ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR PENTACHLOROPHENOL

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ADDENDUM for PENTACHLOROPHENOL
Supplement to the 2001 Toxicological Profile for Pentachlorophenol

Background Statement

This addendum for the Toxicological Profile for Pentachlorophenol supplements the profile that was released in September 2001.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances and that the profiles be revised "no less often than once every three years." CERCLA further states that the Administrator will "establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide to the public and to federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 2001.

Chapter numbers in this addendum coincide with the Toxicological Profile for Pentachlorophenol (2001). This document should be used in conjunction with the profile. It does not replace it.

3. HEALTH EFFECTS

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

3.2.1 Inhalation Exposure

3.2.1.2 Systemic Effects

An epidemiological study was conducted to investigate the health effects possibly associated with pentachlorophenol (PCP) exposure in workers that were currently being exposed and workers previously exposed to PCP in the timber industry (Walls et al.1998). Iinterpretations of the results of the study may be limited, because of lack of exposure levels, a lack of specific data indicating a predominant route of exposure, and exposure to a number of chemicals, since technical grade PCP contains many other contaminants including polychlorinated biphenyls (PCBs), and other chlorophenols. The investigators conducted a non-random questionnaire-based survey among 137 male participants, but10 of the participants were excluded from the survey, because they had never worked in the timber industry. Workers exposed to PCP were calculated as low, medium, or high, and were based on duration of exposure, type of PCP work, type of PCP vehicle used, use of personal protection, and intensity of exposure. Data collected from the 127 responses to the questionnaires showed an exposure-response association with significant trends found for dermatitis, reddened eyes, sore throats ($p \leq 0.01$), fever, sweating ($p \leq 0.01$), weight loss, fatigue, and impairment of higher brain functions ($p \leq 0.05$). The routes of exposure were not reported and were presumed to be inhalation and dermal, because of the symptoms reported. There were no reference or control groups used in this study. The authors also indicated that it was difficult to associate these health effects with PCP exposure, because the workers most likely were exposed to various other chemicals used in the timber industry (e.g., chromate copper arsenate, boric acid) and other past occupational exposures, and actual exposures to PCP were not measured. Therefore, the authors indicated that the results need more investigation, and should be regarded as preliminary findings (Walls et al. 1998).

3.2.1.3 Immunological and Lymphoreticular Effects

Daniel et al. (2001) investigated the dose-response relationship of PCP, hexachlorohexane, (HCH), PCBs and hexachlorobenzene (HCB) blood levels with immunological abnormalities of 146 patients who had known histories of being occupationally exposed primarily to PCBs for more than 6 months (Daniel et al. 2001). The investigators assumed that the subjects were exposed via inhalation (Daniel et al. 2001). The

results showed that exposure to HCHs, PCBs or HCB were associated with weak suppressant immune responses (Daniel et al. 2001). The results were in contrast to the results of a previous study which showed that PCP had strong immune-deficient responses (Daniel et al. 1995). In that study, patients who had blood levels of PCP at 10 micrograms/liter (µg/L) or greater had diminished lymphocyte stimulation responses and increased proportions of blood monocytes as well as elevated levels of (interleukin) IL-8 serum levels. The authors concluded that general fatigue and repeating respiratory infections in those subjects may have been the result of immune-suppressant effects that were associated with elevated levels of PCP in blood (Daniel et al. 1995). Therefore, the current study was designed to assess immune-deficiency in subjects which had PCP blood plasma levels less than 10 µg/L, which was in the background range. Subjects who had PCP blood levels greater than 10 µg/L were excluded from this study (Daniel et al. 2001). There was no PCP or other blood contaminants determined for controls. In the current study, twelve of the subjects were studied for clinical symptoms at least twice over 2.5 years, and the results from the last determination were used for clinical evaluation. The clinical analysis indicated that 82% of the patients lacked mental concentration; 80% were rapidly exhausted; 39% experienced bronchitis; 14% experienced sleeplessness; 8% complained of irritation of the throat and nose; and 7% suffered general fatigue (Daniel et al. 2001). In contrast, the investigators reported an inverse dose-response association between blood levels of PCP and the following immunological parameters: total lymphocyte counts; CD4/CD8 ratio; absolute CD3+ counts; CD4+, CD16+, CD25+, DR+, CD8+/56+, and CD19+ cell counts; and plasma levels of interleukin-2 (IL-2), soluble IL-2, IL-6, IL-10, interferon-gamma, tumor necrosis factor-alpha, transforming-growth factor-beta2, soluble IL-1 receptor antagonist, soluble intercellular adhesion molecule-1, and immunoglobulin M-anti-Fab type auto-antibodies. Additionally, there were positive associations between blood PCP levels and the number of impaired stimulation assays per subject; number of circulating CD11b+ monocytes; and plasma levels of neopterin, IL-4, and sIL-6R (Daniel et al. 2001).

3.2.2 Oral Exposure

3.2.2.5 Reproductive Effects

No human studies were located regarding adverse reproductive effects from oral exposure to PCP. However, animal studies have provided increasing evidence to support the hypothesis that some environmental contaminants, such as PCP, interfere with normal reproductive functioning in adulthood. Because guinea pigs display cyclic and luteal similarities to humans, they were selected as a model for the purpose of assessing the effects of PCP's binding capacity to estrogenic receptors in the female reproductive tract. The authors found that PCP can substitute for the female hormone estradiol in

regulating the micro-anatomy of the female reproductive system. They also found that the binding of PCP to estrogenic receptors provides evidence of a molecular basis for an estrogenic toxic effect (Danzo et al. 2002). Earlier, other researchers stated that epidemiological and circumstantial evidence indicated that PCP has similar adverse effects in humans (Sharpe et al. 1993).

3.2.2.6 Developmental Effects

Thyroid hormones (triiodothyronine [T_3] and thyroxine [T_4]) are essential in the regulation of neuronal development, proliferation, cell migration and differentiation, which includes the control over when differentiation starts, and when cell proliferation ends (Bernal, 2009). Researchers studied PCP umbilical cord plasma and thyroid hormones, thyroid-stimulating hormone [TSH], and thyroxine-binding globulin [TBG] concentrations in two remote maritime populations in Nunavik, and Lower North Shore of the Gulf of St. Lawrence Quebec, Canada (Sandau et al. 2002). Thyroid hormones are produced by follicular cells in the thyroid gland. This production is regulated by TSH produced by thyrotoph cells in the anterior pituitary gland. Animal studies have shown that transport of thyroid hormones to the brain and the placenta require binding of T_4 to a transport protein transthyretin (TTR) (Sandau et al. 2002). Halogenated phenolic compounds such as PCP have strong affinities for the TTR receptor, and may interfere with the transport of thyroid hormones in the brain and placenta of newborns by competitive inhibition (Sandau et al. 2002, and Park et al. 2008). For example, blood plasma samples obtained from volunteers from Nunavik, and Lower Shore, Quebec, Canada, had free T_4 concentrations that were reported to be inversely proportional to the chlorinated phenolic compounds [sum of PCPs and sum of HO-PCBs (hydroxylated PCBs)]. These concentrations were not correlated with any PCBs. The authors of the Sandau et al. study suggested that PCP and HO-PCBs may affect the circulating levels of free or unbound thyroid hormones and thus adversely affect the neurodevelopment of infants (Sandau et al. 2002). The authors also suggested the need for more studies to validate whether PCP disrupts hormone homeostatis in the developing fetus, as observed in the present study (Sandau et al. 2002).

3.2.3 Dermal Exposure

McLean et al. (2009) conducted a random questionnaire-based survey of 293 participants who had worked previously from 1970 to 1990 and received primarily dermal exposed to PCP from contact with PCP solutions or PCP-treated timber or were never exposed to PCP. The PCP was used as a pesticide to kill saptain fungi. There were 177 non-exposed and 116 former workers who were previously exposed to PCP. Worker exposure dose re-construction was estimated based on job titles, using 1986-1987 PCP bio-monitoring data, and clinical interviews and examinations with the interviewers not knowing the exposure

status of the person interviewed. Past PCP exposure-intensity was estimated for workers by developing an algorithm which consisted of four job categories. The four job categories were assessed by the proximity to the PCP treatment process, which included (1) dip bath operators; (2) treated timber handlers; (3) sorters, graders, (4) and clerical and administrative truck drivers. The algorithm categories were (1) job title; (2) mixing PCP's solutions; (3) cleaning sludge from the bottom of PCP dip tanks; (4) and backpack spraying of timber or logs with anti-saptain solutions. Exposure categories also included duration of exposure, specifically non-exposed, employed for less than 10 years, and for greater than 10 years (McLean et al. 2009). Since some employees had been exposed to non-PCP substances, such as copper-chrome-arsenate antisaptain solutions, the intensity scoring was based on the proximity of the former worker to the PCP treatment process, i.e., whether the worker mixed PCP solutions, cleaned the PCP dip tanks, was a clerical or administrative worker, or a truck driver with no contact with PCP. A score of 4 was assigned to a former dip bath operator; a score of 3 was assigned to a former worker with less exposure contact such as sorters, maintenance workers, and treated timber handlers; a score of 2 was given to a former dry kiln operator; while a score of 1 was assigned to former clerical and administrative workers and truck drivers. The results of the self-response questionnaires from the 116 previously exposed PCP participants revealed that in the highest PCP exposed group (i.e., 30 participants) there was a statistically significant dose-response trend for tuberculosis (TB), pleurisy, and pneumonia, with a risk four times greater than the non-exposed. When cumulative scores were achieved by combining the exposure score and the duration of employment, the higher PCP exposed group revealed an increased risk of TB, pleurisy, or pneumonia, but a trend analysis found no correlation with increased cumulative exposure score. A trend toward increased frequency of mood changes without cause was of greatest statistical significance. Additionally, a statistically significant dose response relationship was observed between PCP exposure and increased respiratory disease and decreased liver function. The investigators indicated that the results of this study were similar to the results obtained earlier by Walls et al. (1998).

3.2.3.7 Cancer

Demers et al. (2006) designed an epidemiological study that examined the occurrence of cancer from dermal exposure to wood fungicides containing sodium salts of PCP and tetra-chlorophenol (TCP). These investigators used data from a cohort of 26,487 male workers employed for at least one year in 14 sawmills in British Columbia between 1950 and 1995. The sawmills' records were examined for the purpose of characterizing past fungicide formulations and determining the dates that the formulations were used in order to develop individual exposure matrices for PCP and TCP. National registries were used to identify fatal (1950-1995) and incident (1969-1995) cancers, while interviews with older

employees and examination of facility records were used to estimate or predict past dermal exposures (Demers et al. 2006). It was reported that between 1941 and 1965, the workers were exposed to fungicide formulations consisting primarily of PCP. The results showed that there were no statistically significant differences in the specific types and induction rates of cancers observed in this cohort of workers in comparison to British Columbia's general population, but a robust association between the risks of dermal exposure to chlorophenol especially PCP and Non-Hodgkins lymphoma, multiple myeloma, and kidney cancer were observed in this cohort (Demers et al. 2006). The investigators concluded that the associations of the occurrence of these cancers were more robust when exposure was limited to PCP, and the higher relative risks were found in workers with the longest exposure and a 20-year latency period (Demers et al. 2006).

Chang et al. (2003) conducted a skin tumor promoting study in CD-1 female mice to determine if the tumor promoting activity of PCP was due primarily to its metabolite tetra-chlorohydroquinone (TCHQ) or to PCP itself. Animals were randomly divided into eight groups consisting of 10 mice per group. A single dermal application of 100 micrograms (µg) dimethylbenz(a)anthracene (DMBA) in 100 µg/L of acetone was applied to the shaved skin on the back of each mice from each group as a cancer initiator. The next week group one received 100 microliters (µL) of acetone as a negative control, and group two received 12-O-tetra-decacanoylphorbol-13 acetate (TPA) at 2.5 µg/L as a positive control (Chang et al. 2003). Groups three, four and five received dermal applications of 2.5, 50, or 1,000 µg PCP in 100 µl of acetone, respectively. Groups six, seven and eight received dermal applications of 2.5, 50, or 1,000 µg of TCHQ in 100 µl of acetone, respectively. The animals exposed to PCP or TPA received topical applications of these contaminants two times per week for 25 weeks. At the end of the exposure period, 30% of the mice in the 50 µg and 1,000 µg PCP groups had tumors compared to 90% in the positive control exposed to TPA and 0% in the negative control (acetone alone). All of the tumors from each treatment group i.e., PCP, TCHQ and TPA were reported to be benign (papillomas). Statistically significant increases in skin epidermal hyperplasia and proliferating cell nuclear antigen (PCNA) were observed in skin samples from the 1,000 µg PCP exposed group. Proliferating cell nuclear antigen is a biomarker for cell growth and proliferation. Mice treated with 50 µg of PCP, but not with 2.5 or 1,000 µg of PCP revealed higher average weights of liver and spleen organ weight to body weight ratio in comparison to the negative controls that received acetone alone. In contrast, mice treated with 50 µg and 1,000µg of TCHQ revealed significant decreases in organ weights to body weight ratio of the spleen, but not the kidney. Dermal applications of mice with PCP at 50 µg 2 times a week for 25 weeks induced organ enlargement and eventually cancers (lymphoma) in the spleen, liver and kidney in 3 out of 10 mice

(Chang et al. 2003). There were no significant changes in serum tumor necrosis factor-α, or IL-1β after treatment with PCP (Chang et al. 2003).

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.2 Oral Exposure

Pu et al. (2003) examined the blood plasma concentrations of rats exposed to PCP by oral gavage. The authors examined the absolute and relative bio-availabilities of PCP by using freshly spiked and aged soils with different clay and organic carbon content and various measurements of pH. Hydrophobic (lipid soluble) chemicals bind tightly to soils with a high content of organic matter or clay (Pu et al. 2003). This binding reduces the availability and uptake of chemicals after ingestion to animals and humans. These investigators found that un-contaminated soil as well as PCP-contaminated soil matrices reduced the bioavailability of PCP. Four PCP non-contaminated soil samples were obtained from four different wood preserving operations in Indiana and one field-contaminated soil sample containing about 200 milligrams/kilogram (mg/kg) PCP was obtained from a depth of 6 to 9 feet (ft) from the WNC1 site and another soil sample that contained about 200 mg/kg of PCP was collected from the WNC2 site from 8 to10 ft. The non-contaminated soil samples were spiked with 50 mg/kg and 100 mg/kg of PCP to attain a dose of 100 and 200 micrograms/kilogram (µg/kg) body weight, respectively. Different groups of Sprague-Dawley rats 60 to 90 days old were fasted overnight and then received oral gavage (placed directly into the stomach) dosages of un-contaminated soils, PCP-contaminated soils, or corn oil to achieve an exposure dose of 100 µg/kg or 200 µg/kg. Absolute bioavailability referred to the portion of absorbed PCP that reached the circulatory system (blood compartment), whereas, relative bioavailability referred to the comparative bioavailability of various forms of a chemical or from different exposure media (Pu et al., 2003). Equivalent quantities of PCP were administered directly into the circulatory system of a group of rats through intravenous (IV) injections into the tails. The PCP concentrations in plasma samples from IV injected animals were compared to the PCP levels in plasma from animals orally exposed to PCP from contaminated soil sites for determination of absolute bioavailability (Pu et al. 2003). Determination of relative bioavailability was assessed by comparing blood plasma PCP concentrations of soil to PCP in corn oil administered to a group of rats. Blood samples were collected and stored from groups of rats 24 and 36 hours after exposure to 100 µg/kg of PCP soil equivalency dose, and 48 hours after exposure to 200 µg/kg PCP soil equivalency dose. Plasma was separated and stored at -22^{o} C until

analysis. The time course of plasma PCP concentrations was plotted vs. sampling times to determine the levels of PCP. The results showed that the absolute bioavailability of PCP in corn oil was 75% at the 100 µg/kg dose, and 88% at the 200 µg/kg dose. The results also showed significantly decreased PCP bioavailability in all of the 100 µg/kg soil groups in comparison to the bioavailability of PCP from the IV injected group and corn oil group. The absolute bioavailability results of PCP from the 100 µg/kg dosed group indicated that PCP binds tightly to soil and is less available for uptake for both absolute and relative bioavailabilities. Absolute bioavailability ranged from 36% to 65% and the relative bioavailability group ranged from 48% to 82% for the 100 µg/kg group. Similarly, the results for absolute and relative bioavailability groups from the 200 µg/kg dosed group ranged from 46% to 77% and 52% to 82%, respectively (Pu et al. 2003). Therefore, the authors indicated that the results of this study showed that the soil matrices reduced the absolute and relative bioavailabilities of PCP from soil. They also suggested that further studies are needed to elucidate the interaction of various physical and chemical parameters associated with contaminant bioavailability from soil, because gastro-intestinal bioavailability of contaminants from orally ingested soil is complicated, and not very well understood (Pu et al. 2003).

3.4.1.3 Dermal Exposure

Dermal exposure of children to environmental toxicants is of particular importance to human health risk assessors. Human health risk assessors are also particularly interested in the characterization of the systemic uptake and disposition of environmental toxicants from dermal exposures. Pentachlorophenol is readily absorbed in humans through all routes of exposure, and studies have shown that a significant portion of the general population has PCP in the urine (ATSDR, 2001). Wester et al. (1993) showed with both *in vivo* and *in-vitro* studies that PCP is significantly absorbed through monkey and pig skin, with a wide variation of distribution and persistence in the pig (Qiao and Riviere, 2002). Qiao and Riviere (2002) used three porcine skin absorption models to investigate the penetration and absorption of PCP from dermal exposure. The exposure models were (1) *in-vivo*, (2) *ex-vivo*, (3) and *in-vitro*. In the PCP *in-vivo* model study, six animals were randomly assigned to two groups (i.e., three animals per group). One group received pre-treatment with benzo(a)pyrene (BaP) followed by treatment with PCP (sequential exposure), and the second group received only PCP. In the *in-vivo* porcine model animals were either pretreated or not pretreated with BaP before exposure to PCP. A single topical application of PCP was administered to each of the 3 pigs as PCP (^{14}C PCP, 12 µCi or 300 µg PCP dissolved in 100 µL ethanol) on a 7.5 cm^2 skin surface area resulting in a surface dose of 40 µg/cm^2 for either 11 days (PCP alone) or 17 days (BaP and PCP sequentially). For the first two hours after exposure, plasma samples were collected from the animals dosed with PCP alone at 15 minute intervals. Plasma samples were then

taken at one-hour intervals for the next eight hours. Eleven days after the first exposure, 22% of the absorbed dose of PCP was detected in the skin, fat, and muscle tissue, while 18% of PCP was retained in the inner organs, such as the spleen, heart, and diaphragm. Eleven days after dermal exposure, 80% of the absorbed dose of PCP remained in the pigs (Qiao and Riviere, 2002). The *in-vivo* BaP pre-exposure sequential study showed that BaP accelerated PCP absorption initially, but the total absorption over long periods did not appear to be affected. An estimated 14% of PCP was retained in the local skin, fat and muscle tissue while 28% was retained in the inner organs (e.g., spleen, kidneys, liver). The results of the *in-vivo* study also showed that about 80% of the absorbed PCP was retained 17 days later in the body of animals pre-treated with BaP. Furthermore, the results showed that BaP pre-treatment increased PCP dermal absorption 3 fold in the *in-vitro* model and five times in the *ex-vivo* model (Qiao and Riviere, 2002).

3.4.2 Distribution

3.4.2.2 Oral Exposure

Parks et al. (2008) investigated the placental transfer of PCP in pregnant women living in Slovakia by comparing their PCP maternal blood serum to their cord serum levels. The authors indicated that eastern Slovakia is an area where PCP has been involved in food poisoning incidents in several places (Parks et al. 2008). In this study, PCP was of interest because earlier reports indicated that elevated concentrations of phenolic compounds were present in cord blood, and this measurement provides an assessment of developmental effects on exposure to these compounds (Guvenius et al. 2003). The median concentration of PCP in maternal serum was 0.65 nanograms/gram (ng/g) (wet weight), and the median cord serum level was 0.69 ng/g (Park et al. 2008). The maternal blood serum to cord serum PCP ratio was 0.94 (Parks et al. 2008). Guvenius et al. (2003) studied the relationship between maternal and cord blood plasma and found median PCP concentrations of 2.8 ng/g and 1.9 ng/g, respectively, for a ratio of 1.44. The results of Parks et al. 920080 and Guvenius et al. (2003) and studies suggested that PCP can cross the placental barrier and reach the developing fetus.

3.4.4 Elimination and Excretion

Eleven-days after topical exposure of PCP as [^{14}C]PCP (12 µCi or 300 µg/100 µL ethanol) onto a 7.5 cm^2 skin surface area of pigs, 3.3% and 5.6% of total PCP was excreted in the urine and feces, respectively (Qiao and Riviere 2002).

3.5.2 Mechanisms of Toxicity

PCP exerts its acute toxic effects by un-coupling mitochondrial oxidative phosphorylation (Bader et al. 2007), thereby resulting in enhanced aerobic metabolism and accelerated heat production. Earlier, Weinbach (1965) demonstrated in *in-vitro* rat liver mitochondria exposed to PCP, phosphorylation un-coupled and intracellular transfer of energy-rich phosphate is impeded by interfering with the energy-rich conservation of the inner mitochondrial membrane inhibiting the phosphate-ATP exchange reaction.

3.6 ENDOCRINE DISRUPTION

There is increasing evidence that PCP interferes with the normal embryonic development of the male and female reproductive system. PCP substitutes for estradiol in the micro-anatomy of the female reproductive tract and displays a potential to act as an endocrine-disrupting agent (Danzo, et al. 2002). Since guinea pigs display cyclic and luteal similarities to humans, they were selected as a prototype to investigate the endocrine-disrupting effects of PCP (Danzo et al. 2002). The environmental persistent toxicants selected for this study were non-phenol, PCP and 1,1-dichloro-2,2 bis(p-chlorophenyl) ethylene [p,p' DDE] (Danzo et al. 2002). Sesame oil was added to the different concentrations of PCP solutions and stirred overnight in a fume hood to allow the ether to evaporate. The final concentration of PCP in sesame oil was 200 mg/mL and 250 µg/mL for DES. Diethylstilbestrol is a synthetic estrogen that was used in this experiment as a positive control for its endocrine-disrupting effects. Animals were randomly assigned to different treatment groups, and researchers administered single doses of toxicants subcutaneously at 40 mg/kg of PCP, or 50 µg/kg of DES, for 14 continuous days. The potential of PCP to disrupt the endocrine system was investigated in five guinea pigs with their ovaries intact, and six castrated or ovariectomized (without ovaries) guinea pigs. Ten ovary intact animals and five castrated-oil injected animals without exposure to PCP served as controls. The results were reported as the mean of at least three determinations (separate animals) per group. There were no statistically significant differences in serum progesterone levels from animals treated with the other environmental xenobiotics (Danzo et al. 2002). However, the results of PCP treatment of castrated guinea pigs caused significantly increased serum progesterone levels (1.24 ng/mL or ppb) in comparison to the un-treated castrated control animals (0.53 ng/mL or ppb) Since the ovaries are the primary source of progesterone the increases in progesterone following PCP exposure in ovariectomized guinea pigs is somewhat puzzling. However, since the adrenal cortex is also a source of progesterone, it is possible that the Hypothalamic-Pituitary-Adrenal axis may somehow have been involved in the PCP-induced response in these animals (Danzo et al. 2002).

PCP was found to inhibit estrogenic activity in a yeast two-hybrid assay screening system and a reporter gene assay in MCF-1 cells (Jung et al. 2004). PCP was also shown to directly bind to the estrogen receptor α in an estrogen receptor competitive binding assay. The investigators concluded that PCP inhibits estrogen activity by competitive binding with 17β-estradiol to the estrogen receptor (Jung et al. 2004). Similarly, *in-vitro* exposure of the uterine cytosol from ovariectomized guinea pigs to PCP resulted in a 40% inhibition of estradiol binding to the estrogenic receptor (Danzo et al. 2002). In contrast, androgen receptor antagonistic effect or agonistic effect was not detected in an androgen receptor-mediated reporter gene assay system using African monkey kidney CV-1 cell line (Sun et al. 2006).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Mice that were given green tea in their drinking water two weeks prior to receiving PCP in their diet for 23 weeks revealed significant reductions in toxic effects on the liver. The results indicated that green tea prevented an increase in 8-oxodeoxyguanosine levels in liver DNA and this prevention may have exerted an inhibitory effect on PCP promotion of lesions in the liver and bile tissue (Umemura et al. 2003). These findings indicated that regular consumption of green tea may reduce the risk of cancer development posed by similar environmental chemicals. Protective effects were observed on the liver and bile tissue of mice given green tea simultaneously or prior to PCP administration (Unemura et al. 2003).

4. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

No updated data.

6. POTENTIAL FOR HUMAN EXPOSURE

6.3 ENVIRONMENTAL FATE

6.3.2 Transformation and Degradation

6.3.2.2 Water

Chi and Huang (2004) found differences in the photodegradation rates of PCP between the surface microlayer and subsurface water. The difference in the first-order rate constants under natural sunlight was correlated with the dissolved organic carbon enrichment in the surface microlayer. The photodegradation rate decreased with increasing salinity and increased with increasing pH.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

In a study designed to evaluate the potential exposure of pre-school children to environmental PCP, Wilson et al. (2007) measured the levels of PCP in the children's homes and daycare centers in North Carolina and Ohio (Wilson et al. 2007). The 257 children ranged from 1.5 years to 5 years old. For more than a two day period each child's home, daycare center, indoor air, outdoor air, house dust, soils, food, beverages, hand surfaces, and urine were sampled for PCP. Inhalation was presumed to be the predominant route of PCP exposure. PCP was detected in greater than 50% of indoor air, outdoor air, and dust samples. PCP was detected in less than 12% of solid food samples obtained from North Carolina, and in less than 21% of solid food samples obtained from Ohio. The 50^{th} percentile indoor air concentrations of PCP were 1.50 nanograms/cubic meter (ng/m^3) in North Carolina homes, and 2.14 ng/m^3 in Ohio homes. The 50^{th} percentile indoor air concentrations of PCP for daycare centers studied in North Carolina and Ohio were 1.16 ng/m^3 and 1.32 ng/m^3, respectively. The 50^{th} percentile PCP air concentrations for outdoor air samples obtained from near North Carolina and Ohio homes were 0.91 ng/m^3 and 0.43 ng/m^3, respectively. The 50^{th} percentile PCP concentrations in outdoor air samples from near the selected North Carolina and Ohio daycare centers were 0.77 ng/m^3 and 0.22 ng/m^3, respectively (Wilson, et al. 2007). Thus, the children were exposed to higher levels of airborne PCP in and around their homes than the levels to which they were exposed in their daycare centers (Wilson et al. 2007).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Pentachlorophenol was measured in urine samples collected for the Fourth National Report on Human Exposures to Environmental Chemicals (CDC 2009). The levels are presented in Table 6-1. Geometric mean levels were not calculated because the proportions of results below the limit of detection were too high to provide a valid result.

Table 6-1 Urinary Pentachlorophenol

Also a Metabolite of Several Organochlorine Insecticides

Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. population from the National Health and Nutrition Examination Survey.

	Survey years	mean (95% conf. interval)	(95% confidence interval) 50th	75th	90th	95th	Sample size
Total	99-00	*	**.350** (.350-.350)	**.350** (.350-.350)	**.390** (.350-.960)	**1.30** (.500-2.10)	1994
	01-02	*	**< LOD**	**< LOD**	**1.23** (.590-1.76)	**1.94** (1.58-2.53)	2528
Age group							
6-11 years	99-00	*	**.350** (.350-.350)	**.350** (.350-.350)	**.770** (.350-1.51)	**1.65** (.990-2.00)	482
	01-02	*	**< LOD**	**< LOD**	**1.37** (.890-1.70)	**2.10** (1.58-2.75)	577
12-19 years	99-00	*	**.350** (.350-.350)	**.350** (.350-.350)	**.660** (.350-2.60)	**2.00** (.510-5.90)	681
	01-02	*	**< LOD**	**< LOD**	**1.48** (.850-2.30)	**2.30** (1.47-5.04)	826
20-59 years	99-00	*	**.350** (.350-.350)	**.350** (.350-.350)	**.350** (.350-.650)	**1.10** (.350-2.00)	831
	01-02	*	**< LOD**	**< LOD**	**1.01** (<LOD-1.76)	**1.90** (1.45-2.53)	1125
Gender							
Males	99-00	*	**.350** (.350-.350)	**.350** (.350-.350)	**.630** (.350-1.30)	**1.40** (.480-2.60)	973
	01-02	*	**< LOD**	**< LOD**	**1.32** (.680-1.80)	**1.94** (1.47-3.09)	1190
Females	99-00	*	**.350** (.350-.350)	**.350** (.350-.350)	**.350** (.350-.530)	**.890** (.350-2.00)	1021
	01-02	*	**< LOD**	**< LOD**	**1.10** (<LOD-1.78)	**1.98** (1.54-2.42)	1338
Race/ethnicity							
Mexican Americans	99-00	*	**.350** (.350-.350)	**.350** (.350-.350)	**.350** (.350-.350)	**.650** (.350-1.90)	696
	01-02	*	**< LOD**	**< LOD**	**.990** (<LOD-2.37)	**1.62** (.510-3.64)	680
Non-Hispanic blacks	99-00	*	**.350** (.350-.350)	**.350** (.350-.350)	**.980** (.350-2.50)	**1.65** (.860-2.70)	521
	01-02	*	**< LOD**	**< LOD**	**1.73** (1.33-2.33)	**2.83** (2.08-3.67)	696
Non-Hispanic whites	99-00	*	**.350** (.350-.350)	**.350** (.350-.350)	**.390** (.350-1.10)	**1.30** (.350-2.30)	603
	01-02	*	**< LOD**	**< LOD**	**1.18** (<LOD-1.76)	**1.91** (1.48-2.42)	951

Limit of detection (LOD) for Survey years 99-00 and 01-02 was 0.25 and 0.5, respectively.
< LOD means less than the limit of detection, which may vary by year and by individual sample.* Not calculated: proportion of results below limit of detection was too high to provide a valid result.

Table 6-1 (continued) Urinary Pentachlorophenol (creatinine corrected)

Also a Metabolite of Several Organochlorine Insecticides

Geometric mean and selected percentiles of urine concentrations (in µg/g of creatinine) for the U.S. population from the National Health and Nutrition Examination Survey.

	Survey years	Mean (95% conf. interval)	(95% confidence interval) 50th	75th	90th	95th	Sample size
Total	99-00	*	**.300** (.290-.320)	**.570** (.500-.650)	**1.16** (.950-1.35)	**1.67** (1.35-2.11)	1994
	01-02	*	**< LOD**	**< LOD**	**1.52** (1.25-1.75)	**2.26** (1.67-3.09)	2527
Age group							
6-11 years	99-00	*	**.370** (.340-.420)	**.650** (.580-.780)	**.990** (.900-1.30)	**1.83** (1.10-2.95)	482
	01-02	*	**< LOD**	**< LOD**	**1.84** (1.29-3.18)	**3.18** (1.84-4.52)	577
12-19 years	99-00	*	**.250** (.220-.290)	**.400** (.330-.490)	**.760** (.500-1.40)	**1.57** (.700-2.51)	681
	01-02	*	**< LOD**	**< LOD**	**1.21** (.910-1.56)	**1.82** (1.25-2.82)	825
20-59 years	99-00	*	**.300** (.270-.320)	**.610** (.510-.730)	**1.25** (1.00-1.40)	**1.67** (1.30-2.19)	831
	01-02	*	**< LOD**	**< LOD**	**1.52** (<LOD-1.75)	**2.19** (1.67-2.99)	1125
Gender							
Males	99-00	*	**.260** (.240-.280)	**.470** (.380-.560)	**.920** (.780-1.25)	**1.67** (1.16-1.84)	973
	01-02	*	**< LOD**	**< LOD**	**1.13** (.950-1.40)	**1.73** (1.25-2.92)	1190
Females	99-00	*	**.360** (.310-.430)	**.650** (.560-.830)	**1.26** (1.09-1.35)	**1.67** (1.35-2.19)	1021
	01-02	*	**< LOD**	**< LOD**	**1.75** (<LOD-2.06)	**2.69** (1.94-3.55)	1337
Race/ethnicity							
Mexican Americans	99-00	*	**.300** (.270-.320)	**.500** (.430-.560)	**1.06** (.710-1.40)	**1.57** (1.21-2.00)	696
	01-02	*	**< LOD**	**< LOD**	**1.09** (<LOD-2.36)	**1.94** (1.06-3.55)	680
Non-Hispanic blacks	99-00	*	**.250** (.220-.310)	**.440** (.360-.590)	**.850** (.590-1.30)	**1.34** (.950-1.90)	521
	01-02	*	**< LOD**	**< LOD**	**1.30** (.800-1.78)	**1.94** (1.48-2.79)	695
Non-Hispanic whites	99-00	*	**.320** (.290-.350)	**.630** (.510-.800)	**1.25** (1.00-1.40)	**1.67** (1.40-2.19)	603
	01-02	*	**< LOD**	**< LOD**	**1.52** (<LOD-1.78)	**2.10** (1.67-3.08)	951

< LOD means less than the limit of detection for the urine levels not corrected for creatinine.
* Not calculated: proportion of results below limit of detection was too high to provide a valid result.

Pentachlorophenol levels were measured in urine samples from pregnant women (n=361), as part of a multi-ethnic study conducted in New York City (Berkowitz et al. 2003). The 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentile concentrations were 1.1, 2.4, 7.3, 28.4, and 76.0 μg/g creatinine, respectively.

Bader et al. (2007) conducted a study in Germany and analyzed PCP in post-shift urine samples of 189 painters and 148 bricklayers one to four years after the use of PCP was banned. The results revealed a median PCP urinary level of 2.4 μg/g creatinine in the painters, which was significantly higher than the median PCP level of 1.8 μg/g creatinine detected in urine samples from the bricklayers. The range of PCP detected in urine samples from the painters was less than 0.2 to 52 μg/g creatinine, while the range of PCP detected in urinary samples from the bricklayers was less than 0.2 to 25 μg/g creatinine (Bader et al. 2007). Continued exposure of painters to residual PCP from contaminated wood surfaces may have accounted for the elevated PCP levels observed in the painters in comparison to the bricklayers in this study (Bader et al. 2007).

6.6 EXPOSURES OF CHILDREN

Breast milk from lactating mothers is a primary food for nursing infants (Hong et al. 2005). Furthermore, it has been suggested that breast milk from lactating mothers is also a reliable predictor of exposure to environmental toxicants (Hong et al. 2005). Heudorf et al. (2003) examined German children and adolescents from an urban area who volunteered their blood plasma for PCP analysis. At the time, in Germany, PCP was no longer used in agriculture for protection of crops. Three age groups of volunteers were studied 0 to 6, 6 to 12, and 12 to 18 years. The median plasma PCP levels and (95^{th} percentiles) were 2.48 (17.32), 2.69 (5.85) and 2.08 (8.40), respectively. The authors suggested that the PCP plasma levels might be used as a preliminary background level of exposure in Germany, because representative data of this type for children are currently not available (Heudorf et al. 2003).

Prenatal and postnatal exposures to PCP were investigated in the developing offspring of 15 Swedish women (Guvenius et al. 2003). The results of this study showed that the median level of PCP in breast milk samples from the women was 20 picograms/gram (pg/g) or parts per trillion (ppt) (Guvenius et al. 2003). The breast milk concentrations of PCP ranged from10 pg/g to 570 pg/g. The results indicated that breast milk levels of PCP were lower than the maternal blood plasma levels (Guvenius et al. 2003). The results also indicated that the fetus is probably continuously exposed to PCP throughout development, and additional studies are necessary to ascertain the entire exposure situation throughout development (Guvenius et al. 2003). In another study, Hong et al. (2005) examined the breast milk of 11 Chinese

women. They found that the median PCP level was 3.63 ng/g (ppb), which was much higher than the levels reported by Guvenius et al. (2003).

Potential exposures to PCP and other pesticides from multiple environmental and personal media were examined in a study of 257 children selected randomly from households and daycare centers from selected counties in North Carolina and Ohio. The results suggested that the potential for children's exposures to PCP is primarily via inhalation, while indirect ingestion may have made a modest contribution. The potential exposure dose of PCP from inhalation exposure for these children was estimated to be 12 nanograms/day (ng/d) for North Carolina, and 18 ng/d for Ohio. The potential exposure dose from indirect ingestion for the children was estimated to be 3.4 ng/d North Carolina, and 1.8 ng/d in Ohio. Furthermore, based on an assumption of 50% of chemical absorption in these children, the estimated potential absorbed dose of PCP from inhalation was 0.34 ng/kg/d for North Carolina, and 0.58 ng/kg/d for Ohio (Wilson, et al. 2007). PCP was detected in 89% of the urine samples from the North Carolina children, and in 99% of the urine samples from the Ohio children. The overall arithmetic mean for urinary PCP levels was 0.605 nanograms/milliLiter (ng/mL) for the children who lived in North Carolina, and 1.27 ng/mL for the children who lived in Ohio. The level of PCP excreted in urine by the children in this study over a 48-hour sampling period significantly exceeded the estimated intake based on environmental sampling, a finding that suggested that the children may have been exposed to other compounds that are bio-transformed to PCP (Wilson et al. 2007). However these levels were lower than the 95th percentile values for children reported in the NHANES report (CDC, 2009) and the authors noted that they were much lower than established reference levels (Wilson et al. 2007).

7. ANALYTICAL METHODS

No updated data.

8. REGULATIONS AND ADVISORIES

Table 8-1 Regulations and Guidelines Applicable to Pentachlorophenol

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No	IARC 2009
WHO	Air quality guidelines	No	WHO 2000
	Drinking water quality guidelines	0.009 mg/L[a,b]	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	0.5 mg/m^3 [c]	ACGIH 2009
	TLV-basis (critical effect)	Upper respiratory tract and eye irritation; central nervous system impairment; cardiac impairment	
NIOSH	REL (10-hour TWA)	0.5 mg/m^3 [d]	NIOSH 2010
	IDLH	2.5 mg/m^3	
	Potential occupational carcinogen	No	
	Target organs	Eyes, skin, respiratory system, cardiovascular system, liver, kidneys, central nervous system	
OSHA	PEL (8-hour TWA) for general industry	0.5 mg/m^3 [d]	OSHA 2009 29 CFR 1910.1000, Table Z-1
b. Water			
EPA	Drinking water standards and health advisories		EPA 2006
	1-day health advisory for a 10-kg child	1 mg/L	
	10-day health advisory for a 10-kg child	0.3 mg/L	
	DWEL	1 mg/L	
	Lifetime	No	
	10^{-4} Cancer risk	0.03 mg/L	

Table 8-1 Regulations and Guidelines Applicable to Pentachlorophenol

Agency	Description	Information	Reference
	National primary drinking water standards		EPA 2009
	MCL	0.001 mg/L	
	Potential health effects from long-term exposure above the MCL	Liver or kidney problems; increased cancer risk	
	Common sources of contaminant in drinking water	Discharge from wood-preserving factories	
	Public health goal	Zero	
c. Other			
ACGIH	Carcinogenicity classification	A3[e]	ACGIH 2009
	Biological exposure indices		
	Total PCP in urine (prior to last shift of workweek)	2 mg/g creatinine[f]	
	Free PCP in plasma (end of shift)	5 mg/L[f]	
EPA	Carcinogenicity classification	B2[g]	IRIS 2009
	Oral slope factor	1.2×10^{-1} (mg/kg-day)$^{-1}$	
	Drinking water unit risk	3×10^{-6} (µg/L)$^{-1}$	
	Inhalation unit risk	No	
	RfC	No	
	RfD	3×10^{-2} mg/kg-day	
NTP	Carcinogenicity classification	No	NTP 2005

[a]For substances considered to be carcinogenic, the guideline value is the concentration in drinking-water associated with an upper-bound excess lifetime cancer risk of 10^{-5} (one additional cancer per 100,000 of the population ingesting drinking water containing the substance at the guideline value for 70 years).Concentrations associated with upper-bound estimated excess lifetime cancer risks of 10^{-4} and 10^{-6} can be calculated by multiplying and dividing, respectively, the guideline value by 10.
[b]Provisional guideline value, as there is evidence of a hazard, but the available information on health effects is limited.
[c]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, by contact with vapors, liquids, and solids.
[d]Skin designation: indicates the potential for dermal absorption.
[e]A3: confirmed animal carcinogen with unknown relevance to humans.
[f]Background notation: the determinant may be present in biological specimens collected from subjects who have not been occupationally exposed, at a concentration that could affect interpretation of the result.
[g]B2: probable human carcinogen; based on inadequate human data and sufficient evidence of carcinogenicity in animals; statistically significant increases in the incidences of multiple biologically significant tumor types in one or both sexes of B6C3F1 mice using two different preparations of pentachlorophenol. In addition, a high incidence of two uncommon tumors was observed with both preparations. This classification is supported by mutagenicity data, which provides some indication that pentachlorophenol has clastogenic potential.
ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

9. REFERENCES

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