bile duct lesions (NTP, 1989). Liver toxicity was more severe in mice than rats at similar doses, which could be partially attributable to differences in biotransformation of PCP. Additionally, rats in one of the chronic studies (NTP, 1999) were treated with analytical-grade PCP (aPCP), whereas mice in the chronic NTP (1989) study received technical grades of PCP, either tPCP or Dowicide EC-7 (EC-7), which are higher in chlorinated dibenzo-p-dioxins and dibenzofuran contaminants and may contribute to the severity of the response in mice compared with rats. NTP (1989) studies showed very little difference between the toxicity of tPCP and EC-7 in mice, except for bile duct hyperplasia, which may be associated with the impurities in tPCP. Liver lesions in the dog (Mecler, 1996) were similar to those observed in the mouse (NTP, 1989), but the doses inducing the lesions in the dog were lower than those that induced these lesions in the mouse (1.5 mg/kg-day compared with 17–18 mg/kg-day for the mouse). Studies in domestic animals showed that pigs, but not cattle, exhibited liver lesions similar to those observed in mice. The pig exhibited liver toxicity at a lower dose (10 versus 17–18 mg/kg-day for the mouse) and for a shorter duration (30 days versus 2 years) than the mouse.

Other noncancer targets identified in long-term studies include the kidney (pigment deposition in the proximal convoluted tubules) of rats (Schwetz et al., 1978) and the spleen (decrease in organ weight) of mice (NTP, 1989), rats (Bernard et al., 2002), and calves (Hughes et al., 1985).

A two-generation reproductive toxicity study in rats showed that exposure to tPCP is associated with decreased fertility, delayed puberty, testicular effects, decreased litter size, decreased viability, and decreased pup weights at a dose of 30 mg/kg-day (Bernard et al., 2002). These effects occurred at the same doses causing systemic toxicity in parental animals. A one-generation reproductive study in mink (1 mg/kg-day aPCP) showed evidence of reproductive effects in which many of the dams refused to accept the males for a second mating. Additionally, the whelping rate was reduced (Beard et al., 1997). However, a two-generation reproductive study of similar design reported no reproductive effects in mink administered 1 mg/kg-day PCP (Beard and Rawlings, 1998). Additionally, no effects on reproduction were noted in sheep (both ewes and rams) at a PCP dose of 1 mg/kg-day (Beard et al., 1999a, b).

The majority of developmental toxicity studies on PCP provided no evidence of teratogenic effects, but some older studies showed toxic effects of PCP in offspring that occurred at dose levels below those producing maternal toxicity. In Welsh et al. (1987), effects were observed in rat fetuses at 13 mg/kg-day compared with 43 mg/kg-day in the dams. Schwetz et al. (1974) similarly reported sensitivity in fetuses at 5 mg/kg-day aPCP and 15 mg/kg-day tPCP compared with 30 mg/kg-day in the dams treated with either grade of PCP.

Studies show that treatment with PCP affected the levels of circulating thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4). Serum T_3 and T_4 levels were significantly decreased by both aPCP and tPCP in rats (at a dose of 3 mg/kg-day [Jekat et al., 1994]) and cattle (at doses of 1 mg/kg-day [Hughes et al., 1985] and 15 mg/kg-day [McConnell et al., 1980]). Serum T_4 levels were significantly decreased by PCP (purity not reported) in ram and ewe lambs, and mink (at a of dose 1 mg/kg-day [Beard et al., 1999a, b; Beard and Rawlings, 1998]), and by aPCP in mature ewes (at a dose of 2 mg/kg-day [Rawlings et al., 1998]). PCP treatment did not affect the degree to which thyroid-stimulating hormone (TSH) stimulated thyroid hormone levels (Beard et al., 1999a, b). Only Jekat et al. (1994) reported changes in TSH levels following administration of PCP to rats for 28 days. Along with a decrease in T_4, there was a noted decrease in TSH. Because TSH levels were not elevated in response to the reduced thyroid hormone levels, the investigators concluded that PCP interfered with thyroid hormone regulation at the hypothalamic and pituitary levels. Additionally, the peripheral interference with thyroid hormone metabolism was suggested by the greater reduction in T_4 compared with T_3 (Jekat et al., 1994). The mechanism by which PCP affects thyroid hormones has not been identified.

Studies examining the immunotoxic effects of PCP showed that the humoral response and complement activity in mice were impaired by tPCP, but not by aPCP, when administered to adult animals (at doses as low as 38 mg/kg-day [NTP, 1989]; 10 mg/kg-day [Holsapple et al., 1987; Kerkvliet et al., 1982a, b]; and 2 mg/kg-day [Kerkvliet et al., 1985a, b]). Treatment of

mice with doses as low as 4 mg/kg-day from the time of conception to 13 weeks of age resulted in impaired humoral- and cell-mediated immunity (Exon and Koller, 1983). Blood measurements in humans with known exposure to PCP showed that immune response was impaired in patients who had blood PCP levels >10 µg/L and in particular, in those whose levels were >20 µg/L (Daniel et al., 1995; McConnachie and Zahalsky, 1991).

An NTP (1989) study in mice showed decreased motor activity in rotarod performance in male rats treated with tPCP for 5 weeks and increases in motor activity and startle response in females receiving aPCP and tPCP for 26 weeks. Another in vivo study showed that treatment of rats with 20 mg/L PCP for up to 14 weeks caused biochemical effects in the rat brain (Savolainen and Pekari, 1979), although the authors considered these transient effects. The most definitive study showed that rats receiving 3 mM PCP in drinking water for at least 90 days had marked morphological changes in sciatic nerves (Villena et al., 1992). It is possible that some of the neurotoxic effects are related to PCP contaminants. Most of the neurotoxicity studies were performed using tPCP or PCP of unknown purity. NTP (1989) utilized four grades (aPCP, tPCP, Dow PCP DP-2 Antimicrobial [DP-2], and EC-7) of PCP at doses ranging from 36 to 458 mg/kg-day, and found that the majority of the neurotoxic effects were observed in male mice with tPCP; however, similar effects were also observed in female mice treated with all four grades of PCP. Effects were observed at the lower doses (36–102 mg/kg-day) and exhibited dose-related increases.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Study − Medium
Database − High
RfD − Medium

The overall confidence in this RfD assessment is medium. Confidence in the principal study, Mecler (1996), is medium. The 52-week study in beagle dogs is an unpublished Office of Pollution, Prevention and Toxic Substances (OPPTS) guideline study that used three dose groups plus a control and collected interim data at 13, 26, and 39 weeks. The study is limited by the use of relatively small group sizes (4 dogs/sex/dose). Because the incidence of two of the key liver effects (i.e., hepatocellular pigmentation in males and females and chronic inflammation in males) increased from 0% in the controls to 100% in the lowest dose tested, and remained at 100% in both the mid- and high-dose groups, the study provided limited resolution of the dose-response curve at low doses. However, liver effects observed in this study (i.e., the critical effect for the RfD) are well-supported by other oral subchronic and chronic studies. PCP also induced toxicity in reproductive and immunological studies, but at

doses higher than those used in the principal study. Confidence in the database is high because the database includes acute, short-term, subchronic, and chronic toxicity studies and developmental and multigenerational reproductive toxicity studies in multiple species, and carcinogenicity studies in two species.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document − U.S. EPA, 2010

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Pentachlorophenol* (U.S. EPA, 2010). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

Agency Completion Date − 09/30/2010

I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Substance Name – Pentachlorophenol
CASRN − 87-86-5
Section I.B. Last Revised − 09/30/2010

The RfC is 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 effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects

peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

An inhalation RfC for PCP was not previously available on the IRIS database.

I.B.1. CHRONIC INHALATION RfC SUMMARY

Adequate data are not available to derive an inhalation RfC for PCP. No chronic or subchronic animal studies for inhalation exposure are available.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES

Not applicable.

I.B.3. UNCERTAINTY FACTORS

Not applicable.

I.B.4. ADDITIONAL STUDIES/COMMENTS

Not applicable.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Not applicable.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC

Source Document – U.S. EPA, 2010

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Pentachlorophenol* (U.S. EPA, 2010). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

Agency Completion Date – 09/30/2010

I.B.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name – Pentachlorophenol
CASRN − 87-86-5
Section II. Last Revised − 09/30/2010

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per µg/m^3 air breathed (see Section II.C.1.). Second,

the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

The previous cancer assessment for PCP was posted on the IRIS database in 1991. At that time, PCP was classified as a B2 carcinogen (probable human carcinogen), based on the finding of treatment-related hepatocellular adenomas and carcinomas, adrenal medulla pheochromocytomas and malignant pheochromocytomas, and/or hemangiosarcomas and hemangiomas in one or both sexes of $B6C3F_1$ mice using two different formulations of PCP. An oral slope factor (SF) of 1.2×10^{-1} $(mg/kg\text{-}day)^{-1}$ was derived using linear extrapolation procedures and pooled hepatocellular and hemangiosarcoma tumor incidence data in the female $B6C3F_1$ mouse (NTP, 1989). An inhalation unit risk (IUR) was not available.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), PCP is "likely to be carcinogenic to humans." This cancer weight of evidence determination is based on: (1) evidence of carcinogenicity from oral studies in male mice exhibiting hepatocellular adenomas and carcinomas, and pheochromocytomas and malignant pheochromocytomas, and in female mice exhibiting hepatocellular adenomas and carcinomas, pheochromocytomas and malignant pheochromocytomas, and hemangiomas and hemangiosarcomas (NTP, 1989); (2) some evidence of carcinogenicity from oral studies in male rats exhibiting malignant mesotheliomas and nasal squamous cell carcinomas (Chhabra et al., 1999; NTP, 1999); (3) strong evidence from human epidemiologic studies showing increased risks of non-Hodgkin's lymphoma and multiple myeloma, some evidence of soft tissue sarcoma, and limited evidence of liver cancer associated with PCP exposure (Demers et al., 2006; Hardell et al., 1995, 1994; Kogevinas et al., 1995); and (4) positive evidence of hepatocellular tumor-promoting activity (Umemura et al., 2003a, b, 1999) and lymphoma and skin-adenoma promoting activity in mice (Chang et al., 2003).

U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) indicate that for tumors occurring at a site other than the initial point of contact, the cancer descriptor may apply to all routes of exposure that have not been adequately tested at sufficient doses. An exception occurs when there is convincing toxicokinetic data that absorption does not occur by other routes. Oral studies of PCP carcinogenicity demonstrate that tumors occur in tissues remote from the site of absorption, including the liver, adrenal gland, circulatory system, and nose. Information on the carcinogenicity of PCP via the inhalation and dermal routes is unavailable. Studies of the absorption of PCP indicate that the chemical is readily absorbed via all routes of exposure, including oral, inhalation, and dermal. Therefore, based on the

observance of systemic tumors following oral exposure, and in the absence of information to indicate otherwise, it is assumed that an internal dose will be achieved regardless of the route of exposure. Accordingly, PCP is considered "likely to be carcinogenic to humans" by all routes of exposure.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

II.A.2. HUMAN CARCINOGENICITY DATA

Epidemiological studies of various designs (cohort, population-based case-control, and nested case-control within occupationally exposed workers) have examined the relationship between occupational PCP exposure and cancer risk. The strongest of the cohort studies, in terms of design, is the large sawmill cohort study conducted in British Columbia, Canada, recently updated by Demers et al. (2006). In addition to the sample size, important design features that add to the strengths of this study include the exposure assessment procedure developed specifically to address the exposure situations and settings of the study, use of an internal referent group, analysis of PCP and tetrachlorophenol (TCP) exposures, low loss to follow-up, and use of a population-based cancer registry that allowed for the analysis of cancer incidence. Even with this size, however, there is limited statistical power to estimate precise associations with relatively rare cancers. The case-control studies of non-Hodgkin's lymphoma and soft tissue sarcoma (Hardell and Eriksson, 1999; Kogevinas et al., 1995; Hardell et al., 1995, 1994) specifically address this limitation by focusing on these outcomes. Kogevinas et al. (1995) has the additional attribute of providing estimates for the effects of other phenoxy herbicides or chlorophenols, which provides information regarding the issue of co-exposures.

In these studies, moderately high associations (i.e., a two- to fourfold increased risk) were generally seen between occupational exposure to PCP and non-Hodgkin's lymphoma (Demers et al., 2006; Kogevinas et al., 1995; Hardell et al., 1994), multiple myeloma (Demers et al., 2006), or soft tissue sarcoma (four studies summarized in a meta-analysis by Hardell et al., 1994). However, there are some inconsistencies, most notably for soft tissue sarcoma. The relative rarity of this cancer (e.g., only 12 cases were found in the nested case-control study of 13,898 workers exposed to phenoxy herbicides or chlorophenols by Kogevinas et al. [1995]) and the difficulty in classifying the disease, even with a review of the histology, may be reasons for this inconsistency. In contrast to the studies from the 1970s and 1980s, the most recent case-control study of non-Hodgkin's lymphoma, conducted in cases diagnosed 9–13 years after PCP had been banned from use in Sweden, did not observe an association (odds

ratio [OR] 1.2) with PCP exposure (Hardell and Eriksson, 1999). The lack of association in this study could reflect a relatively short latency period between exposure and disease, as has been seen with other lymphoma-inducing agents (e.g., Krishnan and Morgan, 2007).

Demers et al. (2006) developed a cumulative dermal chlorophenol exposure score based on a retrospective exposure assessment that was validated for current exposures in comparison with urinary measurements and with industrial hygienist assessments. This detailed exposure measure allowed for analysis of an exposure-response gradient, with evidence of a trend of increasing mortality or incidence risk seen for non-Hodgkin's lymphoma and multiple myeloma. The other studies with a relatively detailed exposure assessment (Hardell et al., 1995, 1994; Kogevinas et al., 1995) also demonstrated stronger associations with the more refined (e.g., higher exposure probability or frequency) measures of exposure compared with the associations seen with "any pentachlorophenols."

The possibility of the carcinogenic effects of PCP resulting solely from the presence of contaminants of dioxins and furans was examined in this assessment (Demers et al., 2006). The primary contaminants were hexa-, hepta-, and octa-chlorinated dibenzodioxins, and higher-chlorinated dibenzofurans. There are several reasons that this contamination is an unlikely explanation for the observed effects. Specific furans are not generally seen at higher levels in blood from PCP workers compared with the general population (Collins et al., 2007). The cancer risks seen in the large cohorts of workers exposed to dioxins (consistent observations of an exposure-response gradient with total cancer risk) (NAS, 2006; Steenland et al., 2004) differ from the observations seen in studies of PCP exposure. In addition, the associations seen with specific cancers (e.g., non-Hodgkin's lymphoma) and PCP are generally stronger than the associations seen between these cancers and dioxin or other chlorophenol exposures in studies with both of these measures (Demers et al., 2006; Kogenivas et al., 1995).

An increased risk of liver cancer associated with exposure to PCP was seen in the large cohort study of sawmill workers in British Columbia (Demers et al., 2006), and as noted in the previous discussion of non-Hodgkin's lymphoma, an attenuation in the highest exposure group was observed. This study identified strong associations between exposure to PCP and liver cancer, with at least a doubling of the risk in almost all of the exposure categories.

Evidence for PCP-induced deoxyribonucleic acid (DNA) damage has been presented in numerous animal or in vitro studies and was equivocal in studies of PCP-exposed workers (Ziemsen et al., 1987; Bauchinger et al., 1982; Schmid et al., 1982). Evidence for cytotoxicity or apoptosis, reparative cell proliferation, and gap junction inhibition usually cannot be obtained in human studies.

PCP-induced effects on the immune system have been found in humans and animals. Blakley et al. (1998) reported stimulation of mitogen effects in low-dose, gavage-treated male rats. Daniel et al. (1995) observed exposure-dependent impairment of mitogen response in lymphocytes of PCP-exposed humans, and McConnachie and Zahalsky (1991) reported heightened immune response in PCP-exposed humans. Finally, symptoms of porphyria were identified in PCP-exposed humans (Cheng et al., 1993) and animals (NTP, 1989; Kimbrough and Linder, 1978). These findings make a strong point for the plausibility of PCP-related carcinogenesis in humans. In summary, the weight of evidence for the carcinogenic action of PCP (U.S. EPA, 2005a) suggests that this compound by itself (i.e., in the absence of contaminants) is likely to be a human carcinogen.

II.A.3. ANIMAL CARCINOGENICITY DATA

Long-term animal studies employing the oral route of exposure are available that assess the carcinogenicity of PCP in animals. An NTP feeding study in $B6C3F_1$ mice demonstrated that tPCP (17–18 or 35–36 mg/kg-day) and EC-7 (17–18, 35–36, or 117–118 mg/kg-day) caused statistically significant increases in the incidence of hepatocellular adenomas/carcinomas and adrenal gland pheochromocytomas in males and females, and an increased incidence of hemangioma/hemangiosarcoma in female mice (NTP, 1989). tPCP was slightly more effective than EC-7, suggesting that chlorinated dibenzo-p-dioxin and dibenzofuran impurities in tPCP may have only exacerbated the carcinogenic effect of PCP in mice.

Another NTP (1999) feeding study conducted in F344/N rats provided some evidence of carcinogenic activity, demonstrated by increased incidence of mesotheliomas and nasal squamous cell carcinomas in males exposed to aPCP (10–60 mg/kg-day). NTP (1999) concluded that there was no evidence of carcinogenic activity for female rats fed aPCP.

Umemura et al. (1999) examined the initiating and promoting activity of aPCP (98.6% purity) administered in the diet to 20 male $B6C3F_1$ mice/group. Diethylnitrosamine (DEN) was given as the initiator when the promoting activity of aPCP was assessed, and phenobarbital (PB) was administered as the promoter when the initiating activity of aPCP was assessed. The incidence of liver tumors was statistically significantly higher in mice initiated with DEN and promoted with PCP than in control mice receiving DEN only. Tumor multiplicity was statistically significantly increased in mice promoted with aPCP and PB compared with DEN controls. No liver tumors developed in mice initiated with aPCP with or without subsequent promotion with PB. In this study, aPCP showed promoting, but not initiating, activity in mice that were initiated with DEN. Umemura et al. (1999) concluded that aPCP exerts a promoting effect on liver carcinogenesis.

A study by Bionetics Research Laboratories, Inc. (BRL, 1968) showed no carcinogenic response in male and female $B6C3F_1$ and B6AKF1 mice administered EC-7 at a dose of

46.4 mg/kg-day for up to 18 months. This exposure may not have been long enough to reveal carcinogenic effects. BRL (1968) also reported that mice administered 46.4 mg/kg-day EC-7 as a single, subcutaneous injection did not develop tumors that were considered statistically significantly greater than tumors observed in control animals. Schwetz et al. (1978) reported no carcinogenic response in male and female Sprague-Dawley rats administered EC-7 in the diet at doses up to 30 mg/kg-day for 22–24 months. A lack of body or organ weight changes even at the highest dose raises the possibility that a maximum tolerated dose (MTD) was not reached in this study.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Genotoxicity studies following PCP exposure have shown that while mutations have not been detected in prokaryotic systems, there is evidence both in subcellular systems and in human cells in vitro that PCP can induce damage to DNA and proteins via oxidative mechanisms. In addition, gene mutation and recombination in fungi, clastogenic effects in mammalian systems in vitro, and a weakly positive indication of transplacental mutation in mice have been observed in assays with PCP. Tetrachloro-p-hydroquinone (TCpHQ), a metabolite of PCP, has also been shown to induce DNA damage in in vitro studies and oxidative damage in both in vitro and in vivo studies.

See the *Toxicological Review of Pentachlorophenol* (U.S. EPA, 2010) for a more detailed summary of the genetic toxicity data for PCP.

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

II.B.1. SUMMARY OF RISK ESTIMATES

II.B.1.1. Oral Slope Factor – 4×10^{-1} per mg/kg-day

The oral slope factor is derived from the LED_{10}, the 95% lower bound on the exposure associated with a 10% extra cancer risk, by dividing the risk (as a fraction) by the LED_{10}, and represents an upper bound, continuous lifetime exposure risk estimate:

LED_{10}, lower 95% bound on exposure at 10% extra risk – 0.25 mg/kg-day
ED_{10}, central estimate of exposure at 10% extra risk – 0.34 mg/kg-day

The slope of the linear extrapolation from the central estimate ED_{10} is
$0.1/(0.34 \text{ mg/kg-day}) = 2.9 \times 10^{-1}$ per mg/kg-day.

The slope factor for PCP should not be used with exposures exceeding the point of departure (POD) (0.25 mg/kg-day), because above this level, the fitted dose-response model better characterizes what is known about the carcinogenicity of PCP.

II.B.1.2. Drinking Water Unit Risk* - 1×10^{-5} per µg/L

Drinking Water Concentrations at Specified Risk Levels

Risk Level	Lower Bound on Concentration Estimate*
E-4 (1 in 10,000)	9 µg/L
E-5 (1 in 100,000)	0.9 µg/L
E-6 (1 in 1,000,000)	0.09 µg/L

* The unit risk and concentration estimates assume water consumption of 2 L/day by a 70-kg human.

II.B.1.3. Extrapolation Method

Multistage model with linear extrapolation from the POD (LED_{10}).

II.B.2. DOSE-RESPONSE DATA

Tumor type − Hepatocellular adenomas or carcinomas and adrenal benign or malignant pheochromocytomas
Test species – Male $B6C3F_1$ mice
Route – Oral (diet)
Reference – NTP (1989)

Incidence of tumors in male B6C3F$_1$ mice exposed to tPCP in the diet for 2 years			
Tumor type	**tPCP, ppm in diet**		
	0	**100**	**200**
	mg/kg-day[a]		
	0	**18**	**35**
Hepatocellular adenomas or carcinomas	7/32[b]	26/47[c]	37/48[c]
Adrenal benign or malignant pheochromocytomas	0/31[b]	10/45[c]	23/45[c]

[a]Average daily doses estimated by the researchers.
[b]Statistically significant trend ($p < 0.05$) by Cochran-Armitage test.
[c]Statistically significant difference from controls ($p < 0.05$) by Fisher's exact test.

II.B.3. ADDITIONAL COMMENTS

The slope factors ranged from 1.5×10^{-1} to 2.9×10^{-1} $(mg/kg\text{-}day)^{-1}$ for individual tumor sites in the male mouse exposed to tPCP. Considering the multiple tumor types and sites observed in the mice exposed to PCP, the estimation of risk based on only one tumor type/site may underestimate the overall carcinogenic potential of PCP. Therefore, a bootstrap analysis (Efron and Tibshirani, 1993) was used to derive the distribution of the benchmark dose (BMD) for the combined risk of liver and adrenal gland tumors. A simulated incidence level was generated for each exposure group using a binomial distribution with probability of success estimated by a Bayesian estimate of probability. Each simulated data set was modeled using the multistage model in the same manner as was done for the individual risks associated with the liver and adrenal gland tumors. The 5th percentile from the distribution of combined BMDs was used to estimate the BMDL corresponding to an extra risk of 1% for any of the two tumor sites.

II.B.4. DISCUSSION OF CONFIDENCE

A biologically-based model for PCP was not supported by the available data; therefore, a multistage model was the preferred model. The multistage model can accommodate a wide variety of dose-response shapes and provides consistency with previous quantitative dose-response assessments for cancer. Linear low-dose extrapolation from a POD determined by an empirical fit of tumor data has been judged to lead to plausible upper bound risk estimates at low doses for several reasons. However, it is unknown how well this model or the linear low-dose extrapolation predicts low-dose risks for PCP. An adjustment for cross-species

scaling ($BW^{3/4}$) was applied to address toxicological equivalence of internal doses between mice and humans based on the assumption that equal risks result from equivalent constant lifetime exposures.

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not applicable.

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

Source Document – U.S. EPA, 2010

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Pentachlorophenol* (U.S. EPA, 2010). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

II.D.2. EPA REVIEW

Agency Completion Date – 09/30/2010

II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. BIBLIOGRAPHY

Substance Name – Pentachlorophenol
CASRN − 87-86-5

VI.A. ORAL RfD REFERENCES

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VII. REVISION HISTORY

Substance Name – Pentachlorophenol
CASRN − 87-86-5
File First On-Line 01/31/1987

Date	Section	Description
03/01/1991	II.	Carcinogenicity assessment on-line
09/30/2010	I., II., VI.	RfD and cancer assessment sections updated. RfC message added.

VIII. SYNONYMS

Substance Name – Pentachlorophenol
CASRN − 87-86-5
Section VIII. Last Revised – 09/30/2010

- 87-86-5
- Chem-Tol
- Chlorophen
- Cryptogil OL
- Dowcide 7
- Dowicide EC-7
- DP-2, technical
- Durotox
- EP 30
- Fungifen
- Glazd penta
- Grundier arbezol
- 1-Hydroxy- 2,3,4,5,6-pentachlorobenzene
- Lauxtol
- Lauxtol A
- Liroprem
- NCI-C54933
- NCI-C55378
- NCI-C55389
- NCI-C56655
- PCP
- Penchlorol
- Penta
- Pentachloorfenol
- Pentachlorofenol
- Pentachlorofenolo
- Pentachlorophenate
- Pentachlorophenol
- 2,3,4,5,6-Pentachlorophenol
- Pentachlorphenol
- Pentaclorofenolo
- Pentacon
- Penta-Kil
- Pentasol

- Penwar
- Peratox
- Permacide
- Permagard
- Permasan
- Permatox
- Permatox dp-2
- Permatox penta
- Permite
- Phenol, pentachloro-
- Preventol P
- Priltox
- Santobrite
- Santophen
- Santophen 20
- Sinituho
- Term-i-trol
- WLN: QR BG CG DG EG FG