PENTACHLOROPHENOL
(PCP)

RISK CHARACTERIZATION DOCUMENT

Medical Toxicology and Worker Health and Safety Branches

Department of Pesticide Regulation

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TABLE OF CONTENTS

LIST OF TABLES

List of Tables (continued)

List of Tables (continued)

I. SUMMARY

A. CHEMICAL IDENTIFICATION

Pentachlorophenol (PCP), in common with other chlorophenols, has a broad range of biocidal activity. In particular, PCP has been found to be effective as an algicide, bactericide, fungicide, herbicide, insecticide, and molluscicide (WHO, 1987). The mechanism of pesticidal action in insects, mollusks, algae, and plants appears to be related to the ability of PCP to uncouple oxidative phosphorylation in mitochondria. At higher concentrations, PCP is also capable of disturbing the integrity of the plasma membrane. In bacteria, which lack mitochondria, the toxicity of PCP may be due to its ability to disrupt ion transport at the level of the plasma membrane.. Because toxic and carcinogenic effects of PCP have been reported in animal studies, a risk assessment for potential human health effects of PCP exposure has been conducted.

This Risk Characterization Document (RCD) addresses potential human health risks due to PCP exposure within the State of California. The exposure scenarios considered include occupational exposure during pressure treatment of lumber and logs, residential exposure in PCP-treated log homes, and dietary exposure from potentially contaminated milk products.

B. REGULATORY HISTORY

Pentachlorophenol (PCP) is currently registered for sale in California by a single registrant, Vulcan Materials Company. PCP is used in California for the pressure treatment of logs or lumber by a single facility; this facility has been licensed by the United States Environmental Protection Agency (U.S. EPA) to treat wood with PCP in accord with mandated guidelines for worker protection during plant operations.

Prior to being assigned to Restricted Use status by the U.S. EPA in 1984, PCP and its water-soluble sodium salt, sodium pentachlorophenate, were used much more extensively in the United States. Numerous wood preservative uses that were once routinely employed are now banned at the federal level, including application to logs or lumber utilized in the construction of log homes and to structures housing livestock. Such earlier uses often resulted in considerable human exposure, particularly to unprotected wood-treatment workers, owner-builders and residents of log homes, and heavy consumers of milk, liver, or other products derived from PCP-contaminated livestock.

The U.S. EPA established an oral Reference Dose (RfD) for PCP at 30 ug/kg-day and assigned a weight of evidence classification for carcinogenicity of B_2 (probable human carcinogen).

PCP was listed on January 1, 1990 under Proposition 65 as “known to the State of California to cause cancer.”

C. ENVIRONMENTAL FATE

Photodegradation is the principal means by which PCP is removed from the aquatic environment and from air. PCP is extremely stable in deep or turbid waters which limit sunlight penetration. PCP concentrations in freshwater fish and algae indicate high bioaccumulation potential. In soils, microbial degradation can be a major factor in the removal of PCP. PCP can also be taken-up by the roots of higher plants.

D. TOXICOLOGY

The Risk Characterization Document for PCP provides a comprehensive, critical review of studies pertinent to potential health effects in humans. In addition to the toxicology studies submitted by past and current California registrants, relevant articles in the published literature have been reviewed and included in this document.

1. Toxic Contaminants

Polychlorinated dibenzo-*p*-dioxins (pCDDs), polychlorinated dibenzofurans (pCDFs), and hexachlorobenzene are among the contaminants of technical grade (*i.e.*, commercial) PCP formulations. Investigators attempted to determine if the toxicity seen in the test species was attributable to the PCP itself or one or more of the potential impurities found in the test materials (formulations). In various studies, investigators sought to answer the question by tandem administration of purified and technical grades of PCP. This led to the identification of health effects associated with purified PCP and other health effects dependent upon the contaminants present in technical grade formulations. Interpretation of results was further complicated by the fact that some effects, which may be associated with PCP, are known to independently occur in response to individual contaminants.

PCP sold for wood preservative use today must comply with U.S. EPA rulings which were established between 1984 and 1987. These regulations limited the levels of hexachlorobenzene and specific pCDD contaminants which were considered to pose the greatest potential harm to human health. While in compliance with federal mandate, the product currently registered in California contains measurable amounts of many other contaminants also found in the older technical grade formulations. It is clear that, regardless of whether a given health effect is attributable to PCP or a contaminant, animal studies of the partially purified, older material should be considered relevant to the potential for the currently registered product to produce health effects in humans.

2. Pharmacokinetics

***Absorption*:** PCP is readily absorbed by oral, inhalation, and dermal routes of exposure. The time for peak plasma levels following an oral dose of PCP has been found to be comparable in rodents (1.5-6 hrs) and humans (4 hrs), while in monkeys the duration is at least twice as long (12-24 hrs). The oral absorption efficiency has been found to be greater than 90% in rats, monkeys, and humans. The slow time course of excretion along with the completeness of absorption into the bloodstream are evidence that enterohepatic recirculation plays an important role in the disposition of PCP in all species examined.

Biotransformation: A comparison of urinary excretion profiles indicates that the *in vivo* metabolism of PCP in rodents is quantitatively and possibly qualitatively dissimilar to its metabolism in monkeys and humans. In mice and rats, a substantial, dose-dependent fraction (16-48%) of ingested PCP is excreted in the urine as tetrachloro-1,4-hydroquinone (TeCHQ), a compound known to be genotoxic. Humans and monkeys do not appear to metabolize PCP to TeCHQ, although there has been some controversy surrounding this question. Some recent *in vitro* studies indicated that PCP can be metabolized to TeCHQ in experimental systems containing human cytochrome P 450 enzymes. The potential influence of exposure route on the biotransformation of PCP has not been studied methodically; however, there is no evidence to suggest route-dependence of either rates or pathways.

Distribution: Based on limited human data, the volume of distribution appears to be larger in humans than in rats by a factor of approximately 1.3 to 1.9. Discounting differences in biotransformation, this interspecies difference in the volume of distribution would suggest that PCP might produce greater systemic toxicity per unit dose in humans than in rats. This would be particularly true for acute exposures, in which steady-state plasma PCP levels are not expected to be achieved. *In vitro* studies using rat plasma indicate that binding to plasma proteins is strong enough to influence distribution and metabolism.

Elimination: There is good agreement in the published literature on plasma half-lives of PCP in various experimental animals. Following oral or i.v. administration, mean plasma half-lives of 5-6 hrs in mice, 2-11 hrs in rats, and 72-84 hrs in monkeys have been calculated. Urinary excretion rates are similar to the corresponding plasma distribution rates, with estimated mean half-lives of 13 hrs in rats and 41-92 hrs in monkeys. In rats, excretion by combined urinary and fecal routes has also been measured with an estimated mean half-life of 13-27 hrs. The single human study to examine the rate of decline of PCP in plasma reported a mean half-life of 30 hrs, nearly identical to the urinary excretion mean half-life found in the same study (33 hrs). The other human studies of urinary excretion reported much longer half-lives (128-480 hrs).

3. Acute Toxicity

The acute toxicity of PCP appears to be greatest by the inhalation route. An aerosol of technical grade PCP at a concentration of 2.2 mg/L killed all exposed rats, indicating that the LC_{50} was less than 2.2 mg/L. Technical grade PCP formulations have been tested in a number of acute oral toxicity studies in rats; most LD_{50} values reported were in the 100-400 mg/kg range. Acute dermal toxicity studies of technical grade PCP formulations in rabbits have resulted in dermal LD_{50} values of 885 mg/kg and above. In primary acute irritation studies in rabbits, technical grades of PCP have been found to produce mild dermal irritation, moderate ocular irritation, and irreversible corneal changes.

4. Subchronic Toxicity

Thirty-day and 6-month dietary exposures of mice to purified PCP or various technical grades has produced liver toxicity (centrilobular cytomegaly, karyomegaly, nuclear atypia, degeneration, necrosis) in both sexes; LOELs were as low as 27 mg/kg-day while NOELs ranged from 2.8-4.1 mg/kg-day. The results of these studies indicate that an important component of the liver toxicity is attributable to PCP rather than to any contaminants present in the formulations. By

contrast, hematological changes (altered platelet or reticulocyte counts) developed only upon exposure to product formulations, indicating an association with impurities. The limited data available from dietary exposure of rats to purified PCP for 28 days or 27 weeks indicate that liver toxicity (morphological alterations, centrilobular hepatocellular hypertrophy, necrosis) is induced by PCP in both sexes of this species also. Mild anemia and elevated kidney weights were also found in female rats in response to 28-day dietary exposure to purified PCP at the only dose tested, 53 mg/kg-day. Increased liver weights were observed in rats of both sexes following 90-day dietary exposure to distilled technical grade PCP at 10 mg/kg-day but not 3 mg/kg-day; because histopathological examination was not performed at either of these doses, a true representation of any toxic effects present is unavailable. A 28-day gavage study in female rats designed to examine the effects of purified PCP and technical grade NaPCP on thyroid hormone levels found marked changes in serum levels of both total thyroxine and total triiodothyronine in all treatment groups at the lowest dose tested, 3 mg/kg-day.

5. Chronic Toxicity (Non Cancer)

In a NTP bioassay, a large proportion of both male and female $B6C3F_1$ mice treated with the lowest dose (17-18 mg/kg-day) of either partially purified (Dowicide EC-7) or technical grade PCP developed non-neoplastic liver lesions (including cytomegaly, multifocal proliferation of hematopoietic cells, diffuse chronic inflammation, and acute diffuse necrosis). In animals treated with the lowest dose of the technical grade formulation, hyperplasia of the bile duct was produced in males while hyperplasia of the hematopoietic tissues of the spleen occurred in both males and females. In a rat study, the PCP formulation under test was intermediate in purity between the partially purified and technical grades of PCP tested in the NTP mouse study. Microscopic signs of toxicity in the liver (nodular hyperplasia) and kidney (granular pigmentation of epithelia) appeared in female rats at doses as low as 10 mg/kg-day; the NOEL for these effects was 3 mg/kg-day. In a chronic study in beagle dogs, treatment at the lowest dose (1.5 mg/kg-day) of technical grade PCP produced evidence of liver toxicity, including increased relative liver weight, granular cytoplasmic pigment accumulation, chronic inflammation (lymphocytic aggregations), and increased serum alkaline phosphatase.

6. Genotoxicity and Oncogenicity

The weight of evidence suggests that with or without rat liver microsomes (S9), PCP does not induce gene mutation in bacteria. The results of gene mutation assays of PCP in yeast are largely positive, although the data base contains a number of reports which are incomplete. The yeast gene mutation study of PCP submitted to DPR was judged to be positive both in the presence and absence of S9. PCP has not been shown to be mutagenic in any other eukaryotic system. Evidence for the clastogenicity of PCP is mixed, with the most convincing changes occurring only in the presence of rat liver S9. In a mammalian cell line, PCP was positive or equivocal for production of chromosomal aberrations when S9 was present in the culture medium. In two studies of mice exposed to PCP *in vivo*, the response was equivocal in a coat-color spot test and negative for abnormal sperm morphology. Human lymphocytes exposed to PCP *in vitro* showed no cytogenetic changes. Results were either equivocal or negative in two cytogenetic studies of men exposed occupationally to PCP and/or NaPCP. Attempts to detect DNA binding to PCP have yielded uniformly negative results.

TeCHQ is a primary metabolite of PCP in mice and rats but apparently not in humans; this biotransformation is assumed to occur in the liver. *In vitro* metabolism of PCP by a microsomal fraction of the rat liver (S9) has been shown to result in significant concentrations of TeCHQ. Additionally, recent *in vitro* studies using human cytochrome P450 enzymes indicate that TeCHQ can be slowly formed from PCP. Therefore, the *in vivo* conversion of PCP to TeCHQ in humans may be more quantitatively than qualitatively different from the metabolism in rodents. TeCHQ is clearly mutagenic and clastogenic in mammalian cells *in vitro*. Unlike PCP, TeCHQ covalently binds DNA and produces breaks in single-strand DNA *in vitro*. Although not nearly as widely tested as PCP, the disparity in the genotoxicity of the two chemicals is unambiguous. TeCHQ has yielded definitively positive results in every one of the small number of genotoxicity tests to which it has been subjected.

An oncogenicity study of chronic dietary PCP exposure in rats was performed by Dow Chemical; the results were negative for oncogenicity. However, because of serious limitations in design and outcome, the Dow rat study was considered unacceptable to DPR for determining the oncogenic potential of PCP. Another study of chronic dietary PCP exposure in rats was recently completed by the NTP. There was some evidence of carcinogenic potential in male rats based on the incidence of malignant mesothelioma and squamous cell carcinoma of the nasal area. These findings were only significant in males at the high dose (~60 mg/kg-day); no neoplasia were reported in female animals. A two-year oncogenicity study of dietary exposure to PCP in mice over a dose range of 17-118 mg/kg-day was completed by the NTP in 1989. This mouse study found evidence for the oncogenicity of both partially purified and technical grade PCP. In male mice, the partially purified PCP produced dose-related increases in both benign and malignant liver tumors (adenoma and carcinoma). In female mice, the partially purified PCP produced significant elevation of benign tumors of the liver (adenoma) and adrenal gland (pheochromocytoma) and a malignant blood vessel tumor (hemangiosarcoma).

7. Reproductive and Developmental Toxicity

The single-generation rat reproductive study submitted to DPR was considered unacceptable under FIFRA guidelines due to design limitations. In the absence of an acceptable study, a provisional reproductive NOEL was derived from this study. A reproductive study of oral exposure to a partially purified PCP formulation found reproductive effects (reduced pup survival, reduced neonatal body weight) at 30 mg/kg-day, a dose which also resulted in reduced body weight gain in the dams. At this dose, the newborns appear to have been more severely affected by continuing perinatal exposure *via* lactation than by prenatal exposure. The NOEL for both maternal toxicity and reproductive effects was 3 mg/kg-day. The results are summarized in Table III-F-1. No other reproduction studies using PCP were identified in the open literature. An acceptable FIFRA guideline, two generation reproduction study has been recently completed and submitted to DPR. No empirical NOEL was established for general toxicity; the overall LOEL for this study was the lowest dose tested, 10 mg/kg-day. Reproductive findings were either associated with maternal toxicity, were accompanied by general growth delays in young rats, or were of no evident functional importance; therefore, no adverse reproductive effects were indicated in this study with PCP

Three teratology studies of oral PCP exposure in rats were submitted to DPR. In the most recent rat study, contemporaneous lots of the technical grade PCP were tested in Crl:CD®BR

VAF/Plus® rats, yielding a developmental NOEL of 30 mg/kg-day based on teratogenic effects (gross external and soft-tissue malformations, 14th vertebra, 14th pair of ribs) at 80 mg/kg-day. In an older study, delayed ossification was produced by the lowest dose of purified PCP tested (5 mg/kg-day), while for a technical grade of PCP the developmental NOEL was 5.8 mg/kg-day based on subcutaneous edema and lumbar spurs at 15 mg/kg-day. An FDA study produced a developmental NOEL of 4 mg/kg-day using highly purified PCP based on possible teratogenicity (misshapen centra) at 13 mg/kg-day. . In the single rabbit teratology study reviewed, no developmental toxicity was observed in New Zealand white rabbits exposed by gavage to representative lots of technical grade PCP at doses up to the highest dose tested, 30 mg/kg-day.

8. Other Toxicity Studies

One acute study examined the effect of PCP on thyroid hormones in rats and a subchronic study using Holstein cows looked at various parameters to evaluate endocrine and immune functions In the acute study in rats, circulating levels of the thyroid hormone thyroxine declined following i.p. injection of purified PCP at 1.8 mg/kg; the no-observed-effect level (NOEL) was 0.6 mg/kg. Concurrent with this study, the investigators also performed an identical study of the acute effects of TeCHQ on serum levels of the thyroid hormones TT4 and TT3 in male WAG/RIJ-MBL rats. The results of this study indicate a NOEL of 6.5 mg/kg for acute, i.p. exposure to TeCHQ based on decreased serum TT4 and TT3 in rats at 8.5 mg/kg.

The competitive inhibition of T4-binding sites in serum by PCP and TeCHQ has been examined in an attempt to explain the actions of these compounds on thyroid hormone levels. The results demonstrated a possible mechanism for the action of PCP only. In *ex vivo* experiments, PCP, but not TeCHQ, was a competitive inhibitor of T4 binding to rat sera. Thus, the action of PCP on TT4 levels does not appear to require metabolism to TeCHQ.

In the cow study, technical grade PCP at an oral dose of approximately 16 mg/kg-day produced signs of toxicity in multiple organs (including liver, bile duct, gall bladder, urinary bladder, spleen, tonsils, thyroid, eyelid exocrine glands), decreased thymus weight and red cell count, and stimulated the lymphoproliferative response. Purified PCP at the same dose decreased the thyroid hormones thyroxine and triiodothyronine, depressed thymus weight, and increased liver smooth endoplasmic reticulum; the effect on liver may have been adaptive rather than adverse. No NOEL was identified for either PCP formulation. The results of this study in cows indicate that the multi-organ toxicity of technical grade PCP was largely due to contaminants in the test material. However, the finding that oral exposure to purified PCP decreased thymus weight and depressed thyroid hormones in cows supports the results of alterations in immune function and thyroxine levels in rodents by oral or i.p. exposure to purified PCP.

9. Epidemiological Studies and Case Reports

Several epidemiological studies have tested for the existence of associations between occupational PCP exposure and various cancer or non-cancer endpoints. In addition, there have been a number of published accounts (case reports) of severe health effects requiring medical

attention in persons exposed for days, weeks, or months to high levels of PCP in the workplace or at home. In assessing the epidemiologic and case-report evidence for an association between human exposures to PCP and a given health effect, it is important to consider whether the apparent association was confounded by co-exposure to hexachlorobenzene, pCDDs, and other potentially toxic contaminants. This is of interest because hemotoxicity, immunotoxicity, and hepatotoxicity are reported to be associated with human exposures to commercial PCP, but some similar effects are produced by hexachlorobenzene and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in primates and may also be associated with higher pCDDs. In addition, the published epidemiological studies and case reports reflect exposure to PCP formulations which were more highly contaminated with pCDDs than the products allowed to be sold in the U.S. today.

10. Mechanisms of Toxicity and Carcinogenicity

The hepatotoxicity and immunotoxicity of PCP may be explained by the well-known ability of PCP to uncouple mitochondrial oxidative phosphorylation. There is also some recent limited *in vitro* evidence that lipid peroxidation and a decrease in hepatocyte membrane integrity can result from PCP. A separate mechanism, involving a specific interaction with thyroid hormone receptors, may be responsible for the effects of PCP on thyroid hormone levels.

The mechanism of PCP's carcinogenicity in rodents is unknown. However, the genotoxic metabolite, tetrachloro-1,4-hydroquinone (TeCHQ), has been proposed as a candidate carcinogen. In rodents, a significant proportion (approximately 20-50%) of ingested PCP is metabolized to TeCHQ. In humans and other primates, measurable amounts of TeCHQ are not formed *in vivo* following the ingestion of PCP. However, recent in vitro studies indicate that human P 450 enzymes have the capability to slowly biotransform PCP to TeCHQ. TeCHQ has been demonstrated to be genotoxic in numerous short-term tests (including those for mutagenicity), whereas the data base on the genotoxicity of PCP consists of essentially negative or equivocal results. PCP yielded entirely negative results in bacterial mutagenicity assays and in other *in vitro* genotoxicity tests performed in the absence of rat liver microsomes. For this reason, and because PCP is readily metabolized to TeCHQ in rodents and possibly to a somewhat lesser extent in humans, it has been suggested that formation of TeCHQ may play a role in the carcinogenicity of PCP. However, in the absence of mechanistic data on PCP-induced carcinogenesis in rodents or separate rodent oncogenicity studies using TeCHQ, one cannot exclude the possibility that PCP itself is solely or partially responsible for the observed rodent carcinogenicity. Thus, in the absence of additional information, a health-protective approach to human cancer risk assessment calls for proceeding under the assumption that the rodent carcinogenicity of PCP is relevant to human cancer risk.

F. RISK ASSESSMENT

1. Hazard Identification

Acute: In the absence of a NOEL from a single dose acute study, the critical NOEL was derived from a developmental study. The critical NOEL for technical grade PCP in the definitive

developmental study was 5.8 mg/kg-day based on skeletal and soft tissue anomalies observed at higher doses.

Chronic: An oral study of technical grade PCP in beagle dogs was used as the definitive chronic study for calculating a margin of exposure (MOE).The critical chronic LOEL was established at 1.5 mg/kg-day based on signs of liver toxicity, including increased relative liver weight, granular cytoplasmic pigment accumulation, chronic inflammation (lymphocytic aggregations), and increased serum alkaline phosphatase. No NOEL was identified. In the absence of a NOEL, the LOEL was divided by a default uncertainty factor of 10, yielding an estimated no-effect level (NEL) of 0.15 mg/kg-day.

Oncogenicity: The maximum-likelihood estimate (MLE) of the cancer slope was calculated from the hemangiosarcoma incidence in female mice given partially purified, technical grade PCP in the diet. The MLE based on these data is 1.58×10^{-3} $(mg/kg\text{-}day)^{-1}$ and the 95% upper confidence limit (UCL) on this MLE is 2.45×10^{-3} $(mg/kg\text{-}day)^{-1}$. These values were then multiplied by a factor of 6.7 (*i.e.*, normalization on the basis of body weight to the 3/4 power) in order to account for the relative metabolic efficiency of the two species. The expected human cancer potencies corresponding to the MLE and 95% UCL are 1.06×10^{-2} and 1.64×10^{-2} $(mg/kg\text{-}day)^{-1}$, respectively.

2. Exposure Assessment

Occupational exposure to PCP in California currently occurs in only one wood-treatment plant, where logs and lumber are treated with PCP under pressure in retort chambers; less than 12 workers are involved in this operation. In compliance with federal regulations, each worker must wear protective clothing and, for some tasks, a self-contained breathing apparatus.

Use of PCP to treat wood for building log homes was prohibited by the federal government as of 1984. Residents of existing PCP-treated log homes continue to be exposed, but such exposure would be declining over time.

There is also a potential for indirect dietary exposures to PCP *via* meat and dairy products. The U.S. EPA has not established food tolerances for PCP on raw agricultural commodities, processed foods, or animal products (meat, milk, and eggs). However, food-producing animals may be exposed to PCP through treated or contaminated wood (*e.g.*, wood shavings in bedding, wooden pens, wooden flooring), resulting in PCP-contaminated animal products. Therefore, only a modified dietary exposure analysis for milk products was conducted to evaluate this limited, but potential, route of exposure. This use of PCP on wood products around farm animals has been prohibited by the federal government since the mid-1980s, and recent monitoring of milk samples indicate that PCP levels have been decreasing, indicating that exposure potential has been declining and will continue to decrease.

G. RISK CHARACTERIZATION

1. Non-Cancer Endpoints

Margins of exposure (MOEs) based on the acute NOEL and the estimated chronic NEL were calculated for occupational (pressure-treatment of utility poles), residential (living in a PCP-treated log home), and dietary (consumption of PCP-containing animal products) exposures to PCP. Combined occupational/dietary and residential/dietary scenarios were also considered.

For all acute and chronic occupational, residential, dietary, and combined exposure scenarios, MOEs were greater than 100, a value generally considered to be protective of human health for non-oncogenic effects observed in animal studies.

2. Cancer Risk

Based on a linearized multistage model of tumor risk for malignant vascular tumors in female mice, the 95% upper confidence limit (UCL) lifetime cancer risk due to PCP was predicted to be as high as 7.7 × 10-6 for average exposure of the most highly exposed pressure-treatment workers, 1.5 × 10-6 for average exposure in PCP-treated log homes, 5.7 × 10M7 for average dietary intake, 8.3 × 10-6 for combined occupational and dietary exposure, and 2.1 × 10-6 for combined residential and dietary exposure.

H. RISK APPRAISAL

1. Cancer Risk

There are always uncertainties in the extrapolation of human cancer risk from animal tests conducted at much higher doses, even when the tumor data chosen for the risk assessment fit the model reasonably well at the doses under test. The epidemiological evidence for the carcinogenicity of PCP is equivocal; it does not argue strongly for or against the argument that PCP is a human carcinogen. Case reports of severe hemotoxicity in persons exposed subchronically to relatively high dose levels of PCP lend support to the potential relevance of the malignant vascular tumor endpoint observed in chronically exposed female mice. By far the greatest uncertainty associated with the human cancer risk assessment of PCP concerns the possibility that the genotoxic metabolite TeCHQ is formed in rodents but not humans. Further research into the comparative pharmacokinetics of PCP and the mechanisms of PCP carcinogenicity in rodents would help eliminate uncertainty in the use of a rodent model for human cancer risk assessment.

II. INTRODUCTION

A. CHEMICAL IDENTIFICATION

Pentachlorophenol (PCP), in common with other chlorophenols, has a broad range of biocidal activity. In particular, PCP has been found to be effective as an algicide, bactericide, fungicide, herbicide, insecticide, and molluscicide (WHO, 1987). The mechanism of pesticidal action in insects, mollusks, algae, and plants appears to be related to the ability of PCP to uncouple oxidative phosphorylation in mitochondria. At higher concentrations, PCP is also capable of disturbing the integrity of the plasma membrane. In bacteria, which lack mitochondria, the toxicity of PCP may be due to its ability to disrupt ion transport at the level of the plasma membrane.. Because toxic and carcinogenic effects of PCP have been reported in animal studies, a risk assessment for potential human health effects of PCP exposure has been conducted.

This Risk Characterization Document (RCD) addresses potential human health risks due to PCP exposure within the State of California. The exposure scenarios considered include occupational exposure during pressure treatment of lumber and logs, residential exposure in PCP-treated log homes, and dietary exposure from potentially contaminated milk products.

B. REGULATORY HISTORY

Federal (U.S. EPA): Pesticidal use of PCP is regulated at the federal level under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). PCP was designated a Restricted Use pesticide on July 13, 1984 by the Office of Pesticide Programs (U.S. EPA, 1984). Most uses as an herbicide, antimicrobial agent (*e.g.*, in cooling towers), defoliant, disinfectant, and molluscicide (*e.g.*, in marine paint) were discontinued at that time. It is permitted to use PCP as a biocidal agent on wood (but not on wood to used for log homes or the interiors of buildings), in oil field flood waters, and in pulp and paper mill solutions. The label is required to state the terms of allowed PCP use: that it is for sale and use only by certified pesticide applicators who must wear specific items of protective clothing and take required handling precautions. The label also must state that application to logs for use in the construction of log homes is explicitly prohibited. Existing stocks (bearing a pre-Restricted-Use label) were allowed to be sold until November 10, 1986 (U.S. EPA, 1986).

Pursuant to the requirements of the Safe Drinking Water Act, the U.S. EPA has established the maximum contaminant level (MCL) for PCP at 0.001 mg/L (Federal Register, 1991a). Based upon potential carcinogenicity, the maximum contaminant level goal (MCLG) was set at “zero” mg/L (Federal Register, 1991b).

. The U.S. EPA has established an oral Reference Dose (RfD) for PCP of 30 µg/kg-day (IRIS, 1994).

The U.S. EPA's weight-of-evidence classification of carcinogenicity assigned to PCP is B2 (probable human carcinogen). The U.S. EPA has also established a quantitative estimate of cancer risk from oral exposure to PCP (IRIS, 1994). The cancer slope factor (q_1^*) was calculated

as 1.2 × 10-1 (mg/kg-day)-1, and represents the geometric mean of the cancer slope factors derived separately for each of the two PCP formulations used in the NTP study (NTP, 1989). The results of the NTP study also formed the basis of DPR's cancer risk assessment (discussed in Section IV).

Levels of the most toxic contaminants of PCP and PCP salts are regulated by federal statute. Both hexachlorodibenzo-p-dioxin (HxCDD) and hexachlorobenzene (HCB) are considered by the U.S. EPA to pose potential oncogenic, teratogenic, and fetotoxic risks. As of February 2, 1989, the maximum allowed level of HxCDD is 4 ppm in any batch and the maximum allowed monthly average is 2 ppm. The maximum level for HCB was later specified as 75 ppm (U.S. EPA, 1987). The other contaminant specifically regulated in the earlier ruling was the potent rodent carcinogen 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which was required to be below detection by an acceptable method (U.S. EPA, 1984). The later ruling established that the detection limit for TCDD shall be no higher than 1 ppb (U.S. EPA, 1987).

California: PCP was listed on January 1, 1990 under Proposition 65 as “known to the State of California to cause cancer.”

C. TECHNICAL AND PRODUCT FORMULATIONS

The only formulation of PCP currently manufactured in the United States and registered by the U.S. EPA is Glazd™ Penta, a product of Vulcan Materials Company. Glazd™ Penta is also the only PCP product registered in California. The current label for this commercial grade product indicates that the composition is 86% PCP, 10% other chlorophenols and related impurities, and 4% inert ingredients.

D. USAGE

Collectively, PCP and its sodium salt, sodium pentachlorophenate (Na-PCP), previously constituted one of the most heavily used pesticides in the United States. The net production of the three U.S. manufacturers active in 1980 was 30,600 tons (Jones, 1981), although usage may have declined substantially since PCP came under restricted use regulation in 1984.

Although PCP and Na-PCP have numerous biocidal applications, their primary use is for wood preservation. In California, the only current registered use of PCP is in the commercial treatment of lumber, such as telephone poles. Na-PCP use is minuscule in California in comparison to that of PCP; in 1991, the amount of Na-PCP used was only 0.005% of the 219,028 pounds of PCP applied (DPR, 1993).

E. ILLNESS REPORTS

Residential neighbors of a contaminated wood-treatment site in Oroville, California were exposed to PCP present in well water at levels up to 4 ppm. Residents complained of adverse health effects, including diarrhea and skin disorders, which they attributed to the contamination (U.S. EPA, 1986). *(See also Section IV-K for a review of published case reports.)*

F. PHYSICAL AND CHEMICAL PROPERTIES

Common Names: Pentachlorophenol, PCP

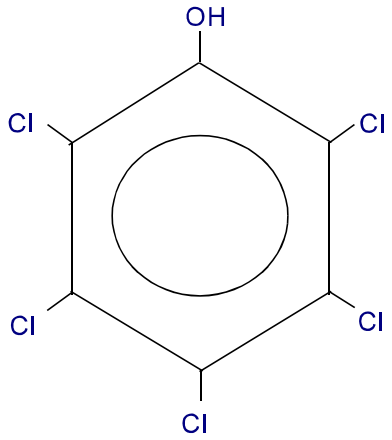
IUPAC Name: Pentachlorophenol

CAS Registry No.: 87-86-5

Molecular Weight: 266.34

Empirical Formula: C_6HCl_5O

Molecular Structure:



Trade Names: Acutox, Chem-Penta; Chem-Tol; Cryptogil; Dowicide 7; Dowicide EC-7; Durotox; EP 30; Fungifen; Fungol; **Glazd Penta;** Grundier Arbezol; Lauxtol; Lauxtol A; Liroprem; Moosuran; NCI-C 54933; NCI-C 55378; NCI-C 56655; DP-2; Pentacon; PentaKil; Pentasol; Penwar; Peratox; Permacide; Permagard; Permasan; Permatox; Priltox; Permite; Santophen; Santophen 20; Sinituho; Term-I-Trol; Thompson's Wood Fix; Weedone; Witophen P (WHO, 1987).

Physical State: Needlelike crystals (Budavari *et al.*, 1989). So-called "pure" PCP (purity approximately 98%) has been described as cream-colored, while technical grade PCP is pale brown in color (NTP, 1989).

Melting Point: 190-191°C (Budavari *et al.*, 1989).

Boiling Point: Decomposes at 309-310°C (Budavari *et al.*, 1989).

Solubility: Almost insoluble in water (8 mg in 100 ml). Freely soluble in alcohol or ether. Soluble in benzene. Slightly soluble in cold petroleum ether (Budavari *et al.*, 1989).

Vapor Pressure: 1.5×10^{-5} mm Hg at 20bC (WHO, 1987).

Partition Coeff.: *n*-octanol/water, log P = 4.84 (pH 1.2), 3.56 (pH 6.5), 3.32 (pH 7.2), 3.86 (pH 13.5) (WHO, 1987).

Density: 1.978 at 22°C, referred to water at 4°C (WHO, 1987).

Odor: Pungent odor when heated. Odor threshold: 1.6 mg/L (WHO, 1987).

G. ENVIRONMENTAL FATE

Most of the information reported in this section was derived from literature reviews by Crosby (1981) and Choudhury *et al.* (1986); the original literature citations can be found therein.

1. Hydrolysis and Reactivity

Electron withdrawal by the ring chlorines causes the hydroxyl group to ionize surprisingly readily (pKa = 4.7 at 25°C in water). The percentage ionization increases with increasing alkalinity; at pH 6.7 (typical of some fresh water systems), PCP is 99% ionized. In seawater (pH 8.1), PCP is more than 99.9% ionized (Crosby, 1981). Ionization, by reducing the lipophilicity of PCP, is expected to result in reduced uptake by aquatic organisms.

The ring chlorines of PCP are resistant to displacement by hydroxide ions or other nucleophiles (Crosby, 1981). Thus, in the absence of biochemical catalysis or photolysis, PCP in solution is quite stable.

2. Photolysis

PCP is readily degraded in sunlight under mild conditions. The long-wave absorption maxima lie near 300 nm below pH 5. The UV component of sunlight can decompose PCP irrespective of whether it is surface-adsorbed, in a thin film, or in solution.

PCP dissolved in water undergoes photochemical reduction to tri- and tetrachlorophenols. In dilute aqueous solutions exposed to sunlight, the ring chlorines of PCP and its salts are replaced by hydroxyl groups. The resulting tetrachlorohydroquinone (TeCHQ), tetrachlorocatechol, and tetrachlororesorcinol are readily oxidized in air to quinones such as chloranil which are subsequently dechlorinated. Under most circumstances, the quinone solution is rapidly degraded to dichloromaleic acid, which is converted to small organic fragments, CO_2, and HCl within a few days (Crosby, 1981).

Exposure of a 100 mg/L solution of PCP in pH 7.3 buffer to outdoor, July sunlight resulted in a photodegradation half-life of 48 hours, with levels dropping to below detection within 10 days. However, field measurements indicated much less extensive photodegradation than in the laboratory experiment. In surface ponds and agricultural drainage water in the vicinity of a wood-treatment plant, PCP, 2,3,4,6-TeCP, and a dichlorophenol were found but, contrary to expectation, dichloromaleic acid was not (Wong and Crosby, 1981). Some of the discrepancy may lie in the dependence of the efficiency of photolysis on water depth. It is possible that photolysis may be the dominant removal mechanism in shallow bodies of water but only a secondary or minor removal mechanism in deeper waters (Choudhury *et al.*, 1986).

Over time, some of the PCP in treated wood migrates to the surface where sunlight can convert it to OCDD, which is subsequently photodegraded to HpCDD and HxCDD (Crosby, 1981).

3. Microbial Degradation

PCP is metabolized by a variety of microorganisms in soil and other media, although degradation of PCP has not been found to occur in all mixed populations grown from soil suspensions or in all activated sludge. Prior exposure to PCP clearly results in selection or activation of PCP-degrading strains. A *Pseudomonas* isolated from soil was able to liberate all 5 chlorine atoms. Several fungal species have been found to deplete PCP from wood blocks (Crosby, 1981).

The rate of decomposition of PCP in laboratory soils increases with increasing moisture and organic content. Anaerobic (flooded) conditions also favor degradation. Half-lives on the order of 2-4 weeks have been recorded both in the laboratory and in a paddy soil under favorable conditions for decomposition. However, in one soil containing little organic matter, 100% of PCP was recovered after 2 months. Formation of pentachloroanisole (PCA)[1] is favored by aerobic conditions; isomers of tetrachlorophenol and trichlorophenol are the other primary degradation products in soil under both anaerobic and aerobic conditions (Crosby, 1981).

4. Mobility

a. Air

PCP is relatively volatile even at ambient temperatures. However, volatilization is unimportant as an environmental fate mechanism in comparison to photodegradation or biodegradation (Choudhury *et al.*, 1976). NaPCP is nonvolatile; its odor is due to incomplete hydrolysis in air to form PCP (Crosby, 1981).

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[1]A pharmacokinetics study of single-dose PCA exposure in Beagle dogs and miniature pigs revealed rapid demethylation to PCP in both species (Ikeda and Sapienza, 1995).

b. Soil

In California, contamination of soil with PCP and its pCDD/pCDF contaminants has been a problem in the past. There were approximately 10 wood-treatment facilities operating in the State as recently as 1986; some of these had been in operation during decades when it was not illegal to release effluent directly into drainage ditches or onto open ground. One representative pressure-treatment facility in Selma, California had soil PCP levels ≤4,500 ppm at the surface to 2 feet depth, ≤ 3,100 at 2 to 5 feet, ≤ 600 ppm at 5 to 10 feet, ≤ 41 ppm at 10 to 20 feet, and ≤ 1.2 ppm below 20 feet. Contaminants associated with technical grade PCP were also found in the soil samples (SWRCB, 1988).

c. Water

Three case studies of contaminated wood-treatment sites in California illustrate the ability of PCP to migrate into surrounding ground and surface waters. At Oroville, California, PCP levels as high as 15 ppm were found in ground water 30 feet below the site. Private wells adjacent to and down the gradient from the site had PCP levels up to 4 ppm. A plume of contamination extending at least 2 miles was detected. At Selma, California, PCP concentrations in surface waters in the area of the facility were as high as 2.3 ppm, while levels in ground water were in the ppb range. In Visalia, California, at the site of a PCP dip tank discovered leaking in 1972, PCP levels in the shallow, unconfined layer of the aquifer peaked in 1977 at 44,000 ppm and had dropped to 17 ppm in 1985 (SWRCB, 1988).

5. Bioaccumulation

a. Aquatic Organisms

PCP bioconcentrates in aquatic organisms. Bioconcentration factors (BCFs) of 10^2 to 10^4 have been measured (primarily for fish species) following exposure for 24 hours or longer in various freshwater aquaria or in natural freshwater bodies contaminated with PCP. Although no information was located on bioaccumulation by higher aquatic plants, BCFs measured for some algae are in the range observed for aquatic animals (Choudhury *et al.*, 1986).

b. Terrestrial Plants

PCP applied to plant roots tends to deposit and remain in the roots, while PCP applied to foliage tends to be recovered in the leaves. Once absorbed, limited metabolism may occur. After one week of growth in soil containing PCP, 1% of the absorbed compound was converted to a tetrachlorophenol isomer, 9% was present as unidentified conjugates, and the remainder (90%) was unmetabolized (Crosby, 1981).

H. MECHANISMS OF TOXICITY

It is well known that PCP is an uncoupler of mitochondrial oxidative phosphorylation. If the mitochondria in the tissue of an animal are uncoupled, there may be insufficient ATP generated to sustain normal cellular functions during periods of high metabolic demand (Lehninger, 1971).

The biochemical mechanisms of PCP toxicity were first explored in the 1950s and 1960s through a series of experiments by Weinbach and colleagues. Weinbach (1957) demonstrated that PCP can uncouple oxidative phosphorylation in isolated rat liver mitochondria. The ability of PCP to interfere with oxidative phosphorylation may explain much of the toxicity of PCP in fungi, plants, insects, and other eukaryotic organisms (including humans), all of which are composed of cells containing mitochondria. However, PCP is also toxic to bacteria (prokaryotes), which lack mitochondria. Thus, there exists an additional interaction site, independent of the mitochondrion; the plasma membrane is the strongest candidate for this alternative site of action.

It is clear that PCP can interact directly with the lipid components of cell membranes. PCP has been found to perturb liposomal bilayers (Danner and Resnick, 1980, Buff *et al.*, 1982) and plasma membranes of intact, cultured mammalian cells (Duxbury and Thompson, 1987). Some experiments performed in nerve axons and muscle fibers suggest that PCP interferes with ion conductances across cell membranes in these tissues (Nwoga and Bittar, 1991). These actions may be a nonspecific function of the ability of PCP to partition into the lipid phase (Cascorbi and Forêt, 1991). There is some limited *in vitro* evidence that PCP was moderately cytotoxic to isolated rat hepatocytes based on cellular "leakage" of lactate dehydrogenase (Suzuki, *et al*., 1997). These investigators also reported that lipid peroxidation of the hepatocyte membrane was slightly increased when exposed *in vitro* to PCP. *In vitro* studies of PCP indicate that uncoupling of oxidative phosphorylation is a much more sensitive endpoint than plasma membrane effects. For example, the concentration of PCP required to produce a 50% inhibition of the fibroblast plasma membrane Na^+/K^+-ATPase is 123 µM (Cascorbi and Forêt, 1991), while approximately 20 µM results in maximal uncoupling of rat liver mitochondria (Weinbach and Garbus, 1965) and 5 µM produces more than a two-thirds decrease in the respiratory quotient (*i.e.*, ATP molecules generated per oxygen atom consumed). The greater PCP sensitivity of mitochondrial coupling *in vitro*, along with the fact that PCP's lipophilicity permits free movement into the intracellular space, suggests that a mitochondrial site of action is likely to be more relevant than the plasma membrane to the toxicity of PCP in mammals.

Barstad, *et al*., 1993 investigated the formation of AHA^- heterodimers of PCP in lipid membranes to explain the mechanism of passive transmembrane transfer of protons by PCP, a class-2 uncoupler. They were not able to detect AHA^- oligomers of PCP in the lipid bilayer; however, they were successful in obtaining the $(PCP^- - H^+)$-PCP^- heterodimer in certain solvents. Furthermore, the results showed the that the AHA^- formation constant was dependent upon the polarity and hydrogen bonding ability of the medium.

In rats and mice exposed to purified PCP, the most sensitive sites of toxicity are the immune system, endocrine system (*i.e.*, thyroid hormone regulation) and liver; possible teratogenicity in rats has also been described. Exposure of mice to a technical grade PCP formulation resulted in malignant tumors of the liver and blood vessels and benign tumors at several other sites. Although the actions of PCP on mitochondrial respiration may be readily invoked as a likely basis for the liver toxicity of PCP, it is less clear to what extent this mechanism is responsible for the toxicity of PCP at other sites or its carcinogenicity. Evidence exists for direct interaction between PCP and thyroid hormone receptors: PCP is a competitive inhibitor of the binding of the thyroid hormone thyroxine to rat sera (van Raaij *et al.*. 1991a). In addition, tetrachlorohydroquinone (TeCHQ), a highly reactive and genotoxic compound, is the primary

metabolite of PCP in rodents (see Section A); TeCHQ, rather than PCP, may act *via* completely different mechanisms to cause or contribute to some of the other adverse effects attributed to PCP exposure, including its carcinogenicity in rodents.

III. TOXICOLOGY PROFILE

A. PHARMACOKINETICS

Summary. PCP has been the subject of a substantial number of pharmacokinetics studies in both animals and humans. A lack of inter-study consistency has been reported for the pharmacokinetics of PCP in rats; however, the discrepancy can be shown to be a consequence of comparing dissimilar parameters. The results of the pharmacokinetics studies of PCP in rats are quite consistent when appropriate comparisons are performed. The data gathered here are judged adequate for interspecies comparison of the pharmacokinetics of PCP. The most important conclusion to be drawn from the comparison is that rodents and primates may manifest differential metabolism of PCP. In rodents, a significant proportion of ingested PCP is metabolized to the genotoxic compound tetrachloro-1,4-hydroquinone (TeCHQ). In primates (including humans), the weight of evidence suggests that TeCHQ is not formed during metabolism of PCP *in vivo*, although the capability of human liver isolates to metabolize PCP to TeCHQ *in vitro* has been demonstrated.

1. Absorption

Summary. PCP is readily absorbed by oral, inhalation, and dermal routes of exposure. The time for peak plasma levels to be attained (t_{max}) following an oral dose of PCP has been found to be comparable in rodents (1.5-6 hrs) and humans (4 hrs), while in monkeys the duration is at least twice as long (12-24 hrs). The oral absorption efficiency has been found to be greater than 90% in the dose range 0.1-15 mg/kg in rats, monkeys, and humans. Approximately 4-20% (dependent on dose and species) of a single ingested dose of PCP is excreted in the feces, while essentially all of the remainder appears in the urine. The slow time course of excretion (discussed in Section A.3) along with the completeness of absorption into the bloodstream are evidence that enterohepatic recirculation plays an important role in the disposition of PCP in all species examined.

a. Oral Exposure

(1) Mouse

Reigner *et al.* (1992a) gave PCP in anionic form (presumably NaPCP) by gastric intubation to eight B6C3F_1 mice and measured plasma levels of PCP by chemical analysis in sequential blood samples. Following a 15 mg/kg dose of PCP, peak plasma levels occurred at a mean (± SD) of 1.5 ± 0.5 hrs. The oral absorption (*i.e.*, bioavailability) was calculated as 106 ± 9%. Because absorption was complete, the investigators suggested that the metabolized and unmetabolized PCP found in the feces (6-9% of the oral dose after 48-hour collection) was of biliary origin.

(2) Rat

Braun *et al.* (1977) measured absorption post-sacrifice in six Sprague-Dawley rats (3 of each sex) given ^{14}C-labeled PCP at 10 mg/kg by corn oil gavage. The authors stated that peak plasma levels of radioactivity occurred at 4 to 6 hrs post-exposure in both sexes. The percentage absorption of an oral dose of PCP was not calculated by the investigators, but a lower limit can be gleaned from the data on urinary excretion. At a dose of 10 mg/kg the mean 8-day recovery from urine was 80%, while essentially all of the remainder (19%) was recovered in the feces.

Faster absorption was observed by Reigner *et al.* (1991) in sequential blood samples drawn from five male Sprague-Dawley rats. Following a 2.5 mg/kg gavage dose of a solution of the sodium salt (NaPCP), plasma levels of PCP measured by chemical analysis peaked at a mean of 1.8 hrs. Bioavailability was estimated as 91-94%.

Absorption rates similar to those found by Reigner *et al.* (1991) were reported by Yuan *et al.* (1994), who used chemical analysis to measure plasma PCP levels in male F344 rats following gavage administration of PCP in 0.5% aqueous methylcellulose. Peak plasma PCP levels occurred at 2-4 hrs following doses of 9.5 and 38 mg/kg. Bioavailability was calculated as 100% at the low dose and 86% at the high dose.

(3) Monkey

In six rhesus monkeys (3 per sex) given ^{14}C-labeled PCP at 10 mg/kg by nasogastric intubation, combined radioactive counting and chemical analysis of blood samples revealed peak plasma concentrations of [^{14}C]PCP at 12-24 hrs post-exposure (Braun and Sauerhoff, 1976). Mean 15-day recoveries of radiolabel in excreta were 73% in urine and 17% in feces. Based on the observation that fecal elimination of PCP was slow and steady, the investigators concluded that enterohepatic circulation had been a factor.

(4) Human

Braun *et al.* (1979) used chemical analysis to measure the concentrations of PCP in the plasma and excreta of four, healthy male volunteers. The maximum mean plasma concentration of PCP (0.2 µg/ml) occurred 4 hrs after ingesting a single 0.1 mg/kg dose. Approximately 86% of the total dose was recovered in the urine, while 4% was excreted in the feces during the 7 days following exposure. Because PCP was excreted in the feces throughout the collection period and was not concentrated in the early samples, the investigators concluded that fecal PCP represented absorbed material subsequently secreted into the bile.

b. Inhalation Exposure

(1) Rat

Hoben *et al.* (1976a) assessed the absorption of inhaled PCP in male Sprague-Dawley rats. Forty-four rats of the same approximate weight were exposed nose-only to an aerosol of NaPCP for 20 minutes. The concentration of PCP flowing into the exposure chamber was continuously

monitored, and the dose was calculated as 5.7 mg/kg based on an assumed minute volume of 80 mL. The absorption and elimination of PCP were determined through chemical analysis of blood, urine, and organs of animals sacrificed serially over a 72-hour period. After 24 hours, plasma, urine, and liver PCP accounted for 70-75% of the dose. During the 72-hour period following exposure, approximately 80% of the dose was recovered in the urine as PCP.

(2) Human

Information regarding absorption of PCP by the inhalation route can be inferred from occupational case reports in which dermal exposure was likely to have been a confounding factor. A study in two volunteers with no previous occupational exposure to PCP resulted in an estimate of the amount of PCP absorbed under conditions in which dermal exposure was expected to be insignificant in comparison to inhalation exposure (Casarett *et al.*, 1969). The two subjects were exposed to PCP for 45 minutes in a wood-treatment plant during a brush application of PCP. One was exposed to mean ambient PCP concentrations of 230 mg/m^3. The other, who actively applied PCP to wood surfaces, was exposed to 432 mg/m^3. Calculated exposure doses were 91 µg and 147 µg, respectively, for the two subjects. Based upon chemical analysis of PCP in the 7-day urine, respiratory tract absorption was calculated as 88% for the volunteer exposed to the lower concentration. A less complete accounting of absorption (76%) was available for the other volunteer, as urinary PCP levels were still well above baseline at the end of the 5-day collection period.

c. Dermal Exposure

The Worker Health & Safety Branch's exposure assessment for PCP (WHS, 1995) discussed a study by Wester *et al.* (1993) on dermal absorption of PCP in four female rhesus monkeys. ^{14}C-labeled PCP (98.6% pure) prepared in either acetone or pre-moistened soil was applied topically to an area of shaved abdominal skin. The administered doses of PCP were 0.7 $\mu g/cm^2$ in soil and 0.8 $\mu g/cm^2$ in acetone. The treated sites were covered to retain the soil against the skin; the covers permitted free transfer of water vapor. To correct for incomplete excretion of an absorbed dose, ^{14}C-labeled PCP in propylene glycol was administered i.v. to four other animals. Urine was collected for 14 days. The percentage of the applied dose absorbed percutaneously was determined to be 24 ± 6% of the soil sample and 29 ± 6% of the acetone sample.

2. Biotransformation

Summary. A comparison of urinary excretion profiles indicates that the metabolism of PCP in rodents is qualitatively and quantitatively dissimilar to its metabolism in monkeys and humans. In mice and rats, a substantial, dose-dependent fraction (16-48%) of ingested PCP is excreted in the urine as tetrachloro-1,4-hydroquinone (TeCHQ), a compound known to be genotoxic. Humans and monkeys do not appear to metabolize PCP to TeCHQ, although there has been some controversy surrounding this question. Some recent *in vitro* studies indicated that PCP can be metabolized to TeCHQ in experimental systems containing human cytochrome P 450 enzymes. The potential influence of exposure route on the biotransformation of PCP has not been studied methodically; however, there is no evidence to suggest route-dependence of either rates or

pathways. Experimentally observed urinary excretion profiles of PCP and TeCHQ following single-dose administration of PCP are summarized in Table III-A-1.

Methodological issues. Exposure of mammals to PCP results in urinary excretion of free[2] and conjugated PCP and in some species, free and conjugated TeCHQ; the conjugated species have been identified as glucuronides and sulfates. All studies of PCP metabolism have reported some effort to hydrolyze the conjugates in question in order to quantify the various chemical species present. However, in the earlier studies, the methods of hydrolysis employed may have been inadequate. The work of Ahlborg *et al.* (1978) and of Edgerton and Moseman (1979) revealed the importance of insuring complete hydrolysis of urinary conjugates; subsequent work by others utilized their methods.

a. Mouse

Jakobson and Yllner (1971) looked for PCP and its metabolic products in the urine of female NMRI mice exposed i.p. to PCP at 7.4-8.2 mg/kg or 15-37 mg/kg. Similar results were obtained for one animal injected subcutaneously. Ahlborg *et al.* (1974) injected NMRI mice (unspecified sex) i.p. with PCP at 10-25 mg/kg. Reigner *et al.* (1992a) quantified the 48-hour urinary excretion of PCP and metabolites following a single gavage dose of PCP at 15 mg/kg in male $B6C3F_1$ mice. Between 80% and 90% of the conjugated species were sulfates (PCP-S and TeCHQ-S) while the remainder were glucuronides (PCP-G and TeCHQ-G). The results of the metabolism studies in the mouse are given in Table III-A-1.

A study by Lin *et al.*, (1997) was conducted to investigate the dosimetry of chlorinated quinones arising from metabolism of pentachlorophenol (PCP) in the livers of male Sprague-Dawley rats and B6C3F1 mice by measuring the cysteinyl protein adducts and estimating the second-order reaction rate constants between the quinones and the proteins. Male B6C3F1 mice (30-36 g) were divided into ten groups of three mice and male Sprague-Dawley rats (320-375 g) (14-20 weeks old) were divided into eight groups of three rats. Nine mice and seven rat groups were given a single dosage of PCP at 20 mg/kg body wt (about 10% of the reported LD_{50}) by gavage. Previous studies demonstrated that metabolism of PCP proceeds primarily through the quinols, tetrachlorohydroquinone (Cl_4HQ) and tetrachlorocatechol (Cl_4CAT), which can then be oxidized to the corresponding quinones [tetrachloro-1,4-benzoquinone (Cl_4-1,4-BQ) and tetrachloro-1,2-benzoquinone (Cl_4-1,2-BQ)] via semiquinone intermediates [i.e., tetrachloro-1,2-benzosemiquinone (Cl_4-1,2-SQ) and tetrachloro-1,4-benzosemiquinone (Cl_4-1,4-SQ)]. Both the quinones and the semiquinones are capable of binding to macromolecules such as liver microsomal proteins, calf thymus DNA, blood proteins, and liver cytosolic and nuclear proteins. Lin *et al.*, (1996) previously demonstrated that Cl_4-1,4-BQ and Cl_4-1,2-SQ were the major producers of liver-protein adducts in Sprague-Dawley rats to which PCP had been administered. This study repeated similar experiments with B6C3F1 mice to determine whether the types and quantities of adducts differed between the two species. The results indicate that Cl_4-1,2-BQ and Cl_4-1,4-BQ were the major producers of liver-protein adducts in B6C3F1 mice to which PCP had been administered. The adducts of Cl_4-1,2-BQ were observed in the livers of mice dosed with

[2]Here,"free" is used to connote unconjugated to glucuronide or sulfate. This use is not meant to reflect protein binding status.

PCP, but not in the livers of rats, suggesting species specificity for production of Cl_4-1,2-BQ. The time course of adduct production in both species indicates that all quinone adducts reached their maximum values earlier in mice (0.5-4 hr) than in rats (8-24 hr), suggesting to more rapid PCP metabolism in the mouse. The estimated tissue doses of the quinones to liver cytosol decreased in the order rat Cl_4-1,4-BQ > mouse Cl_4-1,4-BQ > mouse Cl_4-1,2-BQ and to liver nuclei in the order mouse Cl_4-1,2-BQ > mouse Cl_4-1,4-BQ > rat Cl_4-1,4-BQ. The corresponding doses of Cl_4-1,2-SQ could not be determined because of an inability to estimate the second-order rate constants. After aggregating the estimated contributions of all quinone species, mice had a fourfold greater dose to liver nuclei than rats, whereas rats had a three-fold greater dose to liver cytosol. The increased nuclear dose to mouse liver compared to that of the rat suggests that the mouse is at greater risk to hepatic DNA damage from PCP-derived quinones and that Cl_4-1,2-BQ may play a critical role in PCP carcinogenesis.

b. Rat

Ahlborg *et al.* (1978) analyzed the urinary excretion following i.p. administration of PCP at 10 mg/kg to rats (unspecified sex and strain); results are shown in Table III-A-1. All conjugated species were glucuronides. These investigators also reported that pretreatment of rats with phenobarbital prior to oral PCP administration increased the rate of TeCHQ formation *in vivo* and in isolated liver microsomes. They concluded that the dechlorination of PCP is mediated by microsomal enzymes inducible by phenobarbital.

Braun *et al.* (1977) identified the compounds excreted in urine following a single gavage dose of PCP at 100 mg/kg to male and female Sprague-Dawley rats (Table III-A-1); again, all conjugated species were glucuronides. In rats given a 10 mg/kg dose, both plasma and urine were analyzed. No TeCHQ was detected in the plasma. PCP-G was present in the plasma, although the ratio of PCP-G to PCP was much lower than in the urine. At 12 hrs post-exposure PCP-G represented, on average, 4-6% of the recovered dose in plasma, while after 6 days the percentage had increased to 11-16%.

Engst *et al.* (1976) analyzed the urine of male Wistar rats pooled during the final week of administering PCP at 8 mg/kg-day by gavage for 19 days. The investigators identified PCP, much smaller amounts of 2,3,4,5-tetrachlorophenol (2,3,4,5-TeCP), and still smaller amounts of two other TeCP isomers and 2,3,4-trichlorophenol (TCP). TeCHQ was not reported.

Renner (1989) measured the concentrations of free and conjugated PCP and TeCHQ in the urine of 24 female Sprague-Dawley rats treated by gavage with PCP at 53 mg/kg-day for 28 days. In the 7-day urine samples collected during each week of the treatment period, the excreted PCP was 36-58% unconjugated while the excreted TeCHQ was 10-19% unconjugated. The relative proportions of PCP and TeCHQ were not reported.

Renner and Hopfer (1990) measured urinary metabolites in what seems to have been the same treated animals described by Renner (1989). Apparently, the 7-day urine samples collected during exposure and for 2 weeks post-exposure were combined and analyzed as one lot. Based on their data the investigators suggested that the main degradative pathway for PCP leads via 2,3,5,6-tetrachlorophenol (2,3,5,6-TeCP) to TeCHQ and a minor pathway leads via 2,3,4,6-TeCP

and 2,3,4,5-TeCP to trichlorohydroquinone (TCH). In addition, they reported finding small amounts of the oxidation products of both hydroquinones: trichloro-1,4-benzoquinone and tetrachloro-1,4-benzoquinone.

c. Monkey

In two male and two female rhesus monkeys given ^{14}C-labeled PCP at 10 mg/kg by nasogastric intubation, all radioactivity recovered in the urine occurred as unchanged and unconjugated PCP (Braun and Sauerhoff, 1976). Thus, the pattern of PCP metabolism in rhesus monkeys is unlike rodents in that PCP-c, TeCHQ, and TeCHQ-c are not found in the monkeys' urine following PCP treatment.

d. Human

Braun *et al.* (1979) failed to find TeCHQ in the urine of 4 human male volunteers exposed orally to PCP at a dose of 0.1 mg/kg. The portion of the dose recovered in the 7-day urine consisted entirely of unchanged PCP (86%) and PCP-G (14%).

Uhll *et al.* (1986) found no trace of [^{13}C]-isotopes of TeCHQ, 2,3,4,5-TeCP, or 2,3,4,6-TeCP. In a separate ingestion experiment, Uhl *et al.* (1986) followed the percentage of urinary PCP-G excreted by a subject given 0.31 mg/kg PCP of normal isotopic composition. The percentage of total urinary PCP (free plus conjugated) present as the glucuronide was found to increase from a value of approximately 29% on day one after exposure to 60-65% on day 28, after which the value remained stable throughout the remaining ten days of measurement. This "baseline" level of 60-65% is in agreement with the percentage present as the glucuronide conjugate (range, 61-70%) found by these investigators in the urine of 13 untreated volunteers.

In contrast to the finding of no TeCHQ in the urine of PCP-exposed human volunteers by Uhl *et al.* (1986) and Braun *et al.* (1979), both TeCHQ and PCP were identified (without quantification) in the urine of two occupationally exposed male pesticide applicators by Ahlborg *et al.* (1974). However, these investigators did not obtain complete exposure profiles for the applicators; therefore, one cannot rule out the possibility of co-exposure to another pesticide, such as lindane. Lindane (γ-hexachlorocyclohexane) undergoes hydroxylation followed by aromatization (Gopalaswamy and Aiyar, 1986) to form 2,3,4,6- and 2,3,5,6-TeCP as major metabolites in the rat (Engst *et al.*, 1976), while TeCHQ is the primary metabolite of 2,3,5,6-TeCP administered to rats (Ahlborg and Larsson, 1978). This pathway does not entail formation of PCP. Furthermore, TeCP is a contaminant of technical grade PCP; for example, TeCP was present at 3.8% and 9.4%, respectively, in the two PCP formulations tested in the NTP mouse carcinogenicity bioassay (see Table III-D-1).

Another finding which is in apparent conflict with the *in vivo* observations of no PCP metabolism to TeCHQ is the *in vitro* result of Juhl *et al.* (1985), who found that a microsomal extract (S-9 fraction) from the liver of a 61-year-old woman converted PCP to TeCHQ at a rate comparable to that of a rat liver microsomal extract. Additionally, more recent *in vitro* evidence using human cytochrome P450 3A4 expressed in *Saccharomyces cerevisiae* and a microsomal fraction from the whole yeast cells showed the formation of TeCHQ from hexachlorobenzene, pentachlorobenzene and PCP (Mehmood, *et al*., 1996). These investigators indicated that the

rates of metabolism in all instances were low. Therefore, the apparent *in vivo* differences between rodents and humans to biotransform PCP to TeCHQ may be more quantitative (i.e. rate dependent) than qualitative.

Reigner *et al.* (1992b) suggested that the inability of some investigators to detect TeCHQ in the urine of humans exposed to PCP may reflect the instability of this compound in urine. However, it is not clear why the breakdown product(s) would not then be detected, especially in the [^{13}C]PCP experiment of Uhl *et al.* (1986).

3. Distribution and Elimination

Summary. There is good agreement in the published literature on plasma half-lives of PCP in various experimental animals. Following oral or i.v. administration, mean half-lives of 5-6 hrs in mice, 2-11 hrs in rats, and 72-84 hrs in monkeys have been calculated based on a first-order model representing the major portion of plasma PCP. Urinary excretion rates are similar to the corresponding plasma distribution rates, with estimated mean half-lives of 13 hrs in rats and 41-92 hrs in monkeys. In rats, excretion by combined urinary and fecal routes has also been measured: the major portion of dose is excreted with an estimated mean half-life of 13-27 hrs. The single human study to examine the rate of decline of PCP in plasma reported a mean half-life of 30 hrs, nearly identical to the urinary excretion mean half-life found in the same study (33 hrs). The other human studies of urinary excretion reported much longer half-lives (128-480 hrs). Interindividual variability may account for the nearly 4-fold variation in the upper range, while the difference in ranges between the two studies is unexplained. The kinetics of plasma distribution and excretion kinetics are summarized in Tables III-A-2 and III-A-3.

a. Oral Exposure

(1) Mouse

Reigner *et al.* (1992a) drew sequential tail vein blood samples from B6C3F$_1$ mice following a single gavage or i.v. dose of PCP at 15 mg/kg. The mean (± SD), monophasic, elimination half-lives for PCP (measured by chemical analysis) were 5.8 ± 0.6 hrs for the oral route and 5.2 ± 0.6 hrs for the i.v. route. Urinary excretion accounted for over 90% of the dose removed from the body during the first 48 hrs.

(2) Rat

Braun *et al.* (1977) administered a single gavage dose of ^{14}C-labeled PCP at 10 mg/kg to Sprague-Dawley rats. Plasma radioactivity was measured in animals sacrificed sequentially, 2 of each sex per time point. The decline in plasma ^{14}C was biphasic. DPR estimated half-lives for the rapid (alpha) phase as 6.9 and 11 hrs for males and females, respectively.

Braun *et al.* (1977) also followed the level of radioactivity over time in excreta of Sprague-Dawley rats given a single gavage dose of ^{14}C-labeled PCP at 10 or 100 mg/kg. The mean (± SD) half-life for the rapid, initial phase of the combined urinary and fecal excretion was 17.4 ± 1.7 hrs in males and 13.4 ± 2.3 hrs in females given 10 mg/kg and 12.8 ± 1.1 in males given 100 mg/kg. In

all dose groups, 90% of the dose was excreted in the urine or feces within the first 3 days, indicating that the rapid, initial phase was far more important than the slow phase.

Reigner *et al.* (1991) drew sequential jugular vein blood samples from male Sprague-Dawley rats following a single gavage or i.v. dose of PCP at 2.5 mg/kg. For the oral route, the mean (± SD), monophasic, elimination half-life for PCP (measured chemically) was 7.5 ± 0.4 hrs. For i.v. administration, the half-life for the major portion of the dose was similar (7.1 ± 0.87 hrs), but in addition there was an initial, short-lived, extremely rapid drop (half-life, 0.7 ± 0.5 hrs) which accounted for approximately one-fourth of the decline.

Yuan *et al.* (1994) took orbital blood from male and female F344 rats (3 animals per time point, two time points per animal) following a single i.v. dose of PCP at 5 mg/kg. Plasma PCP (measured by chemical analysis) declined in a biphasic fashion. The investigators estimated that the half-life for the slow phase was 5.6 hrs in the males and 9.5 hrs in the females.

Meerman *et al.* (1983) drew aortal blood from male Wistar rats (2 animals per time point) following a single i.v. dose of PCP at 10.7 mg/kg. Plasma PCP (measured by chemical analysis) declined in two phases. Approximately half the dose was eliminated with a mean rapid-phase half-life of 2.2 hrs, while the slow-phase half-life was 7.2 hrs.

(3) Monkey

Braun and Sauerhoff (1976) administered a single 10 mg/kg dose of [^{14}C]-labeled PCP by nasogastric intubation to three male and three female monkeys. Radioactive counting of ^{14}C was combined with chemical analysis of PCP. The mean half-life in plasma was 72 hrs for males and 84 hrs for females. Excretion from urine had a mean half-life of 41 hrs for males and 92 hrs for females. .

(4) Human

Braun *et al.* (1979) gave single oral doses of PCP at 0.1 mg/kg to four male subjects and measured levels in plasma and urine for 6 days by chemical analysis. Using an open one-compartment model, they calculated a mean (± SD) plasma half-life of 30.2 ± 4.0 hrs. In the urine, approximately one-sixth of the initial PCP dose is excreted as the glucuronide with a half-life of 12.7 ± 5.4 hrs, while the remainder is excreted as unmetabolized PCP with a half-life of 33.1 ± 5.5 hrs.

Table III-A-1. Relative Amounts of Unchanged and Metabolized PCP in Urine Following Single Exposure[a]

Study	Species	Sex	Route	Collection Period	Dose (mg/kg)	Percentage of Urinary Excretion (Mean)			
						PCP	PCP-c	TeCHQ	TeCHQ-c
Jakobson & Yllner, 1971	mouse	F	i.p.	24 hrs	7.4-8.2	54%[b]		44%[b]	
" "	mouse	F	i.p.	24 hrs	15-37	53%	15%	33, 48%[b,c]	
Ahlborg *et al.*, 1974	mouse	n.s.	i.p.	24 hrs	10-25	41%	13%	24%	22%
Reigner *et al.*, 1992a	mouse	M	gav.	48 hrs	15	8%	51%	5%	47%
Ahlborg *et al.*, 1978	rat	n.s.	i.p.	24 hrs	10	60%	9-16%	7%	22%
Braun *et al.*, 1977	rat	M/F	gav.	8 days	100	75%	9%	16%	-
Braun & Sauerhoff, 1976	monkey	M/F	n.g.	7-15 days	10	100%	-	-	-
Braun *et al.*, 1979	human	M	oral	7 days	0.1	86%	14%	-	-
Uhl *et al.*, 1986	human	M	oral	24 hrs[d]	0.31	71%	29%	-	-

[a] *Abbreviations:* PCP-c, PCP conjugate; TeCHQ, tetrachloro-1,4-hydroquinone; TeCHQ-c, TeCHQ-conjugate; n.s., not specified; i.p., intraperitoneal; n.g., nasogastric; gav., gavage.

[b] The percentages of conjugated and unconjugated compound were not reported separately.

[c] Not mean values. Percentages shown are for two individual animals.

[d] Single sample collected 24 hrs after dosing.

In a study performed by Uhl *et al.* (1986), three male volunteers participated in a total of six, single-dose ingestion experiments in which the dosages tested were 0.033-0.31 mg/kg for PCP of normal isotopic composition and 0.016 mg/kg for [^{13}C]PCP. The kinetics of urinary excretion were calculated only for two experiments on one volunteer. This subject ingested PCP of normal isotopic composition at 0.31 mg/kg on one occasion and later, [^{13}C]PCP at 0.016 mg/kg. The results yielded similar half-lives for free PCP in urine: 480 ± 82 hrs and 432 ± 58 hrs, respectively. A half-life in plasma of 384 ± 60 hrs was measured in the ^{13}C experiment. Further experiments indicated possible shorter half-lives which were closer to those seen by Braun *et al.* (1979).

Barbieri *et al.* (1995) used chemical analysis to investigate the urinary excretion of PCP in four workers in Northern Italy (two at a wood-working factory and two at a tannery). Urinary PCP concentrations were from 86 to 470 µg/L in the wood-workers and from 601 to 2,063 µg/L in the tannery workers. PCP levels in morning samples were approximately 2-fold higher than those collected in the evening. The half-life of urinary PCP levels throughout a 4-week holiday period was estimated as 240 hrs.

Young and Haley (1978) developed a pharmacokinetic model based on a case study of intentional PCP ingestion. The patient was a 71-year old male who had ingested an estimated 4-8 ounces of weed killer containing 12% PCP and 1.5% other chlorinated phenols (Haley, 1977). Plasma and urinary PCP levels were measured by chemical analysis. The model was fitted to blood and urine measurements beginning ~2.5 hrs after ingestion. Although the patient was treated with a diuretic during a well-defined portion of his recovery, the observed elimination could be modeled so as to predict the underlying rates of elimination in the absence of the diuretic. The underlying half-life for overall elimination from the body was predicted by this model to be 116 hrs; for urinary elimination alone, the model yielded a half-life of 128 hrs.

4. Volume of Distribution

Based on limited human data, the volume of distribution appears to be larger in humans than in rats by a factor of approximately 1.3 to 1.9. Discounting differences in biotransformation, this interspecies difference in the volume of distribution would suggest that PCP might produce greater systemic toxicity per unit dose in humans than in rats. This would be particularly true for acute exposures, in which steady-state plasma PCP levels are not expected to be achieved. The results of the various studies using rats, monkeys or humans are summarized in Table III-A-4.

5. Plasma Protein Binding.

In plasma isolated from Sprague-Dawley rats, PCP was found to have high- and low-affinity binding constants of approximately 10^6 and 10^4 M^{-1}, respectively, suggesting that binding is strong enough to influence distribution and metabolism (Braun *et al.*, 1977). In an *in vivo* study in the same rat strain, 81% of plasma PCP was bound to protein (Gómez-Catalán *et al.*, 1991) Hoben *et al.* (1976b) reported that the ratio of bound PCP to albumin (mol:mol) was 1.3 for human plasma and 0.86 for plasma from a rat of unspecified strain; they suggested that this difference, which reflects differential binding to non-albumin sites, may contribute to the longer retention time of PCP in human plasma.

Table III-A-2. Half-Lives in Mouse, Rat, Monkey, and Human Plasma Following A Single Dose of PCP[a]

Study	Route	Species	Sex	No.	Dose (mg/kg)	Collection Period	Analytical Method	Half-Life in Plasma (hrs)
Reigner *et al.*, 1992a	oral	mouse	M	6	15	36 hrs	Chem.	5.8[c]
" " "	i.v.	mouse	M	6	15	36 hrs	Chem.	5.2[c]
Braun *et al.*, 1977	oral	rat	M	2[d]	10	6 days	^{14}C	6.9, (24)[b,e]
" " "	oral	rat	F	2[d]	10	6 days	^{14}C	11, (30)[b,e]
Reigner *et al.*, 1991	oral	rat	M	5	2.5	48 hrs	Chem.	7.5[c]
" " "	i.v.	rat	M	5	2.5	48 hrs	Chem.	(0.7), 7.1[e]
" " "	i.v.	rat	M	1	20	96 hrs	Chem.	4.1, (36)
" " "	i.v.	rat	M	1	20	96 hrs	^{14}C	4.5, (45)
Yuan *et al.*, 1994	oral	rat	M	3[d]	9.5	40 hrs	Chem.	8.6[c]
" " "	oral	rat	M	3[d]	38	60 hrs	Chem.	6.3[c]
" " "	i.v.	rat	M	3[d]	5	20 hrs	Chem.	< 3[f], 5.6[e]
" " "	i.v.	rat	F	3[d]	5	20 hrs	Chem.	< 4[f], 9.5[e]
Meerman *et al.*, 1983	i.v.	rat	M	2[d]	10.7	36 hrs	Chem.	2.2, 7.2[e]
Braun & Sauerhoff, 1976	n.g.	monkey	M	3	10	7 days	^{14}C/Chem.	72[c]
" " "	n.g.	monkey	F	3	10	7 days	^{14}C/Chem.	84[c]
Braun *et al.*, 1979	oral	human	M	4	0.1	6 days	Chem.	30[c]

[a] Half-lives given are mean values. *Abbreviations:* n.g., nasogastric; Chem., chemical analysis; ^{14}C, radioactive counts.
[b] Value estimated by DPR using linear extrapolation from data in Figure 2 of the citation.
[c] Monophasic model.
[d] Number of animals sacrificed or sampled per time point.
[e] Biphasic model. Half-lives accounting for only a minor portion of PCP are in parentheses.
[f] Upper limit of initial-phase half-life estimated by DPR from inspection of data in Figure 1 of the citation.

Table III-A-3. Half-Lives in Rat, Monkey, and Human Excreta Following A Single Dose of PCP[a]

Study	Route	Species	No.	Sex	Dose (mg/kg)	Collection Period	Analytical Method	Half-Life in Excreta[b] (hrs)	Half-Life in Urine (hrs)
Braun *et al.*, 1977	oral	rat	3	M	10	9 d	^{14}C	17.4, (40.2)[c]	-
" " "	oral	rat	3	F	10	9 d	^{14}C	13.4, (32.5)[c]	-
" " "	oral	rat	3	M	100	8 d	^{14}C	12.8, (121)[c]	-
" " "	oral	rat	3	F	100	8 d	^{14}C	27.2[d]	-
" " "	oral	rat	3	n.s.	100	8 d	^{14}C	-	13, (31)[c,e]
Braun & Sauerhoff, 1976	n.g.	monkey	3	M	10	7 d	^{14}C/Chem.	-	41[d]
" " "	n.g.	monkey	3	F	10	7 d	^{14}C/Chem.	-	92[d]
Braun *et al.*, 1979	oral	human	4	M	0.1	6 d	Chem.	-	33[d]
Uhl *et al.*, 1986	oral	human	1	M	0.016	53 d	^{13}C	-	432[d]
" " "	oral	human	1	M	0.31	70 d	Chem.	-	480[d]
" " "	oral	human	3	M	0.055-0.15	6-14 d	Chem.	-	@ 144[d,f]
Young & Haley, 1978	oral	human	1	M	A 2,400[g]	7 d	Chem.	116[d]	128[d]

[a] Half-lives given are mean values. *Abbreviations:* n.g., nasogastric; Chem., chemical analysis; ^{14}C, radioactive counts; ^{13}C, isotopic substitution.
[b] Combined urinary and fecal excretion.
[c] Biphasic model. Half-lives accounting for only a minor portion of PCP are in parentheses.
[d] Monophasic model.
[e] Values estimated by DPR using linear extrapolation from data in Figure 4 of the citation. Sex not specified (n.s.)
[f] Estimated from Figure 1 of the citation.
[g] Accidental poisoning case study.

Table III-A-4. Volumes of Distribution for PCP in Mice, Rats, Monkeys, and Humans[a]

Study	Route	Species /Strain	Sex	No.	Dose (mg/kg)	V_d (ml/kg)	V_c (ml/kg)	V_{ss} (ml/kg)	V_β (ml/kg)
Braun *et al.*, 1977	oral	rat/SD	M	3	10	-	136	-	-
" " "	oral	rat/SD	F	3	10	-	127	-	-
Reigner *et al.*, 1991	oral	rat/SD	M	5	2.5	276[b]	-	-	-
" " "	i.v.	rat/SD	M	5	2.5	-	155	251	268
Yuan *et al.*, 1994	oral	rat/F344	M	3[d]	9.5/38	180[c]	-	-	-
" " "	i.v.	rat/F344	M	3[d]	5	-	-	130	-
" " "	i.v.	rat/F344	F	3[d]	5	-	-	200	-
Meerman *et al.*, 1983	i.v.	rat/W	M	2[e]	11	-	192	-	-
Braun *et al.*, 1979	oral	monkey	F	2	0.1[f]	116[f]	-	-	-
Braun *et al.*, 1979	oral	human	M	4	0.1	348	-	-	-

[a] Values represent means. Abbreviations: V_d, volume of distribution in the monophasic model; V_c, volume of distribution in the initial phase of the biphasic model; V_{ss}, volume of distribution in the steady-state phase of the biphasic model; $V\beta$, volume of distribution in the terminal phase of the biphasic model; S, Sprague-Dawley; W, Wistar.

[b] Calculated from V_d/F = 294 mg, with F, the systemic absorption, taken to be the average of the extreme values of the estimated range (0.91-0.97).

[c] The investigators reported this parameter as V_{ss} but apparently calculated it from a monophasic model. Correction for bioavailability was made by the investigators. Value shown is the average of values calculated at the two dose levels.

[d] Three rats per time point; twelve time points.

[e] Two rats per time point; eight time points.

[f] Simulated dose; volume of distribution modeled from experimental data in monkeys given PCP at 10 mg/kg by Braun & Sauerhoff (1976).

B. ACUTE TOXICITY

Summary. The acute toxicity of PCP appears to be greatest for the inhalation route. Exposure of rats to an aerosol of NaPCP at a concentration 0.98 mg/L yielded an inhalation LD_{50} of 12 mg PCP per kg. An aerosol of technical grade PCP at a concentration of 2.2 mg/L killed all exposed rats, indicating that the LC_{50} was less than 2.2 mg/L. Technical grade PCP formulations have been tested in a number of acute oral toxicity studies in rats; most LD_{50} values reported were in the 100-400 mg/kg range. In one rat study of technical grade PCP, effects consistent with cholinergic signs were observed at a sublethal dose of 46 mg/kg (the lowest dose tested). An acute oral toxicity study of purified PCP was performed in mice; the LD_{50} was approximately 130 mg/kg. Acute dermal toxicity studies of technical grade PCP formulations in rabbits have resulted in dermal LD_{50} values of 885 mg/kg and above. In primary acute irritation studies in rabbits, technical grades of PCP have been found to produce mild dermal irritation, moderate ocular irritation, and irreversible corneal changes. Results of acute toxicity studies of PCP by oral, inhalation, dermal, and intraperitoneal routes are presented in Table III-B-1. Results of acute dermal and ocular primary irritation studies are presented in Table III-B-2. Results of acute oral and i.p. toxicity studies of TeCHQ, the major metabolite of PCP, are presented in Table III-B-3.

Table III-B-1. Acute Toxicity of PCP by Oral, Inhalation, Dermal, and Intraperitoneal Routes[a]

PCP	Species	Strain	Sex	Route	LD_{50} (mg/kg)[c]	Observations	Notes[b]
>99%	Mouse	NMRJ	M	Gav.	129 ± 9	-	1
>99%	Mouse	NMRJ	F	Gav.	134 ± 9	-	1
Tech.	Rat	SD	M	Gav.	126	Diarrhea (possible cholinergic sign) at 46 mg/kg (lowest dose tested)	2
Tech.	Rat	SD	F	Gav.	110	"	2
Tech.	Rat	SD	M/F	Gav.	>51	No deaths	3
Tech.	Rat	Albino	M/F	Gav.	>50	No deaths	4
Tech. emulsion	Rat	SW	M	Gav.	400 (0.41 ml/kg)	PCP: 8.6%; PCP LD_{50}: 34 mg/kg	5
Tech. emulsion	Rat	n.s.	n.s.	Gav.	1,400 (1.4 ml/kg)	-	6
Tech. emulsion	Rat	SW	M	Gav.	<623 (<0.5 ml/kg)	5/5 deaths; PCP: 24.7%; PCP LD_{50}: <154 mg/kg	7
NaPCP aerosol	Rat	SD	M	Inh.	12	28-44 min exp.; 0.98 mg/L	8
Tech. aerosol	Rat	SD	M/F	Inh.	>14-20 (nominal)	No deaths; 4 hr exp.; 0.21 mg/L (nominal)	9
Tech. aerosol	Rat	Albino	M	Inh.	n.d.	3/10 deaths; 1 hr exp.; 7.5 mg/L	5
Tech. aerosol	Rat	SD	M/F	Inh.	LC_{50}: <2.2 mg/L (analytical)	1-10/10 deaths; 1-2 hrs exp.; 62 mg/L (nominal); 2.2 mg/L (analytical)	10
Tech. dust	Rat	Albino	M/F	Inh.	n.d.	No deaths; 1 hr exp.; 0.5 mg/L (nominal)	4
Tech. emulsion	Rabbit	Albino	n.s.	Derm.	>200	No deaths	4
Tech. emulsion	Rabbit	NZ	M/F	Derm.	>4,620	No deaths	11
Tech. emulsion	Rabbit	NZ	M/F	Derm.	>201	No deaths	12
Tech. emulsion	Rabbit	Albino	n.s.	Derm.	1,400	-	13

Table III-B-1, cont. Acute Toxicity of PCP by Oral, Inhalation, Dermal, and Intraperitoneal Routes [a]

PCP	Species	Strain	Sex	Route	LD_{50} (mg/kg)[c]	Observations	Notes[b]
Tech. emul	Rabbit	n.s.	n.s.	Derm.	1,400 (1.4 ml/kg)	-	6
Tech. emul	Rabbit	Albino	n.s.	Derm.	885 (0.71 ml/kg)	NaPCP: 24.7%; NaPCP LD_{50}: 219 mg/kg	7
>99%	Mouse	NMRJ	M	I.p.	59 ± 4	-	1
>99%	Mouse	NMRJ	F	I.p.	61 ± 4	-	1

[a] *Abbreviations:* Tech., technical grade; exp., exposure; Gav., gavage; Inh., inhalation; Derm., dermal; I.p., intraperitoneal; n.d., not determined; n.s., not specified.
[b] *Citations:* 1, Renner *et al.*, 1986; 2, WIL Research Laboratories, 1978a; 3, Cannon Laboratories, 1980a; 4, IBR-US, 1974; 5, Biosearch Inc., 1976; 6, Carnegie-Mellon University, 1977; 7, Biosearch Inc., 1973; 8, Hoben *et al.*, 1976c; 9, Cannon Laboratories, 1980b; 10, Cannon Laboratories, 1981; 11, WIL Research Laboratories, 1978b; 12, Cannon Laboratories, 1980c, 1982a, 1982c; 13, Biosearch Inc., 1975, 1976.
[c] Exposure period for dermal LD_{50} determinations was 24 hrs.

Table III-B-2. Acute Dermal and Ocular Irritation Efffects of PCP[a]

PCP	Species	Strain	Sex	Route	Observations	Notes[b]
Tech. emulsion	Rabbit	Albino	n.s.	Derm. abrasion	No irritation	1
Tech. emulsion	Rabbit	NZ	M/F	Derm. abrasion	Mild irritation	2
Tech. emulsion	Rabbit	Albino	M	Derm. abrasion	Mild irritation	3
Tech. emulsion	Rabbit	Albino	n.s.	Eye instil.	Moderate to severe irritation	3
Tech. emulsion	Rabbit	Albino	n.s.	Eye instil.	Moderate irritation	4
Tech. emulsion	Rabbit	NZ	n.s.	Eye instil.	Moderate irritation; reversible corneal opacity	5
Tech. emulsion	Rabbit	NZ	n.s.	Eye instil.	Moderate to severe irritation; irreversible corneal opacity	6

[a] *Abbreviations:* Tech., technical grade; Derm., dermal; n.s., not specified; instil., instillation.
[b] *Citations;* 1, Biosearch Inc., 1975;1978b; 2, Cannon Laboratories, 1980c, 1982a, 1982c; 3, Biosearch Inc., 1971; 4, Biosearch Inc., 1975, 1976; 5, Cannon Laboratories, 1982b; 6, Cannon Laboratories, 1982d.

Table III-B-3. Acute Toxicity of TeCHQ by Oral and Intraperitoneal Routes[a]

TeCHQ	Species	Strain	Sex	Route	LD_{50} (mg/kg)
Pure	Mouse	NMRJ	M	Gav.	368 ± 26
Pure	Mouse	NMRJ	F	Gav.	383 ± 26
Pure	Mouse	NMRJ	M	I.p.	28 ± 2
Pure	Mouse	NMRJ	F	I.p.	30 ± 2

[a] *Abbreviations:* Gav., gavage; Inh., inhalation. I.p., intraperitoneal. Data from Renner *et al.*, 1986.

C. SUBCHRONIC TOXICITY

Summary. Thirty-day and 6-month dietary exposures of mice to purified PCP or various technical grades has produced liver toxicity (centrilobular cytomegaly, karyomegaly, nuclear atypia, degeneration, necrosis) in both sexes; LOELs were as low as 27 mg/kg-day while NOELs (where determined) ranged from 2.8-4.1 mg/kg-day. The results of these studies indicate that an important component of the liver toxicity is attributable to PCP rather than to any contaminants present in the formulations. By contrast, hematological changes (altered platelet or reticulocyte counts) developed only upon exposure to product formulations, indicating an association with impurities. The limited data available from dietary exposure of rats to purified PCP for 28 days or 27 weeks indicate that liver toxicity (morphological alterations, centrilobular hepatocellular hypertrophy, necrosis) is induced by PCP in both sexes of this species also. Mild anemia and elevated kidney weights were also found in female rats in response to 28-day dietary exposure to purified PCP at the only dose tested, 53 mg/kg-day. Increased liver weights were observed in rats of both sexes following 90-day dietary exposure to distilled technical grade PCP at 10 mg/kg-day but not 3 mg/kg-day; because histopathological examination was not performed at either of these doses, a true representation of any toxic effects present is unavailable. A 28-day gavage study in female rats designed to examine the effects of purified PCP and technical grade NaPCP on thyroid hormone levels found marked changes in serum levels of both total thyroxine and total triiodothyronine in all treatment groups at the lowest dose tested, 3 mg/kg-day. The results of studies which supplied data adequate for meaningful evaluation are summarized in Table III-C-6.

1. Mouse

a. Thirty-Day Feeding Study (NTP, 1989)

Prior to conducting a chronic feeding study of the oncogenicity of two PCP formulations in $B6C3F_1$ mice, the National Toxicology Program (NTP) performed a 30-day toxicity study of three PCP formulations administered in feed to the same mouse strain. Results of this study were reported (NTP,1989) and in supplementary material obtained from the NTP.

PCP formulations and doses. The two PCP formulations tested in the 30-day study were subsequently used in the chronic study: technical grade composite (TGC) and a partially purified, technical grade product, Dowicide EC-7 (EC-7). (The source of the TGC is detailed in Section III-D, where the chronic portion of this study is discussed.) The third PCP formulation tested in the 30-day study (analytical grade) was obtained from Aldrich Chemical; this was designated as "pure" by the investigators. Chemical analyses of the important nonphenolic impurities found in TGC, EC-7, and analytical grade (AG) PCP are given in Table III-C-1 (along with that of the additional formulation used in the 6-month study, DP-2). The target test concentrations of the three PCP formulations were 20, 100, 500, 2,500, and 12,500 ppm in feed. The measured concentrations were within the specified tolerance of ± 10% for all formulations except for the 20 and 100 ppm TGC (measured as 14 and 66 ppm, respectively) and the 100 and 12,500 ppm EC-7 (measured as 86 and 11,052 ppm, respectively). Nineteen males per dose group received TGC, EC-7, or AG, 15 females per group received TGC, and 5 females per group received EC-7 or AG. Same-sex, zero-dose control groups for each formulation consisted of 19 males and 11 females per group.

Table III-C-1. Chlorinated Nonphenolic Contaminants of PCP Formulations Tested in the NTP 30-Day and 6-Month Subchronic Toxicity Studies in Mice[a]

PCP Formulation	Contaminant Concentration (ppm)						
	HxCDD	HpCDD	OCDD	PCDF	HxCDF	HpCDF	OCDF
TGC (90% PCP)[b,c]	10.1	296	1,386	1.4	9.9	88	43
EC-7 (91% PCP)[b,c]	0.19	0.53	0.69	n.d.	0.13	0.15	n.d.
DP-2 (91.6% PCP)[c]	0.59	0.28	173	n.d.	13.0	172	320
AG (98.6% PCP)[b,c]	< 1	n.d.	< 1	n.d.	n.d.	n.d.	n.d.

[a] Reproduced from Table 3 of NTP (1989). *Abbreviations:* CDD, chlorodibenzo-*p*-dioxin; CDF, chlorodibenzofuran; P, penta; Hx, hexa; Hp, hepta; O, octa; TGC, technical grade composite; AG, analytical grade; n.d., non-detectible (detection limit not given).

[b] Used in the 30-day study.

[c] Used in the 6-month study.

Dose calculation. Doses were not reported on a body-weight basis. DPR calculated the average body weight for each same-sex group exposed to PCP (BW_g) as the average over the reported mean initial and final body weights. Using the average daily feed consumption for each group (FC_g) reported by the investigators, DPR computed the dose in mg/kg-day as the ratio FC_g/BW_g multiplied by the *measured* concentration of the test compound in ppm (Table III-C-2).

(1) Pre-Sacrifice Observations

Lethality, clinical signs. In all mice receiving the highest concentration (12,500 ppm) of EC-7 or AG, weakness, lethargy, and shallow breathing were observed within 24-48 hours of initial exposure, followed by severe weight loss, convulsions, and death. (Further observations on the 12,500 ppm groups are not presented here.) Similar but less marked effects were observed in the surviving mice (5/19 males, 8/15 females) fed the highest concentration of TGC and in the surviving mice (10/19 males, 4/5 females) exposed to 2,500 ppm EC-7. Deaths in 2 of 19 males occurred with 2,500 ppm AG.

Serum chemistry. In AG-treated animals of both sexes, serum cholesterol was elevated at 500 ppm and above. In the EC-7 groups, serum cholesterol was significantly elevated in females receiving 100-2,500 ppm and males receiving 500-2,500 ppm; in females only there was a dose-related increase in gammaglobulin. In TGC-treated mice, serum cholesterol was significantly elevated at 500-2,500 ppm in females and at 2,500 ppm in males. No other consistent, significant changes in serum chemistry were noted at doses below 2,500 ppm.

(2) Post-Sacrifice Observations

At study termination, histopathologic examinations were performed on 4 or 5 animals per sex in the control groups and the groups receiving 100, 500, or 2,500 ppm of the test compounds (except for females receiving 100 ppm EC-7). The small number of animals in some dose groups diminished the statistical power of the outcome analyses.

Liver, spleen, thymus. TGC at 2,500 ppm produced significant reductions of absolute and relative spleen weight and absolute thymus weight. Liver lesions (centrilobular cytomegaly, karyomegaly, nuclear atypia, degeneration, or necrosis) occurred in 1/5 females receiving 100 ppm AG, all mice of both sexes exposed to TGC or AG at 500 ppm, and 2/5 male mice given 500 ppm EC-7. None of the control group animals displayed these abnormalities. The lesions were more diffuse and severe in the TGC mice and were least apparent in the EC-7 mice. Greater sensitivity of the liver of males to EC-7 and of females to AG was indicated by the pattern of liver porphyrin changes. Dose-related increases in total liver porphyrins occurred in male mice treated with EC-7, AG, or TGC at doses as low as 20 ppm, 100 ppm, or 500 ppm, respectively; in female mice the effect occurred at doses at or above 500 ppm AG or 2,500 ppm TGC.

Hematology. Platelets were significantly elevated following TGC treatment at 20-500 ppm in females and 100-500 ppm in males, but not at higher doses. A dose-related decrease in reticulocytes was observed in all EC-7-treated groups of females. No other marked or consistent treatment-related hematologic changes were noted at doses below 2,500 ppm.

(3) Discussion

From Table III-C-2 it can be seen that males given a diet containing EC-7 at a nominal concentration of 2,500 ppm received a dose that was close to twice the dose given to males in the nominal 2,500 ppm TGC and AG groups. The discrepancy for nominal 2,500 ppm females is similar but not as great. Therefore, wherever 2,500 ppm EC-7 appears more toxic than either of the other two formulations (*e.g.*, in its lethality), the results are deceptive.

Primarily because there were too few animals in several female dose groups, DPR did not find the study to be acceptable for the purpose of indicating effects not observed in other studies. However, the results provide weight of evidence for hepatotoxicity. Furthermore, this study demonstrates that a 30-day exposure is sufficient to bring about initial stages of the more extensive damage to the liver reported in longer-term studies. It has been argued that the liver of the male $B6C3F_1$ mouse is ultra-sensitive to chemical insult and therefore unsuitable as a model for human risk. However, direct and indirect evidence of hepatotoxicity was seen also in females given similar doses. Elevated serum cholesterol occurred in females exposed to 24 mg/kg-day of EC-7 or to 136 mg/kg-day TGC. Serum cholesterol was similarly elevated in females exposed to purified PCP (AG) at a dose of 139 mg/kg-day; these animals also manifested elevated liver porphyrins, an additional indicator of abnormal liver metabolism. Finally, liver lesions, a clearly adverse outcome, occurred in females at doses as low as 27 mg/kg-day AG or 136 mg/kg-day TGC. Males displayed similar sensitivity to the hepatic effects of the three PCP formulations. Based on the liver toxicity observed in animals of both sexes, the LOEL for this study is provisionally determined to be 102, 24, and 27 mg/kg-day for TGC, EC-7, and AG, respectively. This study thus provides strong support for the argument that the hepatotoxicity of PCP is independent of the contaminants found in the formulations; indeed, the results suggest instead that the contaminants may inhibit the hepatotoxicity of PCP.

Table III-C-2. PCP Exposure Doses in the NTP 30-Day Subchronic Toxicity Study in Mice

Group	Nominal Concentration (ppm diet)				
	20	100	500	2,500	12,500
	Exposure Dose (mg/kg-day)[a]				
TGC Females	3.8	18	136	669	3,585
TGC Males	2.8	13	102	552	4,468
EC-7 Females	5.6	24	132	827	3,750[b]
EC-7 Males	4.3	18	97	994	4,507[b]
AG Females	5.8	27	139	631	3,058[b]
AG Males	4.1	24	105	586	2,843[b]

[a] Data from NTP (1989). DPR converted the measured (not nominal) dietary concentrations in ppm to mg/kg-day doses based on mean values of feed consumption and body weight for each dose group.

[b] Due to high mortality, the investigators did not calculate average feed consumption and body weight for these dose groups. DPR calculated the dose in mg/kg-day from the average feed consumption and body weight for the same-sex group receiving 2,500 ppm diet of the same PCP formulation.

b. Six-Month Feed Study (NTP, 1989)

Prior to conducting a chronic feed study of the oncogenicity of two PCP formulations in B6C3F$_1$ mice, the NTP performed a 6-month toxicity study of four PCP formulations administered in feed to the same mouse strain (NTP, 1989). Animals were divided into three subgroups: 10/sex/dose group plus 10/sex/control group in the behavioral/histopathology/clinical (B/H/C) chemistry subgroup, 4 males/dose group plus 10 male controls in the biochemistry subgroup, 5 males/dose group plus 15 male controls in the plaque-forming (immunocompetence) subgroup. An additional 50 control males were used for baseline determination in the plaque-forming test.

PCP formulations and doses. Three of the PCP formulations tested in the 6-month study were similar to those used in the 30-day study discussed above. The fourth PCP formulation tested was DP-2. Selected nonphenolic impurities in DP-2 are listed in Table III-C-1 along with those for the other formulations. The animals were fed diets containing target test concentrations of 200, 600, or 1,800 ppm TGC; 200, 600, or 1,200 ppm EC-7; 200, 600, or 1,200 ppm DP-2; or 200, 500, or 1,500 ppm AG.

Dose calculation. Doses were not reported on a body-weight basis. DPR calculated the dosages in a similar manner as reported for the 30 day study (above); the values are presented in Table III-C-3.

(1) Pre-Sacrifice Observations

Lethality, body weight. All mice (10 male and 10 female) receiving the highest concentration of TGC (1,800 ppm) and 2/10 male mice receiving the highest concentration of DP-2 (1,200 ppm) died prematurely. Surprisingly, there were early deaths at the lower doses but not the intermediate doses. Of groups receiving any of the PCP formulations at a concentration of 200 ppm, 1/10 EC-7 males and 2/10 AG males died before the study end. Final mean body weights of males and females receiving the highest dose of EC-7, DP-2, or AG were depressed 6-13% relative to the controls. Feed consumption in the 200 and 500 ppm male AG groups was enhanced by a factor of approximately two. For this reason, the average amount of PCP ingested by the males over the 24-week measurement period was double that ingested by the females.

Neurobehavioral parameters. Neurobehavioral testing was conducted during exposure weeks 5 and 26. At 26 weeks, TGC at 200 and 600 ppm produced minor motor activity increases in mice of both sexes.

Hematology. A dose-related decrease in lymphocytes (significant in the 600 ppm group) occurred in TGC-treated females; by contrast, TGC-treated males manifested a lesser dose-related *increase*. In females given EC-7, a small, dose-related decrease in RBC hemoglobin concentration and a small, dose-related increase in reticulocyte count were found.

Immune function. Effects on humoral immunity were determined as the plaque-forming cell (PFC) response and the hemagglutination (HA) response of male mice to i.p. injection with sheep RBCs 9 days before the end of the 6-month exposure period. The mean and standard deviations reported by the testing laboratory were given, but the individual animal data were unavailable and had not been reviewed by the NTP investigators. HA titers were reduced in the DP-2 treatment groups, but the

sample sizes were small and the dose-response was weak. The mean PFC count was markedly reduced in a dose-related manner in mice receiving TGC or DP-2; in the 200 ppm dose groups, mean PFCs were 43% and 55% of the respective TGC and DP-2 control values.

Serum chemistry. Serum glutamic-pyruvic transaminase (SGPT) activity was significantly increased in all groups of female mice except for the 200 ppm AG group; for males the elevation was significant at or above 600 ppm in the EC-7, DP-2, and TGC groups and at or above 200 ppm in the AG groups. Serum glutamic-oxaloacetic transaminase (SGOT) activity changes, although erratic, were significantly elevated at the highest dose of TGC, DP-2, and AG in either males or females or both. In male mice, serum gamma-glutamyl transpeptidase (γ-GT) activity was significantly elevated in response to the highest dose of AG and the two highest doses of DP-2. Serum γ-GT activity was not reported for female mice.

(2) Post-Sacrifice Observations

Liver. Absolute liver weights were significantly increased for all groups of dosed females and for all AG or TGC males, all groups of DP-2 males except for the 200 ppm group, and for the highest-dose EC-7 males. Relative liver weights were significantly elevated for all groups of dosed females and some groups of dosed males. Hepatocytomegaly appeared in all animals in every treatment group. Nuclear alterations appeared in all males and in 7/10 to 10/10 females in every treatment group. Hepatocellular degeneration, and necrosis were commonly observed in all treatment groups. The investigators indicated that karyomegaly was also present in all treatment groups, but incidence rates were not reported. The incidence rates for necrosis were 9/10 in all four groups of low-dose males and 6/10, 1/10, 2/10, and 8/10 in females receiving AG, EC-7, DP-2, and TGC, respectively. At the higher doses of each PCP formulation every animal exhibited necrosis of the liver. Liver lesions were less severe in females than in males. None of the control animals manifested liver abnormalities.

Urinary bladder. Granular eosinophilic pigment without inflammation occurred in the epithelia of the urinary bladder in all groups exposed to PCP. The lesions were said to be of minimal severity. Data were not shown.

Spleen. Absolute spleen weights were significantly increased for all groups of dosed males except for the 200 ppm TGC, DP-2, and AG groups. Conversely, absolute spleen weights were significantly *reduced* in 600 ppm DP-2 females and high-dose DP-2, TGC, EC-7 females. Relative spleen weights were significantly increased in males that received 200 ppm EC-7 or at least 500 ppm of the other PCP formulations. In females, relative spleen weights were significantly decreased in 600 ppm and 1,200 ppm DP-2 groups.

Other. Various other compound-related lesions were reported as occurring mainly in animals which died prematurely; these include intrahepatic bile duct hyperplasia and inflammation (primarily in animals receiving TGC), epithelial hyperplasia of the gallbladder, and degenerative changes in the bone marrow, spleen, thymus, and testis. No data were provided in support of these observations.

Table III-C-3. PCP Exposure Doses in the NTP 6-Month Subchronic Toxicity Study in Mice

Group	Nominal Concentration (ppm diet)					
	200	500	600	1,200	1,500	1,800
	Exposure Dose (mg/kg-day)[a]					
TGC Females	63	---	206	---	---	761[b]
TGC Males	43	---	357	---	---	549[b]
EC-7 Females	82	---	207	432	---	---
EC-7 Males	54	---	144	309	---	---
DP-2 Females	59	---	200	408	---	---
DP-2 Males	44	---	126	441	---	---
AG Females	62	168	---	---	522	---
AG Males	116	225	---	---	330	---

[a] Data from NTP (1989). DPR converted the measured (not nominal) dietary concentrations in ppm to mg/kg-day doses based on mean values of feed consumption and body weight for each dose group. The mean feed consumption was taken to be the mean of the averages for weeks 8 and 24 (the only weeks for which data were provided).
[b] Due to high mortality, 24-week data were not available. The estimated dose in mg/kg-day was based on the average feed consumption at 8 weeks and the initial body weight.

(3) Discussion

The results of this study are useful for providing weight-of-evidence support for the results of the subsequent NTP chronic exposure study and for estimating time to effect. Potentially adverse effects occurred with each PCP formulation at the lowest dose tested in females (59-82 mg/kg-day) and males (43-116 mg/kg-day). The most uniformly affected sites were the liver (as indicated by histopathological as well as serum chemistry changes) and urinary bladder, although effects in the latter organ were of minimal severity. Technical grades of PCP at doses as low as 43-63 mg/kg-day were associated with immunosuppression and minor hematological changes.

One main purpose of this study was to distinguish the toxic effects of relatively pure PCP from those of the chlorinated dibenzo-*p*-dioxins and dibenzofurans present as impurities at much higher levels in the TGC and DP-2 formulations. In this regard, the study revealed that immunosupression occurred at 330-522 mg/kg-day when analytical grade PCP was given, but that much lower doses (43-59 mg/kg-day) of the technical grade formulations (TGC or DP-2) produced an even greater effect.

2. Rat

a. Twenty-Eight-Day Gavage Study (Renner *et al.*, 1987)

Renner *et al.* (1987) administered PCP (purity @ 99%) by corn-oil gavage to a group of 24 female Sprague-Dawley rats for 28 days at a dose of 53 mg/kg-day. Animals were observed for an additional 14 days after dosing. Three PCP-treated rats died during the observation period. Relative liver and kidney weights were significantly elevated in the treatment group. Microscopic examination of liver, spleen, lung, heart, kidney, pancreas, stomach, and duodenum was performed. The only abnormalities found were in the livers of PCP-treated animals; these included hepatocytomegaly, hepatocellular degeneration, and necrosis. All liver effects diminished during the recovery period. Hematological investigation revealed mild anemia which persisted throughout the recovery period.

Renner *et al.* (1987) also looked at the effects of 28-day administration of TeCHQ utilizing the same protocol as for PCP. Recrystallized (highly purified) TeCHQ was administered by corn-oil gavage to 24 female Sprague-Dawley rats at a dose of 50 mg/kg-day for 28 days. TeCHQ, unlike PCP, produced no relative organ weight changes, nor did it affect hematologic parameters or the morphology of any organ examined.

Comparison of the subchronic toxicity of PCP and TeCHQ. The possibility of poor systemic absorption or rapid metabolic degradation of ingested TeCHQ should be considered in gauging the relative subchronic toxicities of PCP and TeCHQ. Because TeCHQ is the primary metabolite of PCP in rodents but apparently not in humans, differentiation of the subchronic toxicity of TeCHQ from that of PCP is useful for interpreting the human relevance of PCP toxicity data obtained in rodents. However, comparison of oral subchronic toxicities may be misleading; the results of acute toxicity studies indicate that TeCHQ may not be as completely or efficiently absorbed as PCP (discussed in Section III-B).

b. Interim Sacrifice of Two-Year NTP Feed Study (Kurtz & Hejtmancik, 1993)

The NTP is in the process of conducting a two-year chronic oncogenicity study of purified PCP in F344 rats. An interim sacrifice was performed after 27 weeks of exposure. At the request of DPR, the NTP released an abbreviated data summary describing the interim sacrifice data as well as in-life data through 41 exposure weeks (Kurtz and Hejtmancik, 1993). A letter accompanying the data summary (Eastin, 1993) indicates that the data in the summary are to be considered "preliminary" until such time as they are subjected to the "standard quality assurance process" of the contract laboratory or the NTP. The version received by DPR was a preliminary draft.[3]

The NTP project officer confirmed that the compound in use was a purified grade, of higher purity than either the technical grade or Dowicide EC-7 formulas used in the NTP mouse bioassays (J.

[3]The following tables were referenced in the text but were not included in the abbreviated summary report received by DPR: Table 9, summary clinical observations; Table 10, summary gross pathology data; Table 14, individual clinical observations; Table 18, individual gross pathology data; Table 19, individual microscopic pathology data.

Roycroft, personal communication). No other information was available as to the percent PCP in the "purified" formulation or the identity and levels of its contaminants. PCP at four concentrations (nominally 200, 400, 600, or 1,000 ppm PCP in feed) was administered to groups of male or female rats. There were 60 rats in each control (zero-dose) group, 50 animals in each of the 200, 400, and 600 ppm groups, and 60 animals in each 1,000 ppm group.

. Based on the average body weights and daily food consumption rates for the first 25 weeks of exposure and the assumption that target concentrations were achieved, the average daily doses in the four exposure groups were calculated by DPR and are shown in Table III-C-4.

Table III-C-4. Exposure Doses of Purified PCP During the First 25 Weeks of the NTP Chronic Toxicity Study in Rats

Group	Nominal Concentration (ppm diet)			
	200	400	600	1,000
	Nominal Exposure Dose (mg/kg-day)[a]			
Females	12.0	25.5	39.6	70.8
Males	11.6	24.8	38.6	70.5

[a] Data from Kurtz & Hejtmancik (1989). Nominal exposure doses were calculated by DPR based on nominal concentrations.

After 27 weeks of exposure, 10 rats of each sex in the control and 1,000 ppm groups were sacrificed. Serum chemistry analyses and complete histopathological examinations were performed for the sacrificed animals. The subsequent discussion of this study relates only to effects in the 1,000 ppm rats.

(1) Pre-Sacrifice Observations

Body weight. High-dose males and females displayed a gradual decline in mean body weight gain relative to controls. After 25 weeks of exposure, body weights were diminished approximately 15% in both males and females.

Serum chemistry. Blood was collected prior to interim sacrifice and assayed for serum sorbitol dehydrogenase, SGPT, total bile acids, and serum alkaline phosphatase (SAP). High-dose males demonstrated a small but significant increase (17%) in mean SAP relative to controls. Mean sorbitol dehydrogenase activity was significantly increased 42% in high-dose females and non-significantly increased almost 2-fold in high-dose males relative to controls. The preliminary NTP report stated that two 1,000 ppm males had unusually high SGPT and sorbitol dehydrogenase values; individual animal data for these parameters were not provided.

(2) Post-Sacrifice Observations

Liver. Relative liver weights in the high-dose groups were increased 24% in males and 18% in females relative to same-sex controls; these differences were highly statistically significant. However, absolute liver weights were not significantly different from those of the controls; the relative weight differences are best explained by decreased body weight gain in the high-dose animals.

The only microscopic change which the investigators found to be related to exposure was centrilobular hepatocellular hypertrophy; this lesion occurred in 10/10 male and 10/10 female high-dose rats. The NTP graded the severity as mild (Eustis, 1993). The NTP also found that minimal individual cell necrosis, particularly of the centrilobular region, occurred in several male and most female high-dose rats, but not at all in the controls. Hepatodiaphragmatic nodules occurred in 3/10 high-dose females; these were observed during gross examination and confirmed histopathologically. Although none were found in the control females, the investigators concluded that the nodules were not exposure-related. Such nodules are a developmental anomaly with an historical background incidence rate of 1 to 11% in F344 rats (Eustis *et al.*, 1990).

(3) Discussion

Because the data summary received by DPR was incomplete and the study has not yet undergone complete internal peer review within either the contract laboratory or the NTP, DPR has not conducted a full evaluation. Nevertheless, the microscopic finding of hepatic lesions in every rat receiving PCP at a concentration of 1,000 ppm diet is unlikely to be altered upon further scrutiny of the study.

The protocol called for interim sacrifice of 1,000 ppm and control rats only. Based on the liver toxicity observed, the NTP pathologists decided to stop exposure of the high-dose group at the one-year mark, which was considered to be the first standard stopping point following their review of data from the 27-week sacrifice. The three lower dose groups (200, 400, and 600 ppm) were to continue receiving PCP for the entire 2-year period (Roycroft, 1993).

Note: The final report was received and reviewed by DPR. The evaluation of this study is now presented in the Chronic Toxicity Section III.D.2

c. Ninety-Day Feed Study (Kociba *et al.*, 1973)

Dow Chemical conducted a 90-day subchronic feed study of a partially purified PCP formulation, XD-8108.00L (XD), in Sprague-Dawley rats as the pilot for a subsequent chronic study (Kociba *et al.*, 1973). Ten rats/sex were exposed to PCP at 0, 1, 3, 10, or 30 mg/kg-day. A gross pathological examination of most major organs was performed on all animals in all dose groups. Histopathological examination was confined to the highest dose group and the controls. DPR found the subchronic study to be of limited value for characterizing toxicity at the low end of the dose range.

d. Twenty-Eight-Day Gavage Study (Jekat *et al.*, 1994)

The effects of subchronic gavage exposure to PCP on thyroid stimulating hormone (TSH) and the thyroid hormones thyroxine (T4) and triiodothyronine (T3) in female Wistar rats were studied by Jekat *et al*. (1994). Total T4 (TT4), total T3 (TT3), and TSH were measured by radioimmunoassay. Eight animals per group were treated for 28-days, twice daily, with purified PCP at 3 or 30 mg/kg-day or with technical grade (TG) NaPCP (Malaysia C) at 3 mg/kg-day.

Serum TT4 was reduced to approximately 50% of the control value in both 3 mg/kg-day groups and to approximately 30% of the control value in the 30 mg/kg-day group; the change was statistically significant in each case ($p < 0.0025$). Lesser reductions were seen for serum TT3; statistical significance was achieved with TG NaPCP at 3 mg/kg-day (approximately 80% of control, $p < 0.05$) and with the high dose of purified PCP (approximately 60% of control, $p < 0.01$). Free serum T4 was decreased to approximately 50% and 30% of the control value in animals which received purified PCP at 3 and 30 mg/kg-day, respectively ($p < 0.0025$); effects in the TG NaPCP group were not reported. Free serum T3 was diminished only in the high-dose purified PCP group (approximately 50% of control, $p < 0.01$). The serum TT4:TT3 ratio was substantially reduced in all PCP/NaPCP treatment groups ($p < 0.0025$). In the isolated thyroid glands of animals given TG NaPCP, both TT4 and TT3 were approximately 50% ($p < 0.01$) of their control values; lesser reductions ($p < 0.01$) were seen in animals given the high dose of purified PCP. Serum TSH was depressed to approximately 70% of the control level in all treatment groups ($p < 0.05$).

Discussion. Some of the thyroid hormone effects described for PCP-treated rats in this study are similar to those produced by much lower concentrations of TCDD (Sewall *et al.* 1995); however, TCDD at 125 mg/kg-day produced a 2.5-fold *increase* in TSH. This disparity suggests that the two chemicals exert their similar effects on thyroid hormone levels *via* quite dissimilar mechanisms.

e. Three-Month Feed Study (Kimbrough and Linder, 1975)

This study was reported by scientists at the Centers for Disease Control (CDC) and the U.S. EPA as a one-paragraph abstract (Kimbrough and Linder, 1975). Groups of 10 male rats (strain unspecified) were fed technical grade (TG) or analytical grade (AG) PCP at 0 or 1,000 ppm diet for 3 months. The AG PCP was said to be "relatively" pure while the TG PCP was said to contain "a relatively high concentration" of pCDDs and pCDFs. Because the data could not be examined, the results of this study are not included in Table III-C-5.

Table III-C-5. Subchronic Oral Toxicity of PCP in Mice and Rats[a]

Study	Species /Sex	Route	Duration	PCP Grade	Effects at LOEL[b]	LOEL	NOEL
						(mg/kg-day)	
NTP, 1989[c]	Mouse/ M & F	Diet	30 days	TGC	U serum cholesterol (F); U liver porphyrins (M); U liver lesions[d] (B); U platelets (B).	102	2.8
"	"	"	"	EC-7	U serum cholesterol (F); U liver porphyrins (M); V reticulocytes (F); U γ-globulin (F).	24	4.3
"	"	"	"	Purified	U liver porphyrins (M); U liver lesions[d] (F).	27	4.1
"	"	"	6 mos	TGC/DP-2	Liver lesions[d] (B); urinary bladder changes (B); immune suppression (B).	43	None
"	"	"	"	EC-7/Purified	Liver lesions[d] (B); urinary bladder changes (B).	54	None
Renner *et al.*, 1987	Rat/F	Diet	28 days	Purified	Liver lesions[d]; U relative liver and kidney weights; mild anemia.	53	None
Kurtz & Hejtmancik, 1993[e]	Rat/ M & F	Diet	27 wks	Purified	Liver cell hypertrophy, necrosis (minimal), & enzyme changes (B); V body weight gain (B).	71	None
Kociba *et al.*, 1973[f]	Rat/ M & F	Diet	90 days	Distilled TG	U liver weight (B).	10	3
Jekat *et al.*, 1994[d,g]	Rat/F	Gavage	28 days	Purified/TG	Alterations in thyroid hormone levels.	3	None

[a] Only studies for which data were relatively complete are shown. *Abbreviations:* TG(C), technical grade (composite); EC-7, Dowicide EC-7; LOEL, lowest-observed-effect level.
[b] Sex affected at the LOEL is in parenthesis; B = both sexes.
[c] Data from an NTP Technical Report and addition data supplied upon request by the NTP.
[d] Liver lesions included cytomegaly, karyomegaly, nuclear atypia, hepatocellular degeneration, and necrosis.
[e] Draft report of interim sacrifice data for high-dose animals in a 2-year NTP study: DPR did not subject the study report to comprehensive review.
[f] Dow Chemical study submitted to DPR. DPR found the study to be of limited value for characterizing toxicity at the low end of the dose range. Histopathology was not performed at the LOEL or lower dose. Histopathology performed at 30 mg/kg-day was considered inadequate.
[g] Only thyroid hormone endpoints and organ/body weights were evaluated. The TG compound was NaPCP.

D. CHRONIC TOXICITY AND ONCOGENICITY

Summary of chronic toxicity. In the NTP bioassay, a large proportion of both male and female $B6C3F_1$ mice treated with the lowest dose (17-18 mg/kg-day) of either partially purified (Dowicide EC-7) or technical grade PCP developed non-neoplastic liver lesions (including cytomegaly, multifocal proliferation of hematopoietic cells, diffuse chronic inflammation, and acute diffuse necrosis). In animals treated with the lowest dose of the technical grade formulation (which contained higher concentrations of various pCDD and pCDF contaminants), hyperplasia of the bile duct was produced in males while hyperplasia of the hematopoietic tissues of the spleen occurred in both males and females. In the Dow rat study, the PCP formulation under test was intermediate in purity between the partially purified and technical grades of PCP tested in the NTP mouse study. Microscopic signs of toxicity in the liver (nodular hyperplasia) and kidney (granular pigmentation of epithelia) appeared in female rats at doses as low as 10 mg/kg-day; the NOEL for these effects was 3 mg/kg-day. In a chronic study in beagle dogs, treatment at the lowest dose (1.5 mg/kg-day) of technical grade PCP produced evidence of liver toxicity, including increased relative liver weight, granular cytoplasmic pigment accumulation, chronic inflammation (lymphocytic aggregations), and increased serum alkaline phosphatase. Results of the chronic toxicity studies are summarized in Table III-D-6.

Summary of oncogenicity. An oncogenicity study of chronic dietary PCP exposure in rats was performed by Dow Chemical; the results were negative for oncogenicity. However, because of serious limitations in design and outcome, the Dow rat study was considered unacceptable to DPR for determining the oncogenic potential of PCP. Another study of chronic dietary PCP exposure in rats was recently completed by the NTP[4]. There was some evidence of carcinogenic potential in male rats based on the incidence of malignant mesothelioma and squamous cell carcinoma of the nasal area. These findings were only significant in males at the high dose (~60 mg/kg-day); no neoplasia were reported in female animals. A two-year oncogenicity study of dietary exposure to PCP in mice was completed by the NTP in 1989; this study was considered acceptable to DPR for fulfilling the mouse oncogenicity data requirement. The mouse study found evidence for the oncogenicity of both partially purified and technical grade PCP. In male mice, the partially purified PCP produced dose-related increases in both benign and malignant liver tumors (adenoma and carcinoma). In female mice, the partially purified PCP produced significant elevation of benign tumors of the liver (adenoma) and adrenal gland (pheochromocytoma) and a malignant blood vessel tumor (hemangiosarcoma).

1. Mouse

The NTP conducted a two-year feeding study of PCP in $B6C3F_1$ mice (NTP, 1989).[4] Two formulations of PCP were used: a technical grade composite (TGC) and Dowicide EC-7 (EC-7). Diets containing 100 or 200 ppm TGC or 100, 200, or 600 ppm EC-7 were fed to groups of 50 male and 50 female mice. The average daily dose was 18 or 35 mg/kg for males and 17 or 35 mg/kg for females in the TGC dose groups and 18, 37, or 118 mg/kg for males and 17, 34, or 114 mg/kg for females in the EC-7 dose groups. Two groups of 35 male and 35 female mice were fed control diets.

[4]This study was considered acceptable to DPR based on FIFRA guidelines.

PCP formulations. The TGC consisted of a mixture of technical grade PCP produced by Monsanto Industrial Chemical Company, Reichhold Chemicals, Inc., and Vulcan Materials Company. Concentrations of various chlorinated contaminants in TGC and EC-7 are shown in Table III-D-1.

Table III-D-1. Chlorinated Contaminants of PCP Formulations Tested in the NTP Chronic Toxicity Study in Mice[a]

Contaminant	PCP Formulation	
	EC-7[b]	TGC[b]
tetrachlorophenol	9.4%	3.8%
hexachlorobenzene	65 ppm	50 ppm
TCDD	< 0.04 ppm	n.d.
PCDD	n.r.	n.r.
HxCDD	0.19 ppm	10.1 ppm
HpCDD	0.53 ppm	296 ppm
OCDD	0.69 ppm	1,386 ppm
TCDF	n.r.	n.r.
PCDF	n.d.	1.4 ppm
HxCDF	0.13 ppm	9.9 ppm
HpCDF	0.15 ppm	88 ppm
OCDF	n.d.	43 ppm

[a] *Abbreviations:* EC-7, Dowicide EC-7; TGC, technical grade composite; CDD, chlorodibenzo-*p*-dioxin; CDF, chlorodibenzofuran; T, tetra; P, penta; Hx, hexa; Hp, hepta; O, octa; n.d., non-detectible (detection limit not given); n.r., not reported.
[b] PCP formulations administered in the NTP study. Data are reproduced from Table 3 of NTP (1989).

a. Pre-Sacrifice Observations

Body weight/feed consumption. Mean body weights were marginally depressed in the 200 ppm TGC females and in both the 200 and 600 ppm EC-7 females. Body weight per unit feed consumption was decreased in a dose-related fashion in EC-7 groups of both sexes, up to a maximum of 13% for high-dose males and 17% for high-dose females.

Survival. The male TGC control group had a much lower survival rate (12/35) than that of the male EC-7 control group (25/35); the latter was similar to that of historical controls. The survival of

the two male control groups began to diverge after the first year; no explanation for the divergence was presented.

b. Post-Sacrifice Endpoints (Non-neoplastic)

Liver. A broad spectrum of non-neoplastic lesions (cytomegaly, multifocal proliferation of hematopoietic cells, multifocal pigmentation, diffuse chronic inflammation, acute diffuse necrosis) appeared in the livers of a large proportion of male and female mice in all groups treated with PCP. The incidence of acute diffuse necrosis at the lowest dose (100 ppm) was 87% in TGC-treated males, 98% in males treated with EC-7, 90% in TGC-treated females, and 42% in females treated wiht EC-7. Only for a few lesions (bile duct hyperplasia, clear cell foci) were major differences in severity or incidence observed between the two PCP grades. The incidence of bile duct hyperplasia was markedly elevated (47% *vs.* 0% for controls) in males exposed to 100 ppm TGC, whereas in males exposed to 100 ppm EC-7 there was only a minor elevation (6.3% *vs.* 2.9% for controls); higher-dose EC-7 females also exhibited this abnormality. The incidence of clear cell foci was increased at the lowest dose in males treated with either TGC or EC-7 (23% and 40%, respectively, vs. 0% for both control groups) ; in females the presence of this lesion was significantly elevated only at the higher doses.

Spleen. The incidence of diffuse hematopoietic cell proliferation (extramedullary hematopoiesis) was increased at both doses of TGC in male and female mice. Incidence rates in the control, low-, and high-dose groups were 5/30 (17%), 15/23 (65%), and 18/46 (39%) in males and 2/33 (6%), 4/13 (31%), and 11/47 (23%) in females, respectively. This U-shaped dose-response may reflect the existence of a morphologic continuum leading to splenic hemangiosarcoma, which was elevated in a dose-related manner in both males and females (see below).

Nose. Acute focal inflammation of the mucosal glands and focal metaplasia of the olfactory epithelium were observed at significantly elevated incidences in mice exposed to the high dose of EC-7. Incidence rates for inflammation were 4/35 (11%), 1/13 (8%), 3/16 (19%), and 47/40 (96%) in males and 0/35, 0/14, 2/5 (40%),and 46/48 (96%) in females at the zero, low, mid, and high dose, respectively. Incidence rates for metaplasia were similar to those for inflammation. The investigators did not speculate as to whether this was a systemic effect or a local one that resulted from the inhalation of PCP (*e.g.*volatilized from feed or in expired air following ingestion).

Mammary gland. Cystic hyperplasia was elevated at the high dose in females receiving TGC. Incidence rates were 7/30 (23%), 0/3, and 20/34 (59%) in the control, low-, and high-dose groups, respectively.

c. Post-Sacrifice Endpoints (Neoplasia)

Incidence rates of the major exposure-related neoplasms are given in Tables III-D-2 and III-D-4 for TGC-treated males and females and in Tables III-D-3 and III-D-5 for males and females treated with EC-7, respectively.

Liver. In all groups of male mice exposed to TGC or EC-7, the combined incidence rate for hepatocellular adenoma or carcinoma was significantly elevated. The separate (benign) adenoma

and (malignant) carcinoma incidence rates were also increased (but not always significantly) in all groups of males treated with TGC or EC-7; the Cochran-Armitage trend was just below statistical significance ($p = 0.08$) for carcinoma in the EC-7 groups but achieved significance ($p < 0.05$) for adenomas in the EC-7 groups and for both adenoma and carcinoma in the TGC groups. In female mice, the combined incidence rate for hepatocellular adenoma and carcinoma was elevated in all treatment groups; however, statistical significance was achieved only in the high-dose EC-7 group.

Adrenal medulla. The incidence of benign pheochromocytoma was significantly elevated in male mice in both TGC treatment groups. EC-7 produced elevated incidences of benign pheochromocytoma in males treated with 200 ppm and in both males and females at the high dose. Bilateral occurrence of benign pheochromocytomas was common in animals manifesting this tumor. No significant differences were observed for malignant pheochromocytoma in any treatment group. Proliferative lesions (diagnosed as medullary hyperplasia) and pheochromocytoma were considered by the investigators to be part of a morphologic continuum leading to neoplasia.

Circulatory system. In female mice, the incidence of hemangiosarcoma (a malignant tumor) was significantly elevated at the highest dose of both TGC and EC-7; a significant dose-related trend occurred for the EC-7 groups. Most circulatory system neoplasms in females occurred in the spleen; the remainder were in the liver. In male mice, the incidence rates of hemangiosarcoma (EC-7 groups) or combined hemangioma and hemangiosarcoma (TGC groups) were elevated, but not significantly, at all doses.

d. Discussion

Non-neoplastic endpoints. According to the investigators, a comparison of effects at equal doses of the two PCP formulations suggests that bile duct hyperplasia in males and females and possibly some of the other hepatic lesions in females may be related to pCDD and pCDF impurities (present at a higher level in TGC) rather than to PCP, given that other studies have identified the same lesions following exposure of mice to pCDDs and pCDFs (McConnell, 1984).

Neoplastic endpoints. When survival times were taken into account, the investigators failed to find any significant differences in tumor incidence produced by TGC and EC-7. Because of the disparity in survival of the two control groups, analyses using pooled control group data were performed as a supplemental procedure; these also did not yield significant TGC/EC-7 differences.

Neoplastic effects related to PCP exposure were found in the liver, adrenal medulla, and circulatory system. With respect to the argument that the liver toxicity attributable to pCDD or pCDF contaminants was responsible for the observed hepatocarcinogenicity, the investigators noted that while non-neoplastic lesions of identical morphology and approximately equal severity occurred in females treated with EC-7 at 200 and 600 ppm, liver neoplasms were significantly elevated only in the 600 ppm group. The investigators performed separate analyses for benign adenoma, malignant carcinoma, and the presence of adenoma *or* carcinoma. It is the combined adenoma/carcinoma category which provides the strongest statistical association with PCP exposure. The use of such a

category is not unusual and rests upon histological evidence that hepatocellular adenomas and carcinomas are part of a physiological continuum (Bannasch *et al.*, 1986). It is noteworthy that the incidence of adenoma/carcinoma in males on the 200 ppm EC-7 regime (44%) was lower than the rate in males receiving TGC at either 100 ppm (55%) or 200 ppm (77%). If PCP alone were responsible for the neoplastic response, the incidence at a given dose level of TGC would be expected to be roughly equivalent to the response rate at that same dose of EC-7, since both formulations contain approximately 90% PCP. These results suggest that the contaminants in TGC act as co-carcinogens, *i.e.*, they enhance the hepatocarcinogenic effect of PCP at a given dose level. On the other hand, the 600 ppm EC-7 females had a much higher incidence of adenoma/carcinoma (65%) than females exposed to either 200 ppm EC-7 (12%) or 200 ppm TGC (18%), which suggests that in females, above a threshold exposure concentration there is a sharp increase in the oncogenic dose response to PCP which is unrelated to the contaminants in TGC.

Because non-neoplastic liver toxicity was prevalent in all treatment groups, the possibility exists that the liver oncogenicity of the PCP formulations may have been secondary to toxicity. The Environmental Health Committee of the U.S. EPA's Science Advisory Board was asked to examine the study results and consider this issue, among others. The Committee recommended that "the observed dose-dependent increase in the incidence of hepatocellular carcinomas and adenomas be considered a valid indicator" of the oncogenic potential of PCP. The Committee also pointed out that the mouse strain tested in the study, $B6C3F_1$, is extremely sensitive to hepatocarcinogenesis and therefore recommended that tumorigenicity at this site be considered less relevant to human risk than the production of hemangiosarcomas (U.S. EPA SAB, 1991).

As was found for liver tumors in males, the incidence of malignant blood vessel tumors (hemangiosarcomas) in females at both dose levels of TGC (6% and 12%) were higher than for the same levels of EC-7 (2% and 6%). The finding of elevated incidences of hemangiosarcoma in all exposure groups is indicative that the carcinogenic response is not entirely attributable to the contaminants present in TGC. Furthermore, the data do not indicate the existence of a dose-response threshold within the dose range examined; the trend in increased tumor incidence is apparent in both sexes at the lowest dose tested (100 ppm) for both EC-7 and TGC.

In males, the incidence of benign pheochromocytoma, a tumor of the adrenal medulla, was approximately the same for both 200 ppm groups (51% and 44% for groups exposed to TGC and EC-7, respectively), while in the 100 ppm TGC males the rate was notably higher (22%) than in the 100 ppm EC-7 males (8%). A comparison of the dose responses to TGC and EC-7 in males suggests that the tumorigenicity of the technical-grade impurities is more important at the lower doses. In females, the only elevated pheochromocytoma incidence occurred in the 600 ppm EC-7 group (78%), with a steep increase over the rates at 200 ppm and 100 ppm (4% and 2%). The shape of the dose-response curve for pheochromocytoma in female mice treated with EC-7 was similar to that for hepatocellular adenoma/carcinoma observed in the same treatment groups.

Table III-D-2. Incidence Rates of Neoplasms and Preneoplastic Changes in Male Mice Fed Technical Grade Composite PCP in the NTP Chronic Toxicity Study[a]

Site/Tumor Type	Control	Dose	
		100 ppm (18 mg/kg-day)	200 ppm (35 mg/kg-day)
Liver (hepatocyte) /Adenoma	5/32 (16%)‡‡‡ [28%]	20/47 (43%)** [65%]	33/48 (69%)*** [89%]
Liver (hepatocyte) /Carcinoma	2/32 (6%)‡ [11%]	10/47 (21%) [33%]	12/48 (25%)* [40%]
Liver (hepatocyte) /Adenoma *or* Carcinoma	7/32 (22%)‡‡‡ [36%]	26/47 (55%)* [76%]	37/48 (77%)*** [90%]
Adrenal Medulla /Pheochromocytoma (benign)	0/31 (0%)‡‡‡ [0%]	10/45 (22%)** [38%]	23/45 (51%)*** [85%]
Adrenal Medulla /Hyperplasia	1/31 (3%)+	10/45 (22%)*	10/45 (22%)*
Circulatory system /Hemangioma *or* Hemangiosarcoma	1/35 (3%) [4%]	2/49 (4%) [8%]	3/49 (6%) [11%]

[a] Reproduced from Tables A3 and 30 in NTP (1989). Percentages in square brackets are Kaplan-Meier estimated tumor incidences adjusted for intercurrent mortality.

‡ Dose-related trend is significant at $p < 0.05$ by Cochran-Armitage test.

‡‡‡ Dose-related trend is significant at $p < 0.001$ by Cochran-Armitage test.

+ Not analyzed for dose-related trend. Fisher exact test results according to DPR.

* Significantly different from controls at $p < 0.05$ by Fisher exact test.

** Significantly different from controls at $p < 0.01$ by Fisher exact test.

*** Significantly different from controls at $p < 0.001$ by Fisher exact test.

Table III-D-3. Incidence Rates of Neoplasms and Preneoplastic Changes in Male Mice Fed Dowicide EC-7 in the NTP Chronic Toxicity Study[a]

Site/Tumor Type	Control	Dose		
		100 ppm (18 mg/kg-day)	200 ppm (37 mg/kg-day)	600 ppm (118 mg/kg-day)
Liver (hepatocyte) /Adenoma	5/35 (14%)‡‡‡ [20%]	13/48 (27%) [42%]	17/48 (35%)* [53%]	32/49 (65%)*** [84%]
Liver (hepatocyte) /Carcinoma	1/35 (3%) [4%]	7/48 (15%) [20%]	7/48 (15%) [24%]	9/49 (18%)* [25%]
Liver (hepatocyte) /Adenoma *or* Carcinoma	6/35 (17%)‡‡‡ [24%]	19/48 (40%)* [54%]	21/48 (44%)** [66%]	34/49 (69%)*** [87%]
Adrenal Medulla/ Benign Pheochromocytoma[b]	0/34 (0%)‡‡‡ [0%]	4/48 (8%) [14%]	21/48 (44%)*** [68%]	44/49 (90%)*** [98%]
Adrenal Medulla /Hyperplasia	1/34 (3%)+	19/48 (40%)***	13/48 (27%)**	1/49 (2%)
Circulatory system /Hemangiosarcoma[c]	0/35 (0%) [0%]	4/50 (8%) [13%]	2/50 (4%) [7%]	3/49 (6%) [9%]

[a] Reproduced from Tables C3 and 30 in NTP (1989). Percentages in square brackets are Kaplan-Meier estimated tumor incidences adjusted for intercurrent mortality.

[b] Combined incidence rates for benign *or* malignant pheochromocytoma were 1/34, 4/48, 21/48, and 45/49 in the 0, 100, 200, and 600 ppm groups, respectively.

[c] Combined incidence rates for hemangioma *or* hemangiosarcoma were 1/35, 4/50, 3/50, and 5/49 in the 0, 100, 200, and 600 ppm groups, respectively.

‡‡‡ Dose-related trend is significant at $p < 0.001$ by Cochran-Armitage test.

+ Not analyzed for dose-related trend. Fisher exact test results according to DPR.

* Significantly different from controls at $p < 0.05$ by Fisher exact test.

** Significantly different from controls at $p < 0.01$ by Fisher exact test.

*** Significantly different from controls at $p < 0.001$ by Fisher exact test.

Table III-D-4. Incidence Rates of Neoplasms and Preneoplastic Changes in Female Mice Fed Technical Grade Composite PCP in the NTP Chronic Toxicity Study[a]

Site/Tumor Type	Control	Dose	
		100 ppm (17 mg/kg-day)	200 ppm (35 mg/kg-day)
Liver (hepatocyte) /Adenoma	3/33 (9%) [11%]	8/49 (16%) [20%]	8/50 (16%) [24%]
Liver (hepatocyte) /Adenoma *or* Carcinoma	3/33 (9%) [11%]	9/49 (18%) [21%]	9/50 (18%) [26%]
Adrenal Medulla /Benign *or* Malignant Pheochromocytoma	2/33 (6%)[+]	2/48 (4%)	1/49 (2%)
Adrenal Medulla /Hyperplasia	0/33 (0%)[+]	4/48 (8%)	2/49 (4%)
Circulatory System /Hemangiosarcoma	0/35 (0%)[‡] [0%]	3/50 (6%) [7%]	6/50 (12%)[*] [17%]

[a] Reproduced from Tables B3 and 30 in NTP (1989). Percentages in square brackets are Kaplan-Meier estimated tumor incidences adjusted for intercurrent mortality.

[‡] Dose-related trend is significant at $p < 0.05$ by Cochran-Armitage test.

[+] Not analyzed for dose-related trend. Fisher exact test results according to DPR.

[*] Significantly different from controls at $p < 0.05$ by Fisher exact test.

Table III-D-5. Incidence Rates of Neoplasms and Preneoplastic Changes in Female Mice Fed Dowicide EC-7 in the NTP Chronic Toxicity Study[a]

Site/Tumor Type	Control	Dose		
		100 ppm (17 mg/kg-day)	200 ppm (34 mg/kg-day)	600 ppm (114 mg/kg-day)
Liver (Hepatocyte) /Adenoma	1/34 (3%)‡‡‡ [3%]	3/50 (6%) [11%]	6/49 (12%) [16%]	30/48 (63%)*** [75%]
Liver (Hepatocyte) /Adenoma *or* Carcinoma	1/34 (3%)‡‡‡ [3%]	4/50 (8%) [14%]	6/49 (12%) [16%]	31/48 (65%)*** [78%]
Adrenal Medulla /Benign Pheochromocytoma[b]	0/35 (0%)‡‡‡ [0%]	1/49 (2%) [4%]	2/46 (4%) [5%]	38/49 (78%)*** [86%]
Adrenal Medulla /Hyperplasia	2/35 (6%)+	1/49 (2%)	5/46 (11%)	17/49 (35%)**
Circulatory System /Hemangiosarcoma[c]	0/35 (0%)‡‡‡ [0%]	1/50 (2%) [4%]	3/50 (6%) [7%]	8/49 (16%)* [19%]

[a] Reproduced from Tables D3 and 30 in NTP (1989). Percentages in square brackets are Kaplan-Meier estimated tumor incidences adjusted for intercurrent mortality.

[b] Combined incidence rates for benign *or* malignant pheochromocytoma were 0/35, 2/49, 2/46, and 38/49 in the 0, 100, 200, and 600 ppm groups, respectively.

[c] Combined incidence rates for hemangioma *or* hemangiosarcoma were 0/35, 1/50, 3/50, and 9/49 in the 0, 100, 200, and 600 ppm groups, respectively.

‡‡‡ Dose-related trend is significant at $p < 0.001$ by Cochran-Armitage test.

+ Not analyzed for dose-related trend. Fisher exact test results according to DPR.

* Significantly different from controls at $p < 0.05$ by Fisher exact test.

** Significantly different from controls at $p < 0.01$ by Fisher exact test.

*** Significantly different from controls at $p < 0.001$ by Fisher exact test.

2. Rat

a. NTP Study, 1997 (final report)

In the August 5, 1997 draft of this risk characterization document, the final report of this combined chronic toxicity/oncogenicity study had not been received by DPR; therefore, a summary of the 27-week interim sacrifice information was presented, and is still included, in the Subchronic Toxicity section of this document. The final report was received by DPR in early 1998, and the results are presented below.

Study design. PCP was administered in the diet to 50 F344/N rats/sex/group at 0, 200, 400, 600 or 1000 ppm for 106 weeks, except for the 1000 ppm group (NTP, 1997). These animals were not given PCP after 52 weeks; they were placed on a control diet for the duration of the study. Correspondingly daily dosages were reported to be 0, 10, 20, 30 or 60 mg/kg-day. It is not clear from the study report if these dosages were default conversions from ppm to mg/kg-day or were based on actual food consumption and animal body weights. An additional 10 animals/sex were dosed with 0 or 1000 ppm PCP for an interim evaluation (limited clinical chemistry and histopathology) after 7 months (presented in the Subchronic Toxicity Section).

PCP formulation. The PCP test material was approximately 99%pure active ingredient, with a single impurity identified by GLC comprising about 1% of the primary peak. The impurity was tentatively identified as tetrachlorophenol. This test material is more refined than that used in the Dow Chemical study (see below).

(1) Pre-Sacrifice Endpoints

Body weight. Body weights were reduced in a dose-related manner from 400 ppm to 1000 ppm. The body weight reductions in the 1000 ppm group were approximately 20%.

Survival. Survival was generally good throughout the study; however, a decrease in survival of control male and low dose male groups occurred late in the study. Poorest survival was in control males, where there were only 11 survivors at the scheduled termination of the study.; additionally one animal died during the last week of the study. The majority of the non-survivors were sacrificed moribund, so that no more than 11 rats in any group died spontaneously. As of week 89, no fewer than 34 rats/group were still alive. Therefore, there were sufficient numbers of animals which lived long enough for a valid oncogenicity evaluation. There were many rats which had fungal infections consistent with *Aspergillus sp.*. The report did not discuss whether the degree of infection was contributory to morbidity or death of the rats.

Clinical signs. No clinical signs of toxicity were reported by the investigators.

Hematology/Clinical chemistry. Hematology was not done in the study. Serum chemistry was limited to 10 animals/sex in the control and 1000 ppm groups at the 7-month interim sacrifice, and only alanine aminotransferase, alkaline phosphatase, sorbitol dehydrogenase and bile salts were measured. There was some limited indication of hepatocellular damage and biliary stasis based on the parameters measured.

(2) Post-Sacrifice Endpoints (Non-Neoplastic)

Liver and kidney. At the 7 month interim sacrifice some histopathology was evident in the liver and kidneys of the 1000 ppm rats. Non-neoplastic findings in the 2-year animals were not definitive for any tissues. Hepatocellular cytoplasmic vacuolization and hypertrophy were no longer evident as treatment effects. Basophilic and eosinophillic foci tended to be more common in the higher two dose groups of males; however, there was no comparable change in females, nor were hepatocellular cytoplasmic vacuolization and hypertrophy affected at this time point. Renal tubule pigmentation was seen at 1000 ppm in both sexes at 7 months but was not seen in 7 month control. Tubule pigmentation was nearly universal at 2 years, with the mean severity slightly higher at the 600 ppm level than in controls.

(3) Post Sacrifice Endpoints (Neoplastic)

Study investigators indicated that this study provides "some evidence of carcinogenic activity" in males, based on malignant mesothelioma and squamous cell carcinoma of the nasal area. Significant findings in all cases were limited to the 1000 ppm/stop dose group, and were absent from the 600 ppm dose group, which was treated for the full 2-year term of the study. Comparative historical control data was presented indicating that the incidence in the 1000 ppm group was outside of the historical range for these tumors. Background incidence of keratoacanthomas in control males was 2-6% in recent studies (with a long-term average of 3.1%), suggesting that only the 1000 ppm/stop-dose group was notably high. Background incidence of mesothelioma ranged from 0 to 4%, with mean incidence of 2.3%. Background incidence of squamous cell carcinoma of the nose was 0 in the 7 recent reference studies, with 0.4% as a long-term average incidence. No neoplasia were reported for female animals at any dose level. The possibility of a treatment-associated etiology of squamous cell carcinomas, perhaps involving the fungal infection which involved many of the males on study, has not been fully analyzed in this report.

As indicated above, none of the tumors discussed relating to this study were definitively treatment related. In contrast, the mouse oncogenicity study completed by NTP several years earlier found three well-defined increases in tumor types (hepatocellular, pheochromocytomas, and hemangiosarcomas). This study was discussed above.

(4) Discussion

The apparent chronic toxicity NOEL for this study was 200 ppm, estimated to be equivalent to an average daily dose of 10 mg/kg/day based on decreased body weight. Additionally, this study identified pigmentation of renal tubules as one of the most prominent histopathology findings in 1000 ppm rats at interim sacrifice, but did not evaluate lower dose levels at that stage of the study. At study termination, no treatment-related pigmentation changes were evident. An earlier rat oncogenicity study using a less refined grade of PCP (Schwetz *et al.*, 1976,) found brown granular pigment in hepatocytes and associated reticuloendothelial cells, as well as in kidney tubular endothelial cells at 10 mg/kg/day, but not at 3 mg/kg/day. Similar pigmentation was seen down to the lowest dose tested (1.5 mg/kg/day) in a recent dog chronic study (TSI Mason Labs., 1996). Therefore, there is good consistency between studies in these two species as to affected organs, and the dog is evidently the more sensitive species for evaluation of non-neoplastic chronic effects.

This study lacks hematological and clinical chemistry testing normally performed in a study intended to fulfill the rodent chronic toxicity data requirements . Further, the interim sacrifice was limited to controls and the highest dose on study, and thus did not provide a basis for dose-response evaluation. However, there are now sufficient chronic PCP data that there is no need to require additional long-term study data using rats. A re-review of the 1976 Schwetz study confirms that the most sensitive tissues were liver and kidney, and that there was no indication of important histopathology in these or other tissues other than the pigmentation noted above. The Schwetz, 1976 study also provided hematology and clinical chemistry at 1 year and termination (where survival allowed). Hematology was negative up to the high dose of 30 mg/kg/day, and the only clinical chemistry finding of note was elevated alanine aminotransferase at termination in both sexes at 30 mg/kg/day. This is somewhat similar to the results of the present study, in which a different “liver leakage enzyme”, sorbitol dehydrogenase, was elevated at 1000 ppm (equivalent to about 60 mg/kg/day). Therefore, there is substantial consistency between the results of the older rat study using an unrefined grade of PCP and the newer study using a highly refined grade. The only major element missing from the combination of these rat studies is ophthalmology; however, the lack of any ophthalmologic change in dogs at dose levels well above the dog NOAEL suggests that this is not a critical deficiency.

b. Dow Chemical Study

A chronic feeding study in Sprague-Dawley rats of both sexes was conducted by Dow Chemical (Schwetz *et al.*, 1976). A summary of the study later appeared as a chapter in the proceedings of a symposium (Schwetz *et al.*, 1978). The study report (Schwetz *et al.*, 1976) was submitted to DPR by the registrant; DPR found the study to be unacceptable based on FIFRA guidelines with respect to both chronic toxicity and oncogenicity outcomes. In spite of the study's inadequacies, the results are briefly presented here because it is the only long-term feeding study in rats which has been completed to date.

PCP formulation. The PCP formulation used in this study was drawn from a commercial lot, XD-8108.00L (XD), said to be representative of Dowicide EC-7. However, the impurity composition of XD (given in Table III-C-5) differed from that of the EC-7 used in the NTP dietary study (shown in Table III-D-1). XD was administered to rats for 22 months (males) or 24 months (females) at dose levels of 0, 1, 3, 10, or 30 mg/kg-day. There were 27 animals of each sex per dose group at the start of the study.

(1) Pre-Sacrifice Endpoints

Body weight. The mean body weights of male rats receiving the two highest exposure doses were marginally smaller than those of the controls. The mean body weight of 30 mg/kg-day females was significantly smaller than the control group's mean body weight throughout most of the study.

Serum chemistry. Blood urea nitrogen, alkaline phosphatase, and SGPT were assayed in 3-8 males/group and 10 females/group. Mean SGPT activities were 65% higher in males and 33% higher in females given 30 mg/kg-day in comparison to same-sex controls.

Survival. Survival in males was poor. After 22 months there were only 4-6 survivors per exposure group and 3 surviving controls. Because of the low rate of survival, males were sacrificed after 22 months rather than the 24-month time point dictated by the study protocol. The early deaths in males were unexplained and apparently unrelated to treatment with PCP. The average rate of survival in the female exposure groups was 47%; the survival rate of the female controls was 44%.

(2) Post-Sacrifice Endpoints (Non-Neoplastic)

Liver and kidney. Dark, discolored livers and kidneys were found in approximately half of the 30 mg/kg-day females; none occurred in the controls. Microscopic examination revealed signs of toxicity in the liver (nodular hyperplasia) and kidneys (brown, granular pigment within tubular epithelial cells) in both 10 and 30 mg/kg-day females.

(3) Post-Sacrifice Endpoints (Neoplastic)

No evidence of exposure-related oncogenicity was found.

(4) Discussion

This study has been found by the U.S. EPA and by DPR to be inadequate with respect to both chronic toxicity and oncogenicity data requirements, primarily because too few animals were on study, too few males survived to the end of the dosing period, not all required tissues were examined for animals which died on study, and the blood chemistry/hematology analyses were incomplete. It is especially important to note that about half of the male rats were dead 19 months into the study. Therefore, this cannot be considered to have been a chronic bioassay of PCP in male rats.

The elevated tumor incidences found in the NTP mouse study in response to Dowicide EC-7 (NTP, 1989) did not echo the results of this earlier two-year rat oncogenicity study of a PCP formulation similar to Dowicide EC-7, in which no exposure-related increases were observed in neoplasms of any kind. However, there are two primary reasons why the results of the Dow rat study cannot be taken as definitively demonstrating differential responses of rats and mice to PCP. First, lifetime exposure was not achieved in the male rats. Second, the highest dose administered in the Dow rat study (30 mg/kg-day) was almost four-fold lower than the highest dose administered in the NTP mouse study.

c. NIEHS/U.S. EPA Eight-Month Feed Study

Investigators at the National Institute of Environmental Health Sciences (NIEHS) and the U.S. EPA published a report of a study comparing the effects of technical grade and purified PCP on liver enzyme activity in Sherman rats following 8-month exposure (Goldstein *et al.*, 1977). DPR reviewed the study and found it to be unacceptable based on FIFRA guidelines for chronic toxicity studies, in part because there was no report of systematic microscopic examination of tissues. Therefore, the results of the study are not included in Table III-D-6.

3. Dog

A chronic oral study of PCP in beagle dogs was conducted by TSI Mason Laboratories (1996); the final report was submitted to DPR by the registrant.[5] Four dogs of each sex received either an empty capsule or one containing the test compound at a daily dose of 1.5, 3.5, or 6.5 mg/kg-day for 52 weeks..

PCP formulation. The PCP formulation used in this study was GLAZD Penta, the technical grade product of Vulcan Chemicals (lot EL-064). The reported purity (90.9%) was measured in a sample drawn from a contemporaneous stock of GLAZD Penta.

a. Pre-Sacrifice Endpoints

One high-dose dog of each sex became moribund and was sacrificed prior to the scheduled necropsy. At the end of the study, all high-dose males and females were designated "emaciated/thin." Food consumption differences varied throughout the study in a sex-dependent manner; these differences did not explain the effect of treatment on body weight in either sex. The incidence of dehydration was 0/4, 0/4, 1/4, and 3/4 in males and 1/4, 0/4, 1/4, and 2/4 in females at the 0, 1.5, 3.5, and 6.5 mg/kg-day. The incidence of pale mucous membranes was 0/4, 0/4, 2/4, and 3/4 in males and 0/4, 1/4, 4/4, and 4/4 in these same dose groups.

b. Post-Sacrifice Endpoints

Hematology. At terminal sacrifice, there was a dose-related decrease in RBCs in males. Statistical significance was achieved at the mid and high doses, with decreases of 15% and 21%, respectively. Hb was decreased 16% in high-dose males.

Clinical chemistry. At terminal sacrifice, cholesterol and alkaline phosphatase were elevated in all male and female treatment groups. The increase in cholesterol of 2.3-fold observed in high-dose females was statistically significant, whereas the increases found in other treated females (36-38%) and treated males (16-74%) were not. Alkaline phosphatase was markedly increased at the high dose in both males (4.9-fold) and females (6.8-fold); only the latter was reported to be statistically significant. All clinical chemistry changes were consistent with treatment-related liver injury.

Organ weights. Organ weights in high-dose females were recorded for only three dogs. Relative liver weights were significantly elevated by 15%, 39%, 66% in males and 38%, 40%, and 94% in females at the low, mid, and high dose, respectively. Absolute liver weights were elevated nonsignificantly at the low and mid doses (31-32%) in males and significantly in all treated females (22-50%). Relative thyroid weights in females were significantly elevated at the low (72%) and high (2.4-fold) doses; the absolute thyroid weight in females was significantly elevated at the high dose only (77%). Interpretation of the thyroid weight changes was complicated by the occurrence of an unusually small thyroid in one female control. Relative adrenal gland weight was significantly elevated by 42% at the high dose in males.

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[5]This study was considered acceptable to DPR based on FIFRA guidelines.

Liver histopathology. Granular cytoplasmic pigment accumulation and chronic inflammation (lymphocytic aggregations) appeared in all treatment groups in both males and females. In females, microscopic liver pigmentation was observed in 3/4 females in each treatment group. "Hepatic insufficiency" was determined by the investigators' patholologist to be the primary cause of morbidity in the two high-dose dogs sacrificed prior to study termination.

Stomach mucosa histopathology Other than the liver, the most remarkable histopathologic observation was the occurrence of lymphocytic inflammatory foci of the gastric mucosa in all treatment groups. This finding was reasonably assumed by the investigators to reflect an acute and local response to the administration of the test substance by capsule.

Thyroid histopathology. In the high-dose female with the largest thyroid gland, microscopic findings of atrophy, inflammation, and pigmentation were found.

Kidney histopathology. One high-dose male displayed widespread kidney pigmentation and mild renal congestion, correlated with perturbation of blood urea nitrogen and inorganic solute levels.

Table III-D-6. Non-Neoplastic Lesions in Chronic Toxicity Studies of PCP in Mice and Rats[a]

Study	Species /Sex	Route	PCP Grade	Effects at LOEL	LOEL (mg/kg-day)	NOEL (mg/kg-day)
NTP, 1989	Mouse/M	Diet	TGC	*Liver:* Cytomegaly, multifocal proliferation of hematopoietic cells, multifocal pigmentation, diffuse chronic inflammation, acute diffuse necrosis, bile duct hyperplasia, clear cell foci. *Spleen:* Extramedullary hematopoiesis.	18	None
"	Mouse/F	"	TGC	*Liver:* Cytomegaly, multifocal proliferation of hematopoietic cells, multifocal pigmentation, diffuse chronic inflammation, acute diffuse necrosis. *Spleen:* Extramedullary hematopoiesis.	17	None
"	Mouse/M	"	EC-7	*Liver:* Cytomegaly, multifocal proliferation of hematopoietic cells, multifocal pigmentation, diffuse chronic inflammation, acute diffuse necrosis, bile duct hyperplasia, clear cell foci.	18	None
"	Mouse/F	"	EC-7	*Liver:* Cytomegaly, multifocal proliferation of hematopoietic cells, multifocal pigmentation, diffuse chronic inflammation, acute diffuse necrosis.	17	None
Schwetz *et al.*, 1976	Rat/F	"	XD	*Liver:* Nodular hyperplasia. *Kidney:* Epithelial pigmentation.	10	3
TSI Mason Laboratories, 1996	Dog/M&F	Capsule	GLAZD Penta	*Liver:* Granular cytoplasmic pigment accumulation and chronic inflammation (lymphocytic aggregations)	1.5	None

[a] *Abbreviations:* TGC, technical grade composite; EC-7, Dowicide EC-7; XD, Dow Chemical sample XD-8108.00L.

E. GENOTOXICITY

Tests for gene mutation, chromosome effects, and DNA damage were submitted to DPR by the registrant. Several other genotoxicity studies were identified in the open literature.

Summary of the genotoxicity of PCP. The weight of evidence suggests that with or without rat liver S9, PCP does not induce gene mutation in bacteria. The results of gene mutation assays of PCP in yeast are largely positive, although the data base contains a number of reports which are incomplete or puzzling. The yeast gene mutation study of PCP submitted to DPR was judged to be positive both in the presence and absence of S9. PCP has not been shown to be mutagenic in any other eukaryotic system. Evidence for the clastogenicity of PCP is mixed, with the most convincing changes occurring only in the presence of rat liver S9. In a mammalian cell line, PCP was positive or equivocal for production of chromosomal aberrations when S9 was present in the culture medium. In two studies of mice exposed to PCP *in vivo*, the response was equivocal in a coat-color spot test (an assay which measures nonspecific genetic effects) and negative for abnormal sperm morphology. Human lymphocytes exposed to PCP *in vitro* showed no cytogenetic changes. Results were either equivocal or negative in two cytogenetic studies of men exposed occupationally to PCP and/or NaPCP. Attempts to detect DNA binding to PCP have yielded uniformly negative results. Key findings are summarized in Table III-E-1.

Summary of the genotoxicity of TeCHQ. TeCHQ is formed as a primary metabolite of PCP in mice and rats but apparently not in humans; this transformation is thought to occur in the liver. *In vitro* metabolism of PCP by a microsomal fraction of the rat liver (S9) has been shown to result in significant concentrations of TeCHQ (van Ommen *et al.*, 1986; Witte *et al.*, 1985). Additionally, recent *in vitro* studies using human cytochrome P450 enzymes indicate that TeCHQ can be slowly formed from PCP. Therefore, the *in vivo* conversion of PCP to TeCHQ in humans may be more quantitatively than qualitatively different from the metabolism in rodents. TeCHQ is clearly mutagenic and clastogenic in mammalian cells *in vitro*. Unlike PCP, TeCHQ covalently binds DNA and produces breaks in single-strand DNA *in vitro*. Although not nearly as widely tested as PCP, the disparity in the genotoxicity of the two chemicals is unambiguous. TeCHQ has yielded definitively positive results in every one of the small number of genotoxicity tests to which it has been subjected.

1. PCP

a. Mutagenicity

(1) Bacteria

A comprehensive review of the literature by Seiler (1991) and a more concise review by an anonymous author (NTP, 1989) both indicated that PCP was uniformly negative for induction of gene mutation in bacteria (Anderson *et al.*, 1972; Shirasu, 1975; Simmon and Kauhanen, 1978; Haworth *et al.*, 1983; Moriya *et al.*, 1983) with the exception of one study by Nishimura *et al.* (1982) performed in the presence of rat liver microsomes (S9). More recently, Gopalaswamy and Nair (1992) reported that PCP was mutagenic in *Salmonella typhimurium*, but only in the presence of S9.

Results of a mutagenicity study performed by EG&G Mason Research Institute were reported alongside results of the NTP mouse oncogenicity study (NTP, 1989)[6]. This study, subsequently published by Haworth *et al.* (1983), found that technical grade PCP was negative for mutagenicity in four *S. typhimurium* strains either in the presence or absence of S9.

Also submitted to DPR was an unpublished mutagenicity study by Simmon *et al.* (1979)[1] performed at the Stanford Research Institute (SRI) . With or without addition of S9, the investigators found that partially purified PCP (Dowicide EC-7) had no mutagenic activity in *Escherichia coli* WP2 or in the same four *S. typhimurium* strains tested by Haworth *et al.* (1983).

Repair-deficient mutant assays. The SRI study also included assays of the relative toxicity of PCP in repair-deficient (rec^-) *vs.* repair-competent (rec^+) bacterial strains in the absence of activated rat liver microsomes (Simmon *et al.*, 1979)[1]. The PCP formulation tested (Dowicide EC-7) was positive in the *B. subtilus* rec^+/rec^- assay, *i.e.*, there was greater toxicity to the rec^- strain. However, the opposite result occurred in the *E. coli* $polA^+/polA^-$ assay: PCP was reproducibly less toxic to the repair-deficient ($polA^-$) strain, not what is expected for a DNA-damaging agent. Thus, the results of this study were equivocal for PCP induction of DNA damage. The rest of the data base for repair-deficient mutant assays is similarly inconsistent. PCP did not exhibit differential toxicity in a subsequent *B. subtilus* rec^+/rec^- assay (Matsui *et al.*, 1989), while an earlier report indicated a positive response in an *E. coli* rec^+/rec^- assay (Shirasu *et al.*, 1976).

(2) Lower Eukaryotes

According to Seiler (1991):
"In contrast to the results with assays in bacterial strains, lower eukaryotes have yielded only positive data, although these studies may all be labeled as inadequate, either because of incomplete reporting, because of a doubtful genetic basis, or because of other shortcomings, and thus they may be of equivocal relevance."

These remarks pertain to four studies. One, by Roy *et al.* (1981), examined the synergistic effect of NaPCP on UV-induced mutations in a mold (*Aspergillus niger*); neither a dose-response relationship nor data on untreated controls were presented. The others, by Fahrig and coworkers, were tests of PCP effects in yeast (*Saccharomyces cerevisiae*), for which few experimental details were provided by the investigators. These studies were positive for mitotic gene conversion (Fahrig, 1974) and for induction of mutation and intragenic (but not mitotic intergenic) recombination by 99% pure PCP (Fahrig *et al.*, 1978), while a host-mediated assay in rats given PCP at 500 mg/kg produced an equivocal outcome for mitotic gene conversion in yeast (Fahrig, 1978).

Simmon and Kauhanen (1978, unpublished) reported that PCP did not produce mitotic recombination in *S. cerevisiae* (NTP, 1989). However, a separate report submitted to DPR described

[6]This study was considered acceptable to DPR based on Toxic Substances Control Act (TSCA) guidelines.

a dose-related increase in mitotic recombination in this organism (Simmon *et al.*, 1979)[7]. The partially purified PCP formulation under test (Dowicide EC-7) was positive both in the presence and absence of activated S9.

(3) Drosophila

The only mutational study of PCP in *Drosophila*, a sex-linked recessive lethal test by Vogel and Chandler (1974), produced negative results (Seiler, 1991; NTP, 1989).

(4) Mammalian Cell Lines

Jansson and Jansson (1986) assayed the ability of PCP to induce point mutation in Chinese Hamster V79 cells and found no induction of mutation at the concentrations tested (6-50 µg/ml). Markedly decreased cell survival was observed above 12.5 µg/ml, indicating that a toxic threshold may have been exceeded.

b. Structural Chromosome Changes

(1) Drosophila

In the only cytogenetics assay performed in *Drosophila*, Ramel and Magnusson (1979) found no effect on nondisjunction or chromosome loss (Seiler, 1991; NTP, 1989).

(2) Mammalian Cell Lines

Results of a cytogenetics study of technical grade PCP in Chinese Hamster Ovary (CHO) cells were included in the study report of the NTP mouse oncogenicity study (NTP, 1989)[2] and published separately by Galloway *et al.* (1987). In the absence of S9 the assay was clearly negative for chromosomal aberrations (CAbs). With S9 present there was a distinct increase in the number of cells with CAbs at the highest PCP level tested (100 µg/ml) in one trial (33% *vs.* 3.0%) and a lesser response (deemed "equivocal" by the investigators) in a second trial (12% *vs.* 3.0%) (NTP, 1989). The investigators considered the sister chromatid exchange (SCE) response to be negative in the presence of S9. They concluded that the response was "weakly positive" in the absence of S9 based on 8.3, 8.2, 10.0, 9.0, and 9.4 SCEs/cell at PCP concentrations of 0, 1, 3, 10, and 30 µg/ml; no statistical justification was provided. Such a conclusion does not seem warranted on the basis of only a 20% increase in frequency at one of the lower doses. Furthermore, the SCE assay's relevance to cancer risk assessment has since been called into question due to low specificity (Tennant *et al*., 1987). Ashby (1993) concluded that a weakly positive *in vitro* SCE response may be of little value.

In the absence of an exogenous metabolic activation system, Ishidate (1988) found no induction of CAbs in Chinese hamster lung fibroblasts *in vitro* at concentrations of PCP up to 60 µg/ml. When the toxic threshold was raised to 240-300 µg/ml by changing to an intermittent treatment regimen, an elevated fraction of cells with CAbs (20-30%) was observed in both the presence and absence of exogenous metabolizing enzymes.

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[7]This study was considered acceptable to DPR based on TSCA guidelines.

(3) Human Lymphocytes *in Vitro*

Ziemsen *et al.* (1987) examined lymphocytes from healthy donors and found no increase in SCEs or CAbs following incubation with technical grade NaPCP at concentrations up to 90 µg/ml. Higher concentrations were lethal to the cells.

c. Other Genotoxic Effects

(1) Mammalian Cells *in Vivo*

The mammalian spot test detects mouse coat color changes that arise during fetal development as a result of exposure-related mutation, deletion, monosomy, and recombination events (Fahrig and Neuhäuser-Klaus, 1985). A mammalian spot test of transplacentally exposed hybrid mice yielded equivocal results; maternal PCP doses of 0, 50, 50, and 100 mg/kg-day produced color spots said to be of "definite" genetic relevance in 1/967, 1/169, 1/147, and 2/157 animals, respectively (Fahrig *et al.*, 1978). The response was dose-related, but the small numbers could have arisen by chance.

Male mice injected i.p. with technical or reagent grade PCP at doses up to 50 mg/kg-day for 5 days did not exhibit dose-related increases in the frequency of abnormal sperm morphology 35 days after the initial injection (Osterloh *et al.*, 1983). Seiler (1991) questioned the negative outcome based on the fact that none of the ten pesticides under test produced a positive result. However, the protocol also included a positive control (90 mg/kg-day methyl methane sulfonate) which yielded a high percentage of abnormal sperm.

A study by Umemura *et al.*, (1996) was conducted to examine the occurrence of oxidative DNA damage and cell proliferation in mice following PCP exposure. A total of 40 B6C3F1 (5-week old male) mice were divided into 4 groups of 10 mice each. PCP (98.6% pure) was mixed in a basal powder diet at concentrations of 0.00 (control), 0.03, 0.06, and 0.12%, and the prepared diets were fed to the animals *ad libitum*. The concentration of 0.06% was the same as the high dose in the 1989 NTP bioassay which demonstrated that chronic administration of PCP induced hepatocellular tumors in B6C3F1 mice; however, the NTP study used PCP of purities 90.4 and 91%.. In addition, it was proposed that PCP's major metabolite, tetrachlorohydroquinone (TeCHQ), plays a key role in PCP hepatocarcinogenesis and results in 8-hydroxy-2-deoxyguanosine (8-OHdG) formation, a representative marker of oxidative DNA damage (Dahlhaus *et al.*, 1994). As a result, the study examined 8-OHdG levels in the nuclear DNA from livers of mice fed PCP in their diet for up to 4 weeks. The mean daily PCP intakes were 41, 86, and 200 mg/kg/day in the 0.03, 0.06, and 0.12% groups, respectively. The results indicated that 8-OHdG levels increased with PCP dose after both 2 and 4 weeks. Because it has been suggested that cellular oxidation might also promote cell proliferation and therefore mouse liver tumorigenesis, the study also examined cell proliferation by hepatocytes of PCP-treated mice together with other hepatotoxicological parameters. Cell proliferation was elevated with increasing PCP dose; however, histopathologically there were no obvious necrotic changes in any treated animals, which indicated a lack of severe hepatoxicity of PCP. There were significant elevations in absolute and relative liver weights in all dose groups, which were concurrent with significant increases in their DNA content. Serum AST levels were significantly elevated in mice exposed to doses of 0.12% PCP at 2 weeks, and 0.06 and 0.12% PCP at 4 weeks, indicating some hepatotoxicity. The study demonstrated a correlation between 8-OHdG formation and cell proliferation,

and implied that cell proliferation following PCP exposure might result not only from regenerative response but also from oxidative stress. However, the study failed to clearly define the mechanism by which PCP induces cell proliferation.

(2) Human Lymphocytes *in Vivo*

An investigation of CAbs and SCEs was performed on the peripheral lymphocytes of 22 male workers in engaged in the production of PCP/NaPCP in the former West Germany (Bauchinger *et al.*, 1982). At the time of the measurements, the mean length of employment was 11.4 years. All 22 of the PCP/NaPCP-exposed men were smokers while the sex- and age-matched control group included 9 smokers and 13 nonsmokers. The percentage of cells containing CAbs was significantly elevated in the exposed workers with respect to the controls (1.0 *vs.* 0.51, $p < 0.004$). The investigators stated that the two CAb subsets which were the most elevated in the PCP/NaPCP-exposed group, dicentrics and acentrics, remained significantly elevated when the nonsmoking controls were excluded ($p < 0.05$). The number of SCEs/cell was slightly elevated in the exposed workers, but the difference was no longer significant when the nonsmoking controls were eliminated from the analysis.

Several factors complicate interpretation of the results of this study. One problem is that no indication was given that the chromosome analyses were conducted in a blind fashion with respect to exposure status. In addition, the degree to which smoking may have confounded the CAb results is not clear because the authors did not report individual data or summary statistics for the 9 controls who smoked. Without such data it is not possible to compare the exposed workers and smoking controls with respect to the percentage of cells containing CAbs or to discern the influence of individual controls on the overall comparison. It is also worrisome that the workers were divided into low- and high- PCP and NaPCP exposure groups (with mean blood PCP levels of 2.4 µg/ml [PCP-exposes] and 0.84 µg/ml [NaPCP-exposed] in the low-exposure groups and 2- to 3-fold higher in the high-exposure groups) yet the investigators did not report whether or not they found a relationship between exposure level and CAb incidence. The failure to note the existence of such a relationship can only be interpreted as signifying that no dose dependence was found. Given the apparent absence of a dose response and the relatively low CAb frequency in the exposed workers (*i.e.*, within the expected background range), the overall response is judged to be equivocal.

Ziemsen *et al.* (1987) examined CAb and SCE frequencies in the lymphocytes of 20 West German workers exposed occupationally to PCP. Mean blood PCP levels in the low- and high-exposure groups were 0.058 and 0.33 µg/ml, respectively. There was no control group. The average number of CAbs per cell was slightly greater in the high-exposure group (0.040 *vs.* 0.026), but there were no statistically significant associations with blood PCP level or PCP exposure group. The frequency of SCEs was similar in the two groups. Consideration of the smokers separately yielded a negative result as well.

d. Effects Potentially Related to Genotoxicity

Viral transformation assays. In a transformation assay with simian adenovirus SA7, a dose-related increase in the transformation frequency of primary Syrian hamster embryo cells was found at PCP concentrations above 50 µg/ml (Casto, 1981). However, as noted by Seiler (1991), this result

may be attributable to the protein-binding capability of PCP or to a disruption of plasma membrane function secondary to the inhibitory effect of PCP on oxidative phosphorylation.

DNA binding assays. Witte *et al.* (1985) detected no DNA binding *in vitro* at PCP concentrations up to 27 mg/ml, while Van Ommen *et al.* (1986) reported DNA binding at a PCP concentration of only 27 µg/ml. However, van Ommen *et al.* (1986) included rat liver microsomes in the incubation medium; TeCHQ and other metabolites were detected.

DNA single-strand break assays. At PCP concentrations up to 27 mg/ml and incubation times as long as 14 hours, Witte *et al.* (1985) found no evidence for the induction of single-strand breaks in isolated supercoiled DNA. Ehrlich (1990) also found no evidence for the production of DNA single-strand breaks and/or alkali-labile sites in intact cultured Chinese hamster ovary cells at PCP concentrations up to 10 µg/ml.

Colony-forming assays. Witte *et al.* (1985) found that a 50% reduction in the colony-forming ability of cultured human fibroblasts was produced by approximately 25 µg/ml and 70 µg/ml PCP in the presence and absence of S9, respectively. TeCHQ was identified in the S9-containing assay medium.

2. TeCHQ

a. Mutagenicity

Mammalian cells in vitro. Jansson and Jansson (1991) tested the ability of TeCHQ to induce point mutations to thioguanine and ouabain resistance at two distinct genetic loci in Chinese hamster V79 cells. Treatment of the cells with TeCHQ in the concentration range 4-60 µM resulted in a dose-related increase in the frequency of thioguanine-resistant (TG_r) mutants, while the number of ouabain-resistant (Oua_r) mutants was not increased by TeCHQ treatment. However, the discrepant response to PCP at the two loci was echoed by the positive control chemical (ethyl methane sulfonate), which produced only 13% as many Oua_r as TG_r mutants.

b. Structural Chromosome Changes

Micronuclei induction. When tested in Chinese hamster V79 cells at concentrations of 1.3-5.3 µg/ml, TeCHQ produced a dose-related, 2- to 7-fold increase in the fraction of cells with micronuclei (Jansson and Jansson, 1992).

c. Effects Potentially Related to Genotoxicity

DNA binding assays. In contrast to their negative results with PCP, Witte *et al.* (1985) found covalent DNA binding to TeCHQ *in vitro*.

DNA single-strand break assays. Again in contrast to their negative results with PCP, Witte *et al.* (1985) reported induction of single-strand breaks in isolated supercoiled DNA by TeCHQ; the effect of TeCHQ was approximately linear over the concentration range 0-27 µg/ml. Ehrlich (1990) found that TeCHQ (but not PCP) induced single-strand breaks in intact Chinese hamster ovary cells; a

dose-related increase in DNA single-strand breaks and/or alkali-labile sites was observed at TeCHQ concentrations of 2-10 µg/ml.

Colony-forming assays. Witte *et al.* (1985) found that a 50% reduction in the colony-forming ability of cultured human fibroblasts was produced by approximately 3 µg/ml TeCHQ. This is to be compared with the more than 20-fold higher concentration of PCP required to produce the same level of inhibition in the absence of S9.

Table III-E-1. Genotoxicity of PCP in the Presence or Absence of Activated Rat Liver S9[a]

Study	Assay Type	Assay System	+/> S9	PCP/NaPCP Grade	Result
NTP, 1989[b] (Haworth *et al.*, 1983)	Gene mutation (bacteria)	*S. typhimurium*	+	Tech.	Negative
" " "	"	"	>	Tech.	Negative
Simmon *et al.*, 1979[b]	"	*S. typhimurium, E. coli*	+	EC-7	Negative
" " "	"	"	>	EC-7	Negative
" " "	Toxicity to repair-deficient mutant bacteria	*B. subtilus, E. coli*	>	EC-7	Equivocal
" " "	Gene mutation (yeast)	*S. cerevisiae*	+	EC-7	Positive
" " "	"	"	>	EC-7	Positive
NTP, 1989[b] (Galloway *et al.*, 1987)	Chromosomal aberration	Chinese hamster ovary cell line	+	Tech.	Positive/ Equivocal
" " "	"	"	>	Tech.	Negative
" " "	Sister chromatid exchange	"	+	Tech.	Negative
" " "	"	"	>	Tech.	Equivocal
Ziemsen *et al.*, 1987	Chromosomal aberration/ Sister chromatid exchange	Human lymphocytes	>	Tech.	Negative
" " "	"	Human lymphocytes (occupational exposure)	n/a	Tech./Pure	Negative
Bauchinger *et al.*, 1982	"	"	n/a	Tech.	Equivocal
Osterloh *et al.*, 1983	Abnormal sperm morphology	Mouse (exposure *in vivo*)	n/a	Tech./Anal.	Negative

[a] *Abbreviations:* S9, microsomal fraction from homogenized rat liver; EC-7, a partially purified grade; Tech., technical grade; Anal., analytical grade; n/a, not applicable.

[b] Study was submitted to DPR by the registrant and was considered acceptable based on TSCA guidelines.

F. REPRODUCTIVE TOXICITY

Summary. The single-generation rat reproductive study submitted to DPR was considered unacceptable under FIFRA guidelines due to design limitations. In the absence of an acceptable study, a provisional reproductive NOEL was derived from this study. A reproductive study of oral exposure to a partially purified PCP formulation found reproductive effects (reduced pup survival, reduced neonatal body weight) at 30 mg/kg-day, a dose which also resulted in reduced body weight gain in the dams. At this dose, the newborns appear to have been more severely affected by continuing perinatal exposure *via* lactation than by prenatal exposure. The NOEL for both maternal toxicity and reproductive effects was 3 mg/kg-day. The results are summarized in Table III-F-1. No other reproduction studies using PCP were identified in the open literature. An acceptable FIFRA guideline, two generation reproduction study has been recently completed and submitted to DPR. No empirical NOEL was established for general toxicity; the overall LOEL for this study was the lowest dose tested, 10 mg/kg-day. Reproductive findings were either associated with maternal toxicity, were accompanied by general growth delays in young rats, or were of no evident functional importance; therefore, no adverse reproductive effects were indicated in this study with PCP.

1. Single Generation (Schwetz, 1974)

Study Design Doses of 0, 3, or 30 mg/kg-day of a partially purified PCP formulation (XD-8108.OOL)were fed to groups of 10 male and 20 female Sprague-Dawley rats for 62 days before mating, throughout mating and parturition, and for 21 days following parturition (Schwetz, 1974; Schwetz *et al.*, 1978). This study was considered unacceptable to DPR for filling a FIFRA-guideline reproductive toxicity data gap, based primarily on the limited study design (only one generation, only two treatment groups, too few males under test, treatment period too short); the reported information was considered useful nonetheless.

Endpoints*.* The body weights of dams given XD at 30 mg/kg-day were reduced 11% at the end of the weaning period; this difference was statistically significant. The maternal NOEL was 3 mg/kg-day. At 30 mg/kg-day there were several statistically significant effects on the offspring: progressive depression in neonatal body weight to 74% of the control value at day 21 and progressive reduction in pup survival to 80% of the control rate at day 21. The decreased survival was distributed throughout the litters such that, from day 7 onwards, mean litter size was significantly reduced to approximately 80% of the control size. The NOEL for these effects was 3 mg/kg-day.

Table III-F-1. Reproductive Oral Toxicity of Partially Purified PCP (XD-8108.00L) in Rats

Study	Species/Sex/Route	Effects at LOEL	LOEL (mg/kg-day)	NOEL (mg/kg-day)
Schwetz, 1974[a]	Rat/M & F /Diet	*Maternal:* V maternal body weight	30	3
		Reproductive: V pup survival throughout litters V neonatal body weight	30	3

[a] Study was submitted to DPR and considered unacceptable with respect to FIFRA guidelines, based primarily on limitations in study design (only one generation, only two treatment groups, too few males under test, treatment period too short), although the information reported was considered useful for defining a provisional reproductive NOEL.

2. Two Generation (Oberman, 1997)

Study design. Thirty rats (Crl:CD®BR VAF/Plus®) per group were dosed with 0, 10, 30 or 60 mg/kg-day pentachlorophenol daily by gavage in a 2 generation (one litter per generation) reproduction study. In addition to the normal reproductive parameters, the following endpoints were evaluated: estrous cycling by vaginal cytology, sexual maturation in males (preputial separation) and females (vaginal patency), sperm count, motility, and variability in epididymides, spermatid counts in testes and primordial follicle counts in ovaries.

Test material. PCP, Lot No. EL-064 (88.9% purity) with corn oil used as the vehicle. This was the same material used in the chronic dog study.

Survival. There were several mortalities resulting from intubation accidents, usually in young rats. Deaths were uncommon, not dose-related and there was no indication of husbandry deficiencies.

Endpoints. Clinical observations of urine-stained abdominal fur and excessive salivation were observed at low incidences in higher dose animals.

Sustained body weight effects were limited to the 30 and 60 mg/kg-day groups; however, F_1 pups in the 10 mg/kg-day group had a mean body weight that was statistically lower from controls during the initial 4 weeks of dosing. The differences between the control group and the 10 mg/kg-day group were plausibly treatment-related, but small in magnitude (i.e. equivalent to approximately one day's weight gain). The body weights of the 10 mg/kg-day F_1 pups were no longer significantly different from controls after about 1 month on treatment. Additionally, the statistically significant body weight decrements in the low dose group were not repeated in the next generation and, therefore, appeared to be incidental or of trivial consequence. Mid-dose (i.e. 30 mg/kg-day) females had more definitive weight gain decrements, although females approached control body weights toward the end of the pre-mating period. Significant decrements in body weight persisted in 60 mg/kg-day groups throughout gestation and lactation.

Food consumption during the pre-mating growth period was generally reduced on an absolute basis in the higher dose groups which had reduced body weights, but was typically elevated in these groups relative to body weight. A general reduction in food consumption during lactation appeared consistent with smaller litter sizes and with reduced growth rates of pups.

Necropsy data did not identify specific effects, other than to confirm high-dose group organ weight changes, such as enlarged livers in P_1 males and small prostates in F_1 males. Organ weight data showed substantial and dose-related increases in liver weights at all dose levels. Hepatocellular hypertrophy and vacuolation and the associated liver weight increases were present in all dose groups of adult rats and in the F_2 weanlings at 30 and 60 mg/kg-day. In males of both generations, absolute liver weights were significantly elevated in a dose-related fashion. Hepatocellular pigmentation and single cell necrosis were common finds reported at 30 and 60 mg/kg-day. There was a general decrease in the weights of male reproductive tissues, and F_1 males had a dose-related increase in the incidence and magnitude of epididymal mononuclear cell infiltration at all dose levels, without associated changes. There was also a decrease in brain weights in both sexes and both generations; brain weight decrements were only noteworthy in the 60 mg/kg-day rats and to a much lesser extent in the 30 mg/kg-day males. There was no brain histopathology associated with the decreased brain weights..

In the high dose group there was a reduction in liveborn litter sizes, a reduction in survival prior to day 4 and a reduction in survival after day 4 of lactation. The lactation index was significantly reduced for offspring of F_1 parents at 30 mg/kg-day; however, this result reflected losses in only one litter, and therefore, was not sufficient evidence to attribute the losses to treatment with PCP. In contrast, the evidence for an impact on the lactation index was sufficiently strong for the high dose group. There were 3 of 16 relevant high dose litters with at least one pup missing or found dead after lactation day 4.

There was no apparent treatment-related effect of PCP on sperm motility, epididymal sperm count or concentration, or sperm morphology. The total spermatid counts in the F_1 males of the 30 and 60 mg/kg-day groups were lower than corresponding control in proportion to the reduced testicular weights. As a result, the calculated testicular spermatid concentration was essentially uniform across treatment groups, and no toxicity specific to male germinal tissues is inferred.

The P_1 and F_1 females were evaluated for estrous cycling by vaginal cytology for 22 days prior to cohabitation until evidence of copulation was obtained. The estrous status of each female was similarly evaluated just prior to sacrifice. Although various individual endpoints were statistically significant, there was no coherent dose-response or consistency over time to suggest a treatment effect.

A primordial follicle count was also evaluated. Control counts were approximately 9 for the P_1 females and 15-16 for F_1 females. The high dose group counts were about 12 in both generations, making them significantly elevated compared to P_1 controls and significantly reduced compared to F_1 controls. As a result, no consistent indication of a treatment effect can be made based on this semi-quantitative evaluation. The histopathologic evaluation found nothing unusual with the ovaries or other reproductive tissues.

The indices of sexual maturation evaluated in F_1 rats included the average day of preputial separation in males and vaginal patency in females. In males there was a statistically significant delay in preputial separation at 30 and 60 mg/kg-day; however, only the results in the high dose group were considered biologically significant by the study investigators, since the mean value of 16 contemporary studies was 45.9 days and close to the value in this study for the 30 mg/kg-day group. For vaginal patency evaluations in females, the historical mean value was 31.9 days, with a range of 30.1 to 33.7 days. The investigators considered the small increase at 30 mg/kg-day to be incidental, because it was close to the observed range. In the perspective of concurrent and historical control mean values, there is no basis for assigning any special "reproductive" attributes to the delay of vaginal patency at any dose, if even nominal consideration for retarded body weight is considered.

This study was considered acceptable under FIFRA guidelines for reproduction toxicity. No empirical NOEL was established for general toxicity; the overall LOEL for the study was the lowest dose tested, 10 mg/kg-day. F_1 pups in the 10 mg/kg-day group had slight but statistically significant reduced body weights during the first 4 weeks of the pre-mating period. Hepatocellular hypertrophy and vacuolation was present in all groups of adult rats, and at 30 and 60 mg/kg-day in F_2 weanlings. In males of both generations, absolute liver weights were significantly elevated in a dose-related fashion. F_1 males had a dose-related increased incidence and degree of epididymal mononuclear cell infiltration at all dose levels, without associated changes. Reproductive findings were either associated with maternal toxicity, were accompanied by general growth delays in young rats, or were of no evident functional importance; therefore, no adverse reproductive effects are indicated in this study with PCP.

G. DEVELOPMENTAL TOXICITY

Summary. Three teratology studies of oral PCP exposure in rats were submitted to DPR. In the most recent rat study, contemporaneous (*c.* 1992) lots of the California registrant's technical grade PCP were tested in Crl:CD®BR VAF/Plus® rats, yielding a developmental NOEL of 30 mg/kg-day based on teratogenic effects (gross external and soft-tissue malformations, 14th vertebra, 14th pair of ribs) at 80 mg/kg-day. This study was considered acceptable to DPR for satisfying the rat teratology requirement. It is noteworthy that the NOEL observed in this study is considerably higher than what was observed in the other two rat studies submitted to DPR: an early study sponsored by a former registrant and a relatively recent study performed by investigators at the U.S. Food and Drug Administration (FDA), both in Sprague-Dawley rats. In the older study, delayed ossification was produced by the lowest dose of purified PCP tested (5 mg/kg-day), while for a technical grade of PCP the developmental NOEL was 5.8 mg/kg-day based on subcutaneous edema and lumbar spurs at 15 mg/kg-day. The FDA study produced a developmental NOEL of 4 mg/kg-day for highly purified PCP based on possible teratogenicity (misshapen centra) at 13 mg/kg-day. Neither of these two rat studies was independently acceptable to DPR, the former because it did not provide a developmental NOEL for purified PCP and the latter because there were too few dams in the low-dose group and individual animal data were not provided. However, the two studies taken together were considered by DPR to be sufficient to satisfy the developmental toxicity requirement in rats. Rat teratology results are summarized in Table III-G-2.

In the single rabbit developmental toxicity study of PCP submitted to DPR, no developmental toxicity was observed in New Zealand white rabbits exposed by gavage to contemporaneous lots (*c.* 1992) of the California registrant's technical grade PCP at doses up to the highest dose tested, 30 mg/kg-day. This study was considered by DPR to be acceptable for fulfilling the rabbit developmental toxicity study requirement. Results are summarized in Table III-G-2.

1. Rat

a. Hoberman, 1994a

Hoberman (1994a) performed a rat teratology study using technical grade PCP (88.9%) under contract to the Pentachlorophenol Task Force, an auxiliary of the California registrant.[8] Twenty-five female Crl:CD®BR VAF/Plus® rats per group were mated, presumed pregnant, and then administered PCP by gavage at dose levels of 0, 10, 30, or 80 mg/kg-day on gestation days 6-15. At Caesarean section on gestation day 20, the number of litters was 22 in the control group and 23-24 in the PCP dose groups.

Endpoints. Maternal body weight gain was significantly reduced (p @ 0.01) in animals given PCP at 80 mg/kg-day. Feed consumption also was significantly reduced in the high-dose group during part of the gestation period. The maternal NOEL was 30 mg/kg-day based on decreased body weight at the high dose.

No abortions or premature deliveries were recorded. There were no dose-dependent or statistically significant differences in the litter averages for corpora lutea, implantations, or percent male fetuses. In the 80 mg/kg-day group the mean live litter size was reduced, but not significantly. Also at the high dose there were significantly increased (p @ 0.01) numbers of resorptions per litter, early resorptions per litter, and dams with any resorptions.

The litter and/or fetal incidences of gross external (gastroschisis) and soft tissue (hydrocephaly, diaphragmatic hernia, kidney pelvis dilatation) malformations or variations were increased (significantly or otherwise) at the high dose. Gastroschisis, hydrocephaly, and diaphragmatic hernia occurred in 2/22 litters in the 80 mg/kg-day groups but in none of the other litters. The incidence of "slight to moderate" dilatation of the kidney pelvis was significantly elevated at the high dose (p @ 0.01) compared to the controls, occurring in 4/22 litters (4 fetuses) at this dose, 1/23 litters (1 fetus) at 30 mg/kg-day, and in none of the low-dose or control litters. The only other gross external or tissue lesion in the 30 mg/kg-day group was a ventricular septal defect.

Delays in ossification of the vertebrae, sternal centers, and/or pelvis occurred in 20/22 litters (81 fetuses) at the high dose and in 3/22, 7/24, and 3/22 litters (5, 8, and 3 fetuses) in the 0, 10, and 30 mg/kg-day groups, respectively. Individual vertebral, sternal, forelimb, and hindlimb ossification

[8]This study was considered acceptable to DPR based on FIFRA guidelines.

sites per fetus per litter were significantly decreased (p @ 0.01) at the high dose, except for thoracic vertebrae sites, which were significantly increased (p @ 0.01). There was also a marked increase (p @ 0.01) in the incidence of a 14th thoracic vertebra and a 14th pair of ribs in high-dose fetuses. In the 30 mg/kg-day group, thoracic ossification sites were slightly increased (1%) while those of the lumbar region were decreased (2%). Although these small differences in the mid-dose animals were reported to be statistically significant (p @ 0.05), the investigators indicated that they were within historical control ranges. In the absence of other signs of developmental toxicity at 30 mg/kg-day, the minor ossification changes were judged by DPR to be of no biological significance. Based on the developmental effects observed at the high dose, the NOEL for developmental toxicity was 30 mg/kg-day.

b. Schwetz *et al.*, 1974

Schwetz *et al.* (1974) evaluated the teratogenic potential of sample lots of commercial (TG) and purified PCP in Sprague-Dawley rats. The test substances were given by gavage on gestation days 6-15 at dose levels of 5.8, 15, 34.7, or 50 mg/kg-day for TG PCP and 5.0, 15, 30, or 50 mg/kg-day for purified PCP, with one control group for both PCP formulations. (The TG doses of 5.8 and 34.7 mg/kg-day were chosen to correspond to PCP doses of 5 and 30 mg/kg-day, respectively.) This study was not independently acceptable to DPR, principally because it failed to provide a developmental NOEL for purified PCP. However, DPR allowed that when data from the FDA developmental toxicity study in rats (discussed below) was also taken into consideration, the combination provided sufficient information to satisfy the FIFRA guideline developmental toxicity requirement.

Test Material-Impurities. Both the TG and purified PCP contained nondectible (< 0.05 ppm) levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). The levels of other nonphenolic contaminants are shown in Table III-G-1.

Table III-G-1. Chlorinated Nonphenolic Contaminants of PCP Formulations Tested in the Developmental Toxicity Study in Rats by Schwetz *et al.* (1974)[a]

PCP Formulation	Concentration (ppm)					
	HxCDD	HpCDD	OCDD	HxCDF	HpCDF	OCDF
TG (88.4% PCP)	4	125	2,500	30	80	80
Purified (> 98% PCP)	< 0.5	< 0.5	< 1	< 0.5	< 0.5	< 0.5

[a] Data from Schwetz *et al.*, 1974. *Abbreviations:* CDD, chlorodibenzo-*p*-dioxin; CDF, chlorodibenzofuran; Hx, hexa; Hp, hepta; O, octa; TG, technical grade.

Endpoints. A dose-related decrease in maternal body weight gain was observed with both grades of PCP; statistical significance was achieved at the two highest doses in both cases. With respect to this measure of maternal toxicity, the purified PCP was more potent. Between days 6 and 21, average weight gains in the 30 mg/kg-day purified PCP and 34.7 mg/kg-day TG groups were, respectively, 26% and 74% of the control value. The maternal NOEL was 15 mg/kg-day for both PCP grades.

The percentage of resorbed fetuses (per animal and per litter) was significantly increased in groups receiving TG at doses A 15 mg/kg-day or purified PCP at doses A 30 mg/kg-day. Even though the LOEL for fetal resorption was lower for animals given TG, at the two highest dose levels (30/34.7 and 50 mg/kg-day) the percentages of resorbed fetuses was much greater with purified PCP (98 and 100%) than with TG (27 and 58%). The sex ratio of surviving pups was markedly altered at the higher doses, with male to female ratios of 3.8 to 1 in the 50 mg/kg-day TG group and 4.9 to 1 in the 30 mg/kg-day purified PCP group. Fetal body weights were significantly decreased at the 30 mg/kg-day dose of purified PCP and at TG doses A 34.7 mg/kg-day. Crown-rump length was significantly decreased only in the 30 mg/kg-day purified PCP group. Note that there were no data on fetal sex, weight, and length for the 50 mg/kg-day purified PCP group because all fetuses were resorbed.

The incidence of subcutaneous edema and anomalies of the skull, ribs, vertebrae and sternebrae increased in a dose-related manner in groups receiving purified or TG PCP. At 5.0 mg/kg-day purified PCP, the percentage of litters demonstrating delayed skull ossification was elevated more than three-fold (9/15 *vs.* 6/31 in controls); this difference was significant. The percentage of litters with lumbar spurs was also elevated at this dose (3/15 *vs.* 4/31 in controls), but not significantly so. Based on the dose-related effects on fetal development observed at all doses, this study produced no NOEL for the developmental toxicity of purified PCP. In the 15 mg/kg-day TG group, the percentage of litters with subcutaneous edema (8/16 *vs.* 6/33 in controls) or lumbar spurs (14/16 *vs.* 4/33 in controls) was significantly elevated. Although litters with lumbar spurs were also elevated (5/18) in the 5.8 mg/kg-day TG group, the increase was not significant. In the absence of other signs of adverse effects at the lowest dose, the developmental toxicity NOEL for the technical grade PCP was 5.8 mg/kg-day based on skeletal and soft tissue anomalies detected at higher dose levels.

c. Welsh *et al.*, 1987

Welsh *et al.* (1987) of the U.S. Food and Drug Administration (FDA) examined the teratogenic potential of purified PCP (99%) in Sprague-Dawley rats. Weanling animals of both sexes received PCP at 0, 60, 200, or 600 ppm diet (corresponding to average daily intakes of 0, 4.0, 13, or 43 mg/kg-day for females). After 181 days on this dietary regimen, males and females were permitted to mate with animals from the same dose group. For the teratology phase, females in each group were continued on the same daily dose until Caesarian section on gestation day 20. This study was reviewed by DPR in its published form and as a slightly more detailed report. Although scientifically valid, DPR found that this was not independently acceptable under FIFRA guidelines, primarily due to the small number of litters in the low-dose group and the fact that individual animal data were not provided. However, this study contributed to the acceptability of the Schwetz *et al.* (1974) study (discussed above) by providing a NOEL for purified PCP.

Endpoints. Signs of maternal toxicity observed at the highest dose were reduced body weight gain, "ringed eye" (in 50% of the dams), and vaginal hemorrhaging (in 25% of the dams). The maternal NOEL was established at 13 mg/kg-day.

The dams receiving PCP at 43 mg/kg-day demonstrated essentially complete resorption of fetuses (99.5%), indicating a profound effect on reproductive competence. The percentage of dams in the 13 mg/kg-day group having two or more resorbed fetuses was twice as great as the control incidence. At this dose, the major fetal effects were a highly significant ($p < 0.01$) increase in misshapen centra by litter (12/16 *vs.* 8/28 in controls) and by fetus (22/86 *vs.* 14/167 in controls) and an approximately 10% weight reduction in fetuses of both sexes. Fetal body weight was depressed to a lesser extent (3-4%) in both male and female 4.0 mg/kg-day groups, approaching statistical significance for males ($p = 0.06$). There were no fetal abnormalities at the low dose. The developmental NOEL was 4.0 mg/kg-day based on fetal weight reduction and skeletal abnormalities at 13 and 43 mg/kg-day.

2. Rabbit

Hoberman (1994b) performed a developmental toxicity study of technical grade PCP in New Zealand white rabbits under contract to the Pentachlorophenol Task Force, an auxiliary of the registrant.[9] Twenty does per group were artificially inseminated, presumed pregnant, and then administered PCP by gavage at dose levels of 0, 7.5, 15, or 30 mg/kg-day on gestation days 6-18. At Caesarian section on gestation day 29, the number of litters was 17 in the control group and 17, 13, and 18 in the low-, mid-, and high-dose PCP groups, respectively.

Test Material. The technical grade PCP compound under test was from lot numbers EL-064 (88.9% pure) and JJ-022 (88.1% pure). No information was provided as to the impurity composition. Lot EL-064 was also used in the rat developmental study performed by Hoberman (1994a), described above. It is assumed that both lots of the test compound were the technical grade product of the registrant. The impurity composition of both lots is expected to have been representative of the registrant's technical grade PCP produced in 1991-1993. (See Table II-C-1).

Endpoints. Mean maternal body weight gain in the 15 mg/kg-day group was marginally (@ 2.5%) but significantly depressed during the dosing period but recovered by gestation day 19. Mean maternal body weight gain in the 30 mg/kg-day group was likewise marginally (@ 3.5%) but significantly depressed during the dosing period but remained depressed (@ 3.8%) throughout the entire 29 days of gestation. Mean feed consumption in the high-dose group was reduced approximately 17-19% throughout the dosing period (averaged over 3-day increments); the difference was significant only for gestation days 9-12. The maternal NOEL was 7.5 mg/kg-day based on the observation of transient decreased weight gain in animals receiving 15 mg/kg-day and prolonged decreased weight gain in animals receiving 30 mg/kg-day.

No deaths, abortions, or preliminary deliveries occurred. The litter averages for corpora lutea, implantations, early and late resorptions, percent resorption, litter size, live fetuses, fetal body weight,

[9]This study was considered acceptable to DPR based on FIFRA guidelines.

and percent male fetuses were comparable among the control and treatment groups. No treatment-related developmental toxicity was observed at any dose. The developmental NOEL was 30 mg/kg-day based on the observation of no effects due to treatment at the highest dose tested.

Table III-G-2. Developmental Oral Toxicity of PCP in Rats and Rabbits[a]

Study	Species /Route	PCP Grade	Effects at LOEL	LOEL (mg/kg-day)	NOEL (mg/kg-day)
Hoberman, 1994a[b]	Rat /Gav.	Tech.	*Maternal:* V weight gain.	80	30
			Developmental: U gross malformations (external, soft tissue); U skeletal anomalies (delayed or residual ossification at multiple sites, extra vertebra & rib pair).	80	30
Schwetz *et al.*, 1974[c]	Rat /Gav.	Tech. /Pure	*Maternal:* V weight gain.	30 /34.7	15 /15
			Developmental: U percentage males; V fetal body weight; U subcutaneous edema; U skeletal anomalies (lumbar spurs, delayed skull ossification).	15 /5.0	5.8 /None
Welsh *et al.*, 1987[c,d]	Rat /Diet	Pure	*Maternal:* V weight gain; U "ringed eye"; U vaginal hemorrhaging.	43	13
			Developmental: V fetal body weight; U skeletal anomalies (misshapen centra).	13	4
Hoberman, 1994b[b]	Rabbit /Gav.	Tech.	*Maternal:* V weight gain	15	7.5
			Developmental	None	30 (HDT)

[a] *Abbreviations:* Tech., technical; HDT, highest dose tested; gav., gavage.

[b] Study was submitted to and considered acceptable by DPR based on FIFRA guidelines.

[c] Taken together, these two studies submitted to DPR were considered acceptable based on FIFRA guidelines.

[d] Dosing was initiated 180 days prior to mating.

H. NEUROTOXICITY

A single neurotoxicity study, conducted in Chile, was identified in the open literature. The investigators looked at the effects of PCP on the ultrastructure of the sciatic nerve in male Wistar rats exposed to 0, 0.3, 1 or 3 mM (0-800 mg/L) PCP (presumably a purified grade) in the drinking water for 60, 90, or 120 days (Villena *et al.*, 1992). Assuming default values for drinking water consumption and body weight of 0.032 L/day and 0.217 kg (U.S. EPA, 1988), the PCP doses are calculated to be 12-118 mg/kg-day. Myelin degeneration was reported in rats exposed to 1 mM PCP for 90 days or 3 mM PCP for 120 days. However, insufficient experimental details were provided to allow a reliable assessment of the findings. One potentially serious problem with this study is that the solubility of PCP in water is only 20 mg/L at 30bC (ICPS, 1987); this corresponds to a dose of 2.9 mg/kg-day, a factor of 4-40 less than the target doses. The investigators apparently did not measure the actual concentrations attained.

Neither morphologic nor clinical evidence of PCP neurotoxicity was observed in any other subchronic or chronic animal exposure study, including several well-documented oral studies in rodents exposed subchronically (Kurtz and Hejtmancik, 1993; Kociba *et al.*, 1973) or chronically (NTP, 1989) to PCP at dose levels as high as the MTD. However, as detailed in the Acute Toxicity Section (III-B), cholinergic signs (possibly a function of neurotoxicity) were observed in rats following acute oral exposure to 100 mg/kg (WIL Research Laboratories, 1978a). Claims have been made that chronic exposure in humans is linked to depression, general fatigue, dizziness, sleep disturbances, aggressive behavior, loss of appetite, headache, nausea, diarrhea, fear, thirst, and hyperthermia (Jorens *et al.*, 1991), any of which may be indicative of a neurotoxic effect.

I. IMMUNOTOXICITY

Summary. The immunotoxicity studies reviewed and presented in this document were identified in the open literature. In several studies, technical grade PCP with impurity composition similar to that of the product currently registered in California was found to suppress humoral immunity in mice treated subchronically at oral doses as low as 9 or 10 mg/kg-day; no NOEL was identified. One of these studies also found that both purified and technical grade PCP at subchronic oral doses as low as 9 mg/kg-day produced increased susceptibility to invasive tumorigenesis in mice; again, no NOEL was identified. There is some suggestive evidence for a developmental effect of PCP: purified PCP suppressed delayed-type hypersensitivity and humoral immunity in rats exposed prenatally and then subchronically to oral doses as low as an estimated 0.74 mg/kg-day, the lowest dose tested, although dose dependence was weak or absent. Major immunotoxicity results are summarized in Table III-I-1.

1. Overview

Subchronic oral administration of technical grade PCP formulations to mice at the lowest doses tested (9 or 10 mg/kg-day) suppressed T-cell cytotoxicity, cell-mediated host defense against tumor invasion (Kerkvliet *et al.*, 1982a), and humoral immunity (Kerkvliet *et al.*, 1982b; Holsapple *et al.*, 1987) following *in vivo* sensitization. Kerkvliet *et al.* (1985) concluded that suppression of the antibody response of splenic plasma cells (humoral immunity) by technical grade PCP can be explained entirely as the sum of the suppressive effects of pCDD contaminants. Comparison of the chemical composition

of the formulation studied by Kerkvliet *et al.* (1985) with that of the product registered in California indicates that some of the contaminant pCDDs are present at similar levels.

In two of three studies in mice, subchronic oral administration of purified grades of PCP at dose levels as high as 90 or 100 mg/kg-day failed to suppress the humoral immune response to *in vivo* antigen challenge (Holsapple *et al.*, 1987; Kerkvliet *et al.*, 1982b). These results are contradicted by the suppression of humoral immunity seen by Exon and Koller (1983) in rats following prenatal through subchronic exposure in the diet to purified PCP (97% pure, contaminants not analyzed) at dose levels as low as 0.74 mg/kg-day. The fact that humoral immune effects were observed following exposure begun prenatally whereas no such effects were observed at much higher doses in the subchronic exposure studies is possibly indicative of a developmental effect. However, given the U-shaped dose-response relationship, the humoral response recorded by Exon and Koller (1983) is best interpreted as suggestive rather than conclusive because the was not independent confirmation of dietary doses. In the same study, delayed-type hypersensitivity (a response dependent upon cell-mediated immunity) was suppressed approximately to the same extent at all doses of purified PCP tested.

The only clearly dose-related immunotoxic response to a purified grade of PCP was the occurrence of splenic tumors in mice challenged first with tumor virus and then with sarcoma cells (Kerkvliet *et al.*, 1982a). This unanticipated result occurred at both subchronic oral dose levels of the analytical grade PCP tested (9.0 and 90 mg/kg-day) but not at the same dose levels of technical grade PCP. Apparently there has not yet been any attempt to replicate this finding. Nevertheless, the observed increase in susceptibility to invasive tumorigenesis must be considered as evidence of a potentially important immunotoxic effect of PCP.

Table III-I-1. Immunotoxicity of Oral Exposures to PCP in Mice and Rats[a]

Study[b]	Species	PCP Grade	Exposure Duration	General Immunocompetence	Cell-Mediated Response		Humoral Response (Ab-Mediated)	LOEL	NOEL
					Macrophage	T-cell		(mg/kg-day)	
1	Rat	Purif. (97%)	Prenatal + lactation + 10 wks	-	Enhanced[c]	Suppressed DTH (flat dose-response)	Suppressed T-cell dependent Ab response (U-shaped dose-response)	0.74	None
2	Mouse	Anal. (>99%)	10-12 wks	Suppressed host tumor resistance to virus-transformed tumor cells (spleen = distal site)	No effect	No effect	-	9	None
2	Mouse	Tech.	10-12 wks	Suppressed host tumor resistance to syngeneic tumor cells (local site) and to virus-transformed tumor cells (spleen = distal site)	Enhanced at 90 mg/kg-day	Suppressed at 90 mg/kg-day	-	9	None
3	Mouse	Anal. (>99%)	8 wks	-	-	-	No effect on T-cell dependent Ab response	None	180[d]
3	Mouse	Tech.	8 wks	-	-	-	Suppressed T-cell dependent and independent Ab responses	9	None
4	Mouse	Purif.[e]	2 wks	-	-	-	No effect on T-cell dependent Ab response	None	100[d]
4	Mouse	Tech.	2 wks	-	-	-	Suppressed T-cell dependent Ab response	10	None

[a] Experiments entailed *in vivo* antigen challenge unless otherwise indicated. *Abbreviations:* Ab, antibody; purif., purified;, DTH, delayed-type hypersensitivity; anal., analytical; tech., technical.

[b] 1, Exon and Koller, 1983. 2, Kerkvliet *et al.*, 1982a. 3, Kerkvliet *et al.*, 1982b. 4, Holsapple *et al.*, 1987.

[c] Antigenic activation of isolated macrophages *in vitro*.

[d] Only dose tested.

[e] Dowicide EC-7; 91% pure, 9.4% tetrachlorophenol.

J. OTHER TOXICITY STUDIES

Summary. One acute study examined the effect of PCP on thyroid hormones in rats (van Raaij, *et al.,* 1991b), and a subchronic study using Holstein cows looked at various parameters to evaluate endocrine and immune functions (McConnell *et al.,* 1980). In the acute study in rats, circulating levels of the thyroid hormone thyroxine declined following i.p. injection of purified PCP at 1.8 mg/kg; the no-observed-effect level (NOEL) was 0.6 mg/kg. Concurrent with this study, the investigators also performed an identical study of the acute effects of TeCHQ on serum levels of the thyroid hormones TT4 and TT3 in male WAG/RIJ-MBL rats. The results of this study indicate a NOEL of 6.5 mg/kg for acute, i.p. exposure to TeCHQ based on decreased serum TT4 and TT3 in rats at 8.5 mg/kg. This NOEL is an order of magnitude higher than that obtained for PCP in the same study. It is possible that both the NOEL and the LOEL for TeCHQ would have been lower if the timing of the dose-response measurement had been set to match the timing of maximal depression of the thyroid hormone levels (as was done in the PCP dose-response experiment).

In a separate report, the same group of investigators examined competitive inhibition of T4-binding sites in serum by PCP and TeCHQ in an attempt to explain the actions of these compounds on thyroid hormone levels (van Raaij *et al.*, 1991a). The results demonstrated a possible mechanism for the action of PCP only. In *ex vivo* experiments, PCP, but not TeCHQ, was a competitive inhibitor of T4 binding to rat sera. Thus, the action of PCP on TT4 levels does not appear to require metabolism to TeCHQ.

In the cow study, technical grade PCP at an oral dose of approximately 16 mg/kg-day produced signs of toxicity in multiple organs (including liver, bile duct, gall bladder, urinary bladder, spleen, tonsils, thyroid, eyelid exocrine glands), decreased thymus weight and red cell count, and stimulated the lymphoproliferative response. Purified PCP at the same dose decreased the thyroid hormones thyroxine and triiodothyronine, depressed thymus weight, and increased liver smooth endoplasmic reticulum; the effect on liver may have been adaptive rather than adverse. No NOEL was identified for either PCP formulation. The results of this study in cows indicate that the multi-organ toxicity of technical grade PCP was largely due to contaminants in the test material. However, the finding that oral exposure to purified PCP decreased thymus weight and depressed thyroid hormones in cows supports the results of alterations in immune function and thyroxine levels in rodents by oral or i.p. exposure to purified PCP.

K. EPIDEMIOLOGICAL STUDIES AND CASE REPORTS

Summary. The case report literature on PCP exposure indicates that short-term inhalation of vapors in an unventilated area or prolonged dermal contact have resulted in hemotoxicity (aplastic anemia and thrombocytopenic purpura), toxicity to the nervous system (excessive sweating, tachycardia, tachypnea, anorexia, fever), hepatic and renal degeneration, dermal toxicity (*Pemphigus vulgaris*, urticaria), and death. There have been numerous case reports of hemotoxicity (aplastic anemia and red cell aplasia) and a few of Hodgkin's disease and leukemia following longer-term exposures to PCP. One case-control study of soft-tissue sarcoma found an association with PCP and other chlorophenols while a second found no such link. A case-control study of Non-Hodgkin's lymphoma and another of multiple myeloma each failed to demonstrate a relationship to occupational PCP exposure. In one occupational cohort study, elevated incidences of chronic sinusitis, non-bacterial conjunctivitis, chronic upper respiratory conditions, gout, eye disease, and skin infections occurred in workers exposed to PCP. In a

second occupational cohort study, adverse effects on the liver and depressed T-cell responsiveness were found in the PCP-exposed subjects. In a residential cohort study, autoimmunity and depressed T-cell responsiveness were associated with residence in log cabins treated with PCP.

Relevance of the pCDD contaminants to potential human health effects In laboratory tests conducted in the late 1970s, TCDD levels in the range 0.25 to 1.1 ppb were measured in commercial PCP (IPCS, 1987). Thus, it is expected that this range approximates the TCDD contamination of PCP followed in case reports and epidemiological studies of that time period. Exposure to TCDD has been linked to soft-tissue sarcoma (STS) in several epidemiology studies. Fingerhut *et al.* (1991) examined a cohort consisting of essentially all U.S. chemical workers occupationally exposed to TCDD; a significantly increased risk of cancer mortality, mostly due to STS, was found in the subcohort with at least 1 year of exposure and at least 20 years of latency. Self-reported exposures to TCDD and more highly chlorinated pCDDs have been linked to soft-tissue sarcoma in a Swedish case-control study (Eriksson *et al.*, 1990). The same study found larger odds ratios associated with exposures to PCP and/or other chlorophenols than to TCDD and other pCDDs. It is probably reasonable to assume that the extent of exposure to pCDD contaminants in persons who reported exposure only to PCP and other chlorophenols was generally less than the extent of pCDD exposure in persons reporting exposures only to pCDDs. If so, then it is unlikely that the carcinogenicity associated with PCP in the study of Eriksson *et al.* (1990) can be attributed entirely to pCDD contamination. Case reports link hemotoxicity, immunotoxicity, and hepatotoxicity with human exposures to PCP, while similar effects are produced by TCDD in primates (Allen and Miller, 1978) and may also be associated with higher pCDDs. Although there is uncertainty surrounding the potential role of pCDD contaminants in the development of these endpoints, animal studies of purified PCP suggest that exposure to PCP itself may be implicated.

1. Acute and Short-Term Exposure

Exposure dose could not be determined in the acute/short-term case reports reviewed.

a. Occupational Case Reports

Rugman and Cosstick (1990) reported the case of a 28-year-old male diagnosed with aplastic anemia. Several months earlier he had used PCP in the course of renovating a building. The patient later died of disease secondary to the anemia.

Hay and Singer (1991) treated a 17-year-old female diagnosed as having thrombocytopenic purpura. The woman was currently employed on the production line of a manufacturer of liquid wood preservatives containing PCP, tributyl tin oxide, lindane, and permethrin in a petroleum-based solvent. The factory ventilation was inadequate, and dermal exposure of the hands (through linen gloves) and body (through clothing) occurred frequently.

Inhalation and/or dermal exposures to PCP have been reported to result in abdominal pain, nausea, vomiting, and sweating in nine Australian herbicide sprayers, with death the outcome in five cases (Gordon, 1956, in U.S. EPA, 1991); similar symptoms were observed in four nonfatal cases among Canadian factory workers (Bergner *et al.*, 1965, in U.S. EPA, 1991). A fatal case of occupational PCP poisoning was reported in a 58-year-old male who had been employed for 1 week dipping wood into a petroleum solution of 4.1% PCP and 0.9% other unspecified chlorophenols. Neurologic symptoms

including anorexia, fatigue, sweating, and thirst were followed by a high fever and then death. Autopsy revealed slight hepatic and renal degeneration (Bergner *et al.*, 1965, in U.S. EPA, 1991). Nine deaths over 18 months were reported in Asian sawmill workers; fever, profuse sweating, and moderate abdominal symptoms preceded severe terminal spasms (Menon, 1958, in U.S. EPA, 1991).

Cooper and Macauley (1982) described the case of a 51-year-old male joiner who became ill after applying a PCP-containing wood preservative in a poorly ventilated room without benefit of protective clothing. Abdominal symptoms arose within 2 hours of initial exposure. Upon hospital admission 5 days later, the patient was diagnosed as having pancreatitis accompanied by hepatic and pulmonary damage.

b. Non-Occupational Case Reports

Robson *et al.* (1969) and Armstrong *et al.* (1969) reported 20 cases of PCP poisoning *via* dermal exposure among neonates in a hospital nursery; the infants' diapers and bed linen had been laundered with PCP. Signs potentially associated with neurotoxicity included excessive sweating, tachycardia, tachypnea, respiratory distress, and metabolic acidosis. Hepatic enlargement also occurred, while autopsy of two fatal cases revealed fatty infiltration of the liver and fatty degeneration of the renal tubular cells.

Lambert *et al.* (1986) described 2 cases of skin lesions associated with residential exposure to PCP (U.S. EPA, 1991). *Pemphigus vulgaris* was diagnosed in a 41-year-old male exposed to a PCP-treated bookcase and a 28-year-old female exposed to PCP-treated rafters. Maximum serum PCP levels in these individuals were 47 µg/L and 114 µg/L, respectively; clinical improvement followed declining serum levels in both patients. In a third case report, a 35-year-old man with urticaria had treated wood framework with PCP; his maximum serum PCP level was 96 µg/L. The investigators suggested that photoreactivity and immunotoxicity may underlie the observed dermal toxicity.

2. Subchronic and Chronic Exposure

Case reports, case-control studies, and cohort studies of long-term exposures to PCP were reviewed; exposure dose could not be determined in any study except as indicated. The results of potentially informative case-control and cohort studies are summarized in Table III-K-1.

a. Case Reports (Hemotoxicity)

Roberts (1983) described six cases of aplastic anemia or red cell aplasia associated with exposure to PCP. In one of the cases of aplastic anemia, the patient (a 21-year-old male truck driver) had handled wet lumber processed with a commercial product containing 3% PCP and 1.5% tetrachlorophenol during the year prior to onset of clinical symptoms. Handling resulted in dermal and oral (hand-to-mouth) exposure to the wood preservative. The patient died of related causes 5 months after clinical onset.

In another case, a 27-year-old male physician worked at building a log cabin one day per month. Using cloth gloves, he applied a 5% PCP solution with a brush after diluting a 40% solution with fuel oil. Symptoms were established within 9 months of the initial PCP exposure. Multiple medical measures were taken, but death occurred 6 months later.

The other cases summarized by Roberts (1983) include a 24-year-old male exposed to PCP while working in construction who developed aplastic anemia and Hodgkin's disease 2 years after initial exposure (resulting in death); a 21-year-old male who applied PCP to furniture for 2 days, allowed the furniture to remain in his room, and developed aplastic anemia 1 month later; a 73-year-old male who repeatedly applied undiluted PCP to wood in a poorly ventilated barn, wearing no protective clothing, and developed pure red cell aplasia 4 years after initial exposure (resulting in death); and a 47-year-old male who dipped window panes into PCP at work and developed pure red cell aplasia 2 years after initial exposure, with death due to acute leukemia 2 years later.

Rugman and Costick (1990) reported one case of fatal aplastic anemia in a 28-year-old male computer operator. During the months preceding his admission to hospital, the man had applied PCP to timber in the course of renovating an old building.

b. Case-Control Studies

Pearce *et al.* (1986a) performed a case-control study to investigate whether the incidence of non-Hodgkin's lymphoma (NHL) in New Zealand was associated with the performance of occupational tasks in which likely exposure to pentachlorophenol or other chlorophenols occurred. The case population consisted of male patients with a confirmed diagnosis of NHL other than lymphosarcoma or reticulosarcoma during the years 1977-1981; the number of cases in the final sample was 83. A total of 168 male patients with other types of cancer (matched for age and year of cancer registration) were selected as cancer controls. An additional set of 228 male, general population controls were selected from the compulsory electoral role. All odds ratio (OR) calculations were stratified across decade of birth.

The relative risk for fencing contractors (4 exposed cases) was significantly elevated against the population controls and non-significantly elevated against the cancer controls. The relative risk for fencing as a farmer was significantly elevated against the cancer controls and non-significantly elevated against the population controls. For employment in the pelt department of a meat works (4 exposed cases), the OR was 4.1 against the general population controls (90% CI = 1.1-14) and was non-significantly elevated against the cancer controls. There was no increased relative risk of NHL for sawmill/timber merchants, for persons in the category "potential chlorophenol exposure at sawmill or timber merchant," or for tannery workers.
The results of this study cannot be interpreted as being indicative of an association between PCP exposure (or its technical grade contaminants) and NHL.

Pearce *et al.* (1987) expanded the case-control study of Pearce *et al.* (1986a) on the association between NHL and occupational exposures to chlorophenols to include lymphosarcoma and reticulosarcoma diagnoses among the NHL cases; a total of 183 male NHL cases were included in the final sample. The control group consisted of 338 males diagnosed with other types of cancer. All odds ratio calculations were stratified across decade of birth. The relative risk for fencing work was found to be non-significantly elevated The OR for employment in the pelt department of a meat works was non-significantly elevated, while for employment in any meat works job, the elevation was statistically significant. The results of this study do not support an association between NHL and exposure to PCP or other chlorophenols. Sawmill workers were expected to have the most PCP/chlorophenol exposure but did not exhibit an elevated relative risk for NHL. The investigators suggested that some other factor common to meat works employees, such as a tumor virus, may have been responsible for their increased relative risk.

Appplying the same methods as applied by Pearce *et al.* (1986a, 1987) in their study of NHL, Pearce *et al.* (1986b) selected 76 male cancer patients in New Zealand diagnosed with multiple myeloma during the period 1977-1981 and examined the association with occupational exposures to chlorophenols. The control group consisted of 315 males diagnosed with other types of cancer. All odds ratio calculations were stratified across decade of birth. Relative risk was non-significantly elevated for fencing work, fencing work with self-treated posts, saw mill or timber merchant, saw mill or timber merchant with potential occupational exposure to chlorophenols, and meat works employment). The investigators concluded that their results did not support an association between multiple myeloma and exposure to chlorophenols.

Smith *et al.*, (1984) conducted a case-control study in New Zealand of male soft-tissue sarcoma (STS) cases diagnosed during the years 1976-1980. There were 82 STS cases and 92 mostly age-matched controls diagnosed with other forms of cancer. Of the job categories entailing potential exposures to chlorophenols, non-significantly elevated relative risks were found for fencing contractors saw mill or timber merchants, employment in the pelt department of a meat works, and tannery or meat works pelt department work. The only significantly elevated relative risk was found for meat works. There was no elevation of relative risk linked to job classifications with the highest potential exposure to PCP and other chlorophenols: "potential chlorophenol exposure at saw mill or timber merchant."

Eriksson *et al.* (1990) performed a case-control study based on confirmed cases of soft-tissue sarcoma (STS) in males diagnosed in Uppsala, Sweden during the years 1978-1986. Assessment of exposure to PCP and other chlorophenols was determined by questionnaire and follow-up interview. The final case group size was 78 alive and 140 deceased. Controls were drawn from the national population registry and were matched for age, gender, county of residence, and alive/deceased status. To allow for tumor latency, exposures within 5 years of diagnosis were excluded. Exposure to PCP for at least 1 week continuously or at least 1 month total (in the absence of exposure to phenoxy acetic acid herbicides) was reported in 11 cases and 3 controls (OR = 3.9, 95% CI = 1.2-12.9).

c. Cohort Studies

Klemmer *et al.* (1980) performed a cross-sectional study on Hawaiian workers with differential exposure to PCP. The study's comprehensive health evaluation included standard clinical-chemistry testing (but no thyroid hormone measurement) and physical examination. The initial sample population consisted of 422 individuals, of whom 47 were wood-treatment workers with exposure to PCP (open-vat or pressure-tank processes) and no reported exposures to other pesticides, 333 were pest-control operators (PCOs) or farmers with exposure to various pesticides, and 42 were controls with no occupational exposure to PCP or other pesticides. Long-term exposures to PCP were approximated by one-time measurement of blood PCP concentrations. Mean blood PCP concentrations in the wood-treatment group were 3.8 mg/L for the open-vat workers and 1.7 mg/L for the pressure-tank workers. The mean blood PCP concentrations in the PCOs/farmers and controls were much lower (0.25 and 0.32 mg/L, respectively). Analysis of PCP-associated effects was based on designation of the wood-treaters as the "PCP-exposed" group and the combination of controls and PCOs/farmers as the "non-PCP-exposed" group. The investigators reported summary statistics for the clinical chemistry outcomes for only 45% (189/422) of the available study population. The changes reported as being significantly greater in the PCP-exposed group were the number of immature neutrophils ($p < 0.005$), plasma cholinesterase levels ($p < 0.05$), and alkaline phosphatase levels ($p < 0.05$). In spite of their statistically

significant elevation, the clinical chemistry values observed in both the wood-treaters and the rest of the cohort were within ranges considered normal. Age-standardized prevalence rates of diagnosed illnesses were reported for the 47 PCP-exposed subjects (wood treaters) and 42 controls. The investigators did not specify whether the illness data encompassed all years of exposure or some other time frame. The statistical significance of the elevated prevalence ratios was not given, and insufficient data were provided for an independent determination.

A decade after Klemmer *et al.* (1980), Gilbert *et al.* (1990) performed another cross-sectional study on Hawaiian workers with differential exposure to PCP. The comprehensive health evaluation included standard clinical chemistry testing (but no thyroid hormone assay), standardized physiological testing, physical and neurological examination, and medical history. The subjects were male wood-treatment workers in Hawaii who had been exposed to wood-treating chemicals while using open-vat (PCP) or pressure-tank (PCP, chromated copper arsenate, or tributyl tin oxide) methods for a period of at least 3 months between 1960 and 1981. Out of a total of 182 men identified as falling into this category, 119 (65%) of the survivors were located, and 88 (48%) agreed to participate. Of these, 66 were actively employed in the wood-treatment industry. The median exposure duration in the exposed group was 6.5 years, while 38% had A 10 years exposure. The 88 exposed subjects were matched with 58 nominally nonexposed controls according to age, race, level of physical activity, and weight. Socioeconomic status was not matched and tended to be higher in the controls than in the exposed subjects. The controls were chosen on the basis of never having been employed in the wood-treatment industry, but 13 were carpenters who had been occupationally exposed to one or more of the chemicals of interest to this study. Mean urinary concentrations of PCP were 174 µg/L in the exposed group and 35 µg/L in the control group. There were a few statistically significant differences in clinical chemistry values and other physiological parameters between the exposed and control groups. These included changes in serum protein, heart rate, systolic blood pressure, measures of vision, and measures of skin thickness and fattiness. The investigators failed to state the direction of the effect of exposure for all parameters except systolic blood pressure and heart rate, both of which were slightly higher in the exposed group. One cancer case was reported among the exposed workers. No other data were provided for the parameters noted here or any other tests. Approximately one-third of both the control and exposed groups self-reported a history of some type of problem involving skin or mucous membranes of the nose or eyes. Medical examination revealed rash in 20.5% of the wood treaters and 16.4% of the controls (not significant), while the medical history indicated that rash incidence was higher in the controls. For a number of subjects in both the control and exposed groups, serum levels of lactate dehydrogenase (LDH), alkaline phosphatase, and glutamic oxaloacetic transaminase (SGOT) were found to be outside the range of values considered normal by the testing laboratory. This study found that occupational exposure to PCP did not produce an excess of illness symptoms in the population under study. However, there are several serious problems with this study that preclude taking the results at face value. One problem is that only 48% of the original cohort was followed. It is also troubling that there were so few controls and whether the controls constituted a suitable, healthy baseline group. The investigators failed to provide data for most variables tested; therefore it was not possible to independently assess their conclusions.

Wolf and Karmaus (1995) investigated the effects of chronic exposure to PCP-based wood preservatives (containing pCDDs) on cell-mediated immunity in day-care teachers. The study population consisted of 221 exposed and 189 non-exposed employees of day-care centers in Hamburg, Germany. Exposure averaged 6.9 years (range, 0.2-17.3) and postexposure duration averaged 0.6 years (range, 0-13.5). CD4 count, CD8 count, CD4:CD8 ratio, and skin tests of delayed-type hypersensitivity (DTH) were

performed. In the DTH test, seven recall antigens were applied to the skin; sub-normal responses were classified as hypoergy I (small total diameter of skin reactions), hypoergy II (@ 1 positive reaction), and anergy (no positive reactions). The analysis was stratified into three exposure categories based on surrogate measures of "dioxin" burden (TCDD toxicity equivalent concentrations of 0, 0-6, and >6 pg/m^3) calculated from models of indoor air concentrations. In a subset of the high-exposure group whose exposure occurred @ 6 months earlier, the comprehensively covariate-adjusted odds ratios for hypoergy I and II were 9.5 (95% CI = 2.0-46) and 2.9 (95% CI = 1.1-7.5), respectively. Significantly elevated crude or covariate-adjusted odds ratios were not found for any other comparison. The investigators concluded that this study does not rule out the possibility of a suppressive effect on cell-mediated immunity deriving from exposure to dioxins in wood preservatives.

McConnachie and Zahalsky (1991) performed a cross-sectional study of the peripheral blood lymphocytes (PBLs) from 38 individuals in 10 families living in PCP-treated log homes in Indiana and Kentucky. There were 21 males and 17 females in the cohort, 8-60 years of age (mean, 30 years). Exposure duration was 1-13 years (mean, 7.4 years). The elapsed time between the last exposure and the performance of PBL testing was 0-9 years (mean, 4 years). There were 39 male and 81 female controls, 11-67 years of age. Controls had no known hematologic disorders or illness. No exclusions or data corrections were made for other potentially confounding factors, such as smoking.

The results of this study provide a reasonably coherent body of evidence that autoimmunity and depression of the T-cell proliferative response are associated with residence in log cabins treated with PCP. For the most part, the results are consistent with the suppression of both the T-cell response and general immunocompetence in experimental animals treated with technical grade PCP manufactured in the same decade (1980s) that the human exposures in this study occurred (see Section I).

Colosio *et al.* (1993) evaluated clinical pathology in a cross-sectional study of 32 workers with prolonged exposure to PCP in a Northern Italian wood factory. Of these, 14 subjects (the high-exposure group) had been engaged in brush application of PCP for at least 10 years. The remaining 18 subjects (low-exposure group) had only indirect exposure to PCP from handling the treated wood and from general contamination in the work place. The control group consisted of 37 subjects who worked in a marble factory in the same valley. Plasma PCP levels reflected the differential exposure of the low- and high-exposure groups, while urinary PCP levels were similar in the two groups. Mean PCP concentrations in the high-exposure, low-exposure, and control groups were 289, 145, and 9 µg/L in plasma and 127, 154, and 5 µg/L in urine, respectively. All subjects underwent routine clinical chemistry testing. Fasting serum bile acid (SBA) levels and urinary excretion of D-glucaric acid (a SBA degradation product), porphyrins, and 6-β-hydroxycortisol were determined as additional measures of liver function. *In vitro* tests of humoral and cellular immunity were performed on serum and blood samples. The investigators reported that of the clinical laboratory tests, only the SBA analyses revealed differences between the exposed and control groups. Three of the six measured SBAs were elevated in the high-exposure group relative to the controls; covariate correction (for alcohol and tobacco use and age) did not alter the results. Both the crude and covariate-corrected T-cell mitogenic response to 5% phytohemagglutinin (PHA) were significantly reduced in the high-exposure group relative to both the low-exposure group and the controls. The results demonstrated a potentially adverse effect on the liver associated with long-term occupational exposure to PCP. With respect to potential immunological effects, the observation of a depressed T-cell response to mitogen in PCP-exposed workers is consistent

with the results of treating animals with technical grade PCP (see Section I); however, whereas suppression of humoral immunity was invariably produced in the animal studies of technical grade PCP, none was found in this study. The observation of depressed T-cell activation in occupationally exposed workers is also consistent with the similar finding in residents of PCP-treated log homes described by McConnachie and Zahalsky (1991).

A longitudinal study of nerve conduction velocity (NCV) was performed by Triebig *et al.* (1987) in 10 West German chemical-company workers. The 7 men and 3 women had contact with PCP and PCP-containing substances for a duration of 4-24 years (mean, 16 years). Serum PCP levels in 1980 (mean, 368 µg/L) were similar to those seen in 1984 (mean, 346 µg/L). However, urinary levels had decreased between 1980 (mean, 313 µg/L) and 1984 (mean, 72 µg/L). NCV values measured in 1984 were similar to those measured in 1980 and were in the low-normal range. The only conclusion that can be drawn from this study is that continuing exposure to PCP for an additional 4 years did not diminish NCV in subjects with ongoing, chronic, occupational exposure to PCP. This study did not address the question of whether NCV was lower than normal in these subjects due to exposure which took place prior to 1980.

Gilbert *et al.* (1990) performed a retrospective mortality study of wood-treatment workers in Hawaii who had been exposed to wood-treating chemicals while using open-vat (PCP) or pressure-tank (PCP, chromated copper arsenate, or tributyl tin oxide) methods for a period of at least 3 months between 1960 and 1981. Of the 182 wood-treatment workers identified as potential study subjects, records could be obtained only for 125 (69%). Within this group of 125, six deaths had occurred: four due to coronary artery disease, one due to cerebral thrombosis (stroke), and one due to unknown causes. The investigators stated that the number of expected deaths in this cohort was 8. The investigators indicated further that of the 8 anticipated deaths among men in Hawaii who were 55-64 years of age in 1981, approximately 4 would have been expected to die of cardiovascular disease, 3 of cancer, and 1 of other causes. With respect to the potential carcinogenicity of PCP, one cannot place confidence in the negative findings of this study. The study population was too small, as was the percentage of responders. In addition, the follow-up period may have been of insufficient duration. The statistical limitations of the study are further magnified by the fact that chromated copper arsenate (CCA), not PCP, was the dominant exposure of most of the cohort; the investigators indicated that in 1977, CCA usage in Hawaii was approximately 30 times greater than that of PCP.

Table III-K-1. Health Effect Outcomes in Selected Epidemiological Studies of PCP Exposures

Study	Study Type	Health Effect/Outcome[a]
Pearce *et al.*, 1986a, 1986b, 1987; Smith *et al.*, 1984	Case-control	Non-Hodgkin's lymphoma, multiple myeloma, and soft-tissue sarcoma were *not* associated with job classifications considered likely to entail the most PCP exposure.
Eriksson *et al.*, 1990	Case-control	Soft-tissue sarcoma was associated with exposure to PCP as determined by questionnaire.
Klemmer *et al.*, 1980	Cohort	Elevated incidences of chronic sinusitis, non-bacterial conjunctivitis, chronic upper respiratory conditions, gout, eye disease, and skin infections were seen in subjects occupationally exposed to PCP (statistical significance not reported).
McConnachie and Zahalsky, 1991	Cohort	Autoimmunity and depression of the T-cell proliferative response were associated with residence in log cabins treated with PCP.
Colosio *et al.*, 1993	Cohort	Adverse effects on the liver and depression of the T-cell proliferative response were associated with occupational exposures to PCP.

[a] Outcomes shown reflect statistically significant associations unless otherwise indicated.

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

1. Non-Cancer Endpoints

The non-cancer health effects of PCP to be used in developing margins of exposure (MOEs) for acute and chronic human exposures are summarized in Table IV-A-1.

a. Toxic Effects from Acute Exposure

Case reports. Although no experimental or epidemiological studies of acute PCP exposures in humans have been conducted, toxic effects associated with short-term use of PCP been published in the literature as case reports. Hemotoxicity, neurotoxicity, and hepatotoxicity have been reported in humans following acute and other short-term occupational exposures to PCP, sometimes leading to death. Signs of neurotoxicity were also observed in infants exposed *via* diapers and linens laundered in PCP, while hepatotoxicity and renal toxicity were noted upon autopsy of the fatal cases (see Section K). This information in the case reports, however, was not adequate to derive a critical NOEL for potential acute exposure.

Critical effect level for acute MOE calculation. The PCP toxicity data base does not contain an adequate single-dose acute exposure study that can be used to derive an acute no-observed-effect level (NOEL). In the absence of a study specifically designed to produce a no-observed-effect level (NOEL) for acute oral exposure to PCP, one was obtained from the results of a developmental toxicity study. A gavage study in rats (Schwetz *et al*., 1974) was acceptable to DPR with respect to testing the developmental toxicity of technical grade PCP (see Section III-G). The developmental NOEL for technical grade PCP in this study was 5.8 mg/kg-day based on skeletal and soft tissue anomalies (subcutaneous edema, lumbar spurs) observed at 15 mg/kg-day and higher doses. The acute MOE was derived from the critical developmental NOEL of 5.8 mg/kg found in the definitive study.

b. Toxic Effects from Subchronic Exposure

There are no seasonal human exposure scenarios for PCP; therefore, a NOEL and MOE for subchronic exposures were not derived.

c. Toxic Effects of Chronic Exposure

Critical effect level for chronic MOE calculation. An oral study of technical grade PCP in beagle dogs (TSI Mason Laboratories, 1996) was considered acceptable to DPR for fulfilling the chronic toxicity data requirement for a non-rodent species (see Section D). Both male and female dogs treated with 1.5 mg/kg-day (the lowest dose tested) of technical grade PCP (GLAZD Penta) developed signs of liver toxicity, including increased relative liver weight, granular cytoplasmic pigment accumulation, chronic inflammation (lymphocytic aggregations), and increased serum alkaline phosphatase. No NOEL was identified. In the absence of a NOEL, the lowest-observed-effect level in the definitive study was divided by a default uncertainty factor of 10, yielding an estimated no-effect level (NEL) of 0.15 mg/kg-day. The chronic MOE was based on an estimated NEL of 0.15 mg/kg-day.

Table IV-A-1. No-Effect Levels for Deriving Margins of Exposure[a]

Duration /Route	Species	PCP Grade	Toxic Effect	LOEL	NOEL	Estimated NEL
Acute /Oral[b]	Rat	Tech.	Skeletal and soft tissue anomalies	15 mg/kg	5.8 mg/kg	-
Chronic /Oral[c]	Dog	Tech.	Liver pigmentation & chronic inflammation	1.5 mg/kg-day	None	0.15[d] mg/kg-day

[a] Abbreviations: LOEL, lowest-observed-effect level; NOEL, no-observed-effect level; NEL_e, estimated no-effect level; Tech., technical; purify., purified.

[b] Data from Schwetz *et al.*, 1974.

[c] Data from TSI Mason Laboratories, 1996.

[d] Estimated NEL was derived by dividing the LOEL of 1.5 mg/kg-day by a default uncertainty factor of 10.

2. Oncogenic Effects from Chronic Exposure

Rat. One oncogenicity study from chronic dietary PCP exposure in rats has been completed to date; the results were negative for oncogenicity (Schwetz *et al.*, 1976). However, because of serious limitations in design and outcome, the study was considered unacceptable by DPR. Another study of chronic dietary PCP exposure in rats was recently completed by the NTP (NTP, 1997). There was some evidence of carcinogenic potential in male rats based on the incidence of malignant mesothelioma and squamous cell carcinoma of the nasal area. These findings were only significant in males at the high dose (~60 mg/kg-day); no neoplasia were reported in female animals.

Mouse. A two-year oncogenicity study from dietary exposure to PCP in $B6C3F_1$ mice found evidence for the oncogenicity of both partially purified and technical grade PCP (NTP, 1989). The partially purified compound (Dowicide EC-7) was similar to the California registrant's current commercial product. Animals received 17-18 or 35 mg/kg-day of technical grade PCP or 17-18, 35-37, or 114-118 mg/kg-day partially purified PCP. In male mice, the partially purified PCP produced dose-related increases in both benign and malignant liver tumors (adenoma and carcinoma). In female mice, the partially purified PCP produced dose-related elevation of liver adenoma, pheochromocytoma (a benign tumor of the adrenal gland), and hemangiosarcoma (a blood-vessel malignancy). The Environmental Health Committee of the EPA's Science Advisory Board recommended that "the observed dose-dependent increase in the incidence of hepatocellular carcinomas and adenomas be considered a valid indicator" of the oncogenic potential of PCP (US EPA SAB, 1991). The Committee also pointed out that the mouse strain tested in the study, $B6C3F_1$, is extremely sensitive to hepatocarcinogenesis and therefore recommended that tumorigenicity at this site be considered less relevant to human risk than the formation of hemangiosarcomas.

Calculation of human cancer potency. There is some controversy about the relevance of the genotoxic metabolite, TeCHQ, to oncogenicity in humans potentially exposed to PCP. TeCHQ is formed

as a primary metabolite of PCP in mice and rats but apparently not in humans. *In vitro* metabolism of PCP by a microsomal fraction of the rat liver (S9) has been shown to result in significant concentrations of TeCHQ (van Ommen *et al.*, 1986; Witte *et al.*, 1985). Additionally, recent *in vitro* studies using human cytochrome P450 enzymes indicate that TeCHQ can be slowly formed from PCP (Mehmood, *et al*., 1996). Therefore, the *in vivo* conversion of PCP to TeCHQ in humans may be more quantitatively than qualitatively different from the metabolism in rodents. However, since the potential oncogenicity from PCP in humans cannot be dismissed, a human cancer risk estimate was calculated from the carcinogenicity data obtained in the NTP (1989) mouse bioassay. DPR concurred with the opinion of the SAB Committee that of the tumor types observed, the hemangiosarcomas are potentially the most relevant to human risk. There was a low incidence of these tumors in the concurrent control groups and the tumor incidence provided the best mathematical fit for the linearized multi-stage model. Therefore, the human cancer potency and risk estimates were based on the incidence of hemangiosarcomas in female mice given partially purified PCP (Dowicide EC-7).

The maximum likelihood solution to the linearized multistage model of the hemangiosarcoma data yields a dose-response slope (q^1) of 1.58×10^{M3} $(mg/kg\text{-}day)^{M1}$; the upper 95% confidence limit on this slope (q_1^*) is 2.45×10^{M3} $(mg/kg\text{-}day)^{M1}$ (Figure IV-A-1; Table IV-A-2). These slope values (*i.e.*, cancer potencies) are based on dose levels expressed in units of body weight. For extrapolation from a mouse cancer potency to a human cancer potency, the assumption is made that the dose in an animal is equivalent to that in a human when the amount of chemical given (*i.e.*, chemical weight, CW) is normalized to the 3/4 power of body weight (BW): normalized dose = $CW/(BW)^{3/4}$. When scaled in terms of potency, the relationship becomes:

$$\text{Potency}_h\ (mg/kg\text{-}day)^{M1} = \text{Potency}_a\ (mg/kg\text{-}day)^{M1} \times (BW_h/BW_a)^{1/4},$$

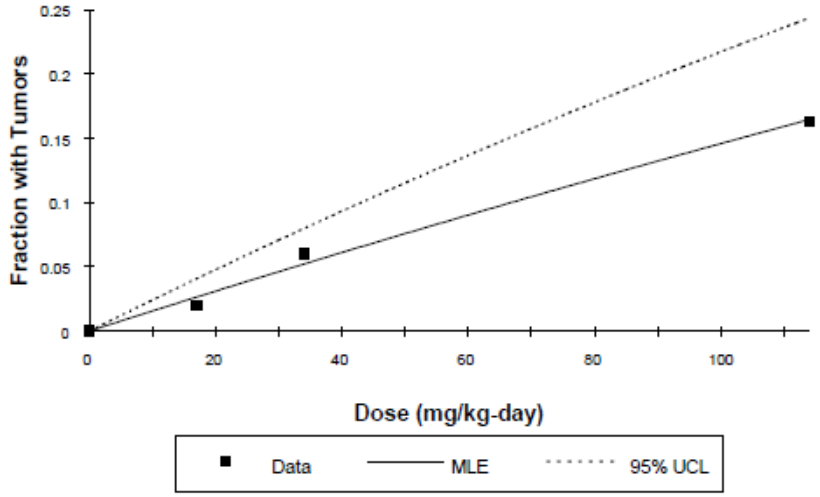
where the subscripts "h" and "a" refer to the human and animal, respectively. The female $B6C3F_1$ mouse body weight in a chronic study is assumed to be the default value of 0.0353 kg (U.S. EPA, 1988); the human body weight is taken to be 70 kg. The scaling factor to be applied to the mouse potency is then $(70/0.0353)^{1/4} = 6.7$. The expected human cancer potencies are then 1.06×10^{M2} $(mg/kg\text{-}day)^{M1}$ based on $q_1$and 1.64×10^{M2} $(mg/kg\text{-}day)^{M1}$ based on q_1^*.

Table IV-A-2. Slope Values for Derivation of Cancer Risk Estimates[a]

Oncogenicity Data/Extrapolation	MLE $(mg/kg\text{-}day)^{M1}$	95% UCL $(mg/kg\text{-}day)^{M1}$
Chronic dietary study of partially purified PCP (Dowicide EC-7) in mice: Hemangiosarcoma in females (NTP, 1989)	1.58×10^{M3}	2.45×10^{M3}
Extrapolated from mice to humans using a scaling factor of 6.7	1.06×10^{M2}	1.64×10^{M2}

[a] *Abbreviations:* MLE, maximum-likelihood estimate of the first-order term (*i.e.*, slope) obtained with the linearized multistage model; 95% UCL, 95% upper confidence limit on the MLE slope.

Figure IV-A-1. Chronic Dietary Study of Partially Purified PCP (Dowicide EC-7) in Mice: Hemangiosarcoma Incidence in Females[a]



[a] Data from NTP (1989). MLE = Maximum Likelihood Estimate of the probability of tumors as a function of dose, P(d), based on the linearized multistage model, derived using the computer program MSTAGE (Crouch, 1992). The 95% upper confidence limit (UCL) = P(d) calculated using the 95% one-sided UCL on the first-order term in dose (*i.e.*, the slope). MLE slope (q_1) = 1.58×10^{-3}; 95% UCL slope (q_1^*) = 2.45×10^{-3}.

B. EXPOSURE ASSESSMENT

1. Occupational Exposure[10]

In the State of California, the only two active uses of PCP are in the pressure treatment of utility poles and their maintenance. Less than 12 individuals (male workers) are involved in this occupational activity.

a. Pressure Treatment of Utility Poles

Pressure treatment of utility poles is the most substantial source of permissible exposure in California, entailing both inhalation and dermal exposure to a 5.5% PCP solution and direct dermal contact with treated wood. Only one pressure-treatment facility (containing two retorts) operates within the State. There are four general tasks associated with exposure at these facilities: loading and dissolving PCP in mixing tanks, loading and unloading the retort, and both short-term and long-term maintenance of the retort.

Typically, PCP is mixed weekly or monthly. Pressure treatments last from 10 hours to 3 days, resulting in each retort being pressurized approximately 150 to 200 times per year. Maintenance inside the retort includes repair work, which might be required approximately four times per year (long-term maintenance), and routine cleaning or upkeep, which is expected to be a monthly occurrence (short-term maintenance). Air levels of PCP measured in pressure-treatment facilities range from 0.2 to 197 $\mu g/m^3$ in the pressure-treatment area, from < 0.1 to 3.9 $\mu g/m^3$ in the general plant area, and from 1 to 15 $\mu g/m^3$ near stacks of treated wood (NIOSH, 1983; Vulcan Chemical, 1993; Wyllie *et al.*, 1972).

Estimates of the average daily dosages absorbed by inhalation and dermal routes during pressure treatment activities are summarized in Tables IV-B-1 and IV-B-2, respectively. The combined (average) absorbed daily dosage (ADD) for each pressure treatment activity was calculated as the sum of the inhalation and dermal ADDs. The ADD, annual average (absorbed) daily dosage (AADD), and the lifetime average (absorbed) daily dosage (LADD) for combined inhalation and dermal exposures are shown in Table IV-B-3.

b. Maintenance of Utility Poles

The maintenance of utility poles includes application of a "bandage" of PCP in a greasy base. There is currently no California-based manufacture of such PCP bandages, although their application is allowed and does occur in the State. When protective gloves and work clothes are worn, exposure is expected to be much less than exposures which occur during pressure treatment. For this reason, the Worker Health & Safety Branch (WH&S) did not develop a PCP exposure assessment for utility pole maintenance workers.

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[10]Summarized from WH&S (1995): *Estimation of Exposure of Persons in California to Pesticide Products Containing Pentachlorophenol*, prepared by R. Brodberg and T. Thongsinthusak, Worker Health and Safety Branch, Department of Pesticide Regulation.

Table IV-B-1. Average Daily PCP Inhalation Doses Estimated for Pressure-Treatment Workers[a]

Job Classification	Task Duration (hr)			Inhalation ADD (µg/kg-day)[e]
	Inside Retort[b]	Retort Area[c]	General Plant Area[d]	
Tank mixing/loading	-	0.5	4.3	0.41 ± 40
Retort loading or unloading	-	0.3	4.5	0.37 ± 0.31
Long-term retort maintenance	2	-	2.8	1.3 ± 0.11[f] (1.1)[g]
Short-term retort maintenance	1	-	3.8	0.80 ± 0.15[f] (0.55)[g]

[a] Adapted from WH&S (1995).

[b] PCP level in air inside the retort was assumed to be 500 µg/m^3, the Threshold Limit Value (TLV). Use of a respirator was assumed to reduce inhalation exposure by 90%.

[c] PCP level in air in the immediate area of the retort was estimated as 23.7 ± 40.8 µg/m^3.

[d] PCP level in air in the general plant area was estimated as 5.8 ± 3.6 µg/m^3.

[e] ADD = (Average) absorbed daily dose (± standard deviation). Calculation assumed a body weight of 75.9 kg, a respiration rate of 0.84 m^3/hour, and an inhalation absorption efficiency of 100%.

[f] Standard deviation calculated assuming no variation was associated with the TLV concentration inside the retort.

[g] Dosage for exposure within the retort only.

Table IV-B-2. Average Daily PCP Dermal Doses Estimated for Pressure-Treatment Workers[a]

Job Classification	Task Duration (hr)		
	Inside Retort	Retort Area	Dermal ADD (µg/kg-day)[b]
Tank mixing/loading	-	0.5	1.3 ± 1.2[c]
Retort loading or unloading	-	0.3	0.82 ± 0.70[c]
Long-term retort maintenance	2	-	1.2 ± 1.3[d]
Short-term retort maintenance	1	-	0.61 ± 0.67[d]

[a] Adapted from WH&S (1995).

[b] ADD = (Average) absorbed daily dose (± standard deviation). Calculation assumed a body weight of 75.9 kg and a dermal absorption efficiency of 29.2%.

[c] Worker was assumed to be wearing a long-sleeved shirt, long pants, and chemical resistant gloves. Hourly dermal exposure was calculated as 696 ± 609 µg/hr.

[d] Worker was assumed to be wearing chemical-resistant clothing and goggles. Hourly dermal exposure was calculated as 156 ± 174 µg/hr.

Table IV-B-3. Combined Absorbed Inhalation and Dermal PCP Doses Estimated for Pressure-Treatment Workers[a]

Job Classification	ADD[c]	AADD[d]	LADD[h]
	(µg/kg-day)		
(1) Tank mixing/loading	1.8 ± 1.6	0.24 ± 0.21[e]	0.13 ± 0.11
(2) Retort loading or unloading	1.2 ± 1.0	0.80 ± 0.70[f]	0.43 ± 0.37
(3) Long-term retort maintenance	2.5 ± 1.4	-	-
(3') Long-term retort maintenance[b]	2.3 ± 1.3	0.076 ± 0.043[g]	0.040 ± 0.024
(1) + (3')	4.1 ± 2.9	0.32 ± 0.24	0.17 ± 0.13
(2) + (3')	3.5 ± 2.4	0.88 ± 0.74	0.47 ± 0.40
(4) Short-term retort maintenance	1.4 ± 0.82	-	-
(4') Short-term retort maintenance[b]	1.2 ± 0.67	0.040 ± 0.022[g]	0.021 ± 0.012
(1) + (4')	2.9 ± 2.3	0.28 ± 0.23	0.15 ± 0.12
(2) + (4')	2.3 ± 1.7	0.84 ± 0.72	0.45 ± 0.38

[a] Adapted from WH&S (1995). *Abbreviations:* ADD, (average) absorbed daily dosage; AADD, annual average (absorbed) daily dosage; LADD, lifetime average (absorbed) daily dosage.

[b] Dosages for exposure within the retort only.

[c] The standard deviation (SD) of the ADD was estimated as the sum of the SDs for the inhalation and dermal ADDs. Summation of means and SDs was performed prior to rounding to 2 significant digits.

[d] AADD = ADD × (number of exposure days/365 days per year).

[e] Number of exposure days = 50.

[f] Number of exposure days = 250.

[g] Number of exposure days = 12.

[h] LADD = AADD × (40 working years/75 years per lifetime).

2. Residential Exposure in PCP-Treated Log Homes

People living in homes built with PCP-treated logs may be exposed to PCP. Federal regulations currently prohibit this use of PCP (U.S. EPA, 1984a; 1986), but many homes built with PCP-treated logs still exist. Airborne PCP concentrations in these homes would be expected to decline with time. In 7 homes built between 3 and 7 years prior to testing, airborne concentrations of PCP sampled over a period of 2 years exhibited a half-life of approximately 0.7 year (Ingram and McGinnis, 1983). As airborne PCP levels in existing PCP-treated log homes continue to decline, it is expected that PCP exposures to residents of such homes will likewise diminish over time.

In estimating residential exposures to persons living in PCP-treated log homes, it was assumed that all PCP absorption was *via* the inhalation route (WH&S, 1995). Additionally, it was assumed that the residential airborne PCP level was the midpoint (5 µg/m^3) of the range (0.5 to 10 µg/m^3) estimated by the U.S. EPA (1984b) for such homes built prior to restriction of such use. Applying default assumptions for

inhalation rate, exposure frequency, and exposure duration, WH&S (1995) calculated daily, annual, and lifetime average exposure dose estimates for an adult male; these are shown in Table IV-B-4.

Table IV-B-4. Absorbed PCP Doses Estimated for Residents of PCP-Treated Log Homes[a]

Population Subgroup	ADD[b]	AADD[c]	LADD[d]
	(µg/kg-day)		
Adult male	0.71	0.68	0.09

[a] Adapted from WH&S (1995). *Abbreviations:* ADD, (average) absorbed daily dosage; AADD, annual average (absorbed) daily dosage; LADD, lifetime average (absorbed) daily dosage.

[b] Exposure was assumed to result only from inhalation. Concentration of PCP within the log home was assumed to be 5 µg/m^3 (1/100 the TLV). The ADD was based on low-activity inhalation (0.72 m^3/hr) for 15 hr/day.

[c] AADD = ADD × (347 exposure days/365 days per year).

[d] LADD = AADD × (10 residential years/75-year lifetime).

3. Dietary Exposure

Only a modified dietary assessment could be conducted because the federal government has not established PCP tolerance levels for raw agricultural commodities, processed foods, or animal products (meat, milk, and eggs). However, food-producing animals may be exposed to PCP through treated or contaminated wood (*e.g.*, wood shavings in bedding, wooden pens, wooden flooring), resulting in PCP-contaminated animal products (Ryan *et al.*, 1985). Results of the most recent food survey of PCP in the United States (Yess *et al.*, 1993) indicate that the major dietary sources of PCP are animal products.

The U.S. Food and Drug Administration (FDA) regulatory monitoring (surveillance sampling) and Total Diet Studies (market basket surveys) for fiscal years (FY) 1985-1991 included analyses for PCP residues (Yess *et al.*, 1993). Summarized below, segregated according to the type of survey in which they were identified, are all commodities for which PCP was found to be above the level of detection, the fraction of samples in which PCP was detected, and the maximum PCP level detected in any sample:

Regulatory monitoring of domestic foods eaten by infants/children:

- Milk, plain: Detected in 179/2,739 samples at levels @ 0.1 ppm.
- Milk, vitamin D: Detected in 5/180 samples at levels @ 0.02 ppm.

Total Diet Study of infant foods (27 market baskets):

- Combination pork jr. dinner: Detected in 2/27 samples at levels @ 0.006 ppm.

Total Diet Study of adult foods eaten by infants/children (27 market baskets):

- Grape jelly: Detected in 1/27 samples at levels @ 0.004 ppm.
- Milk, evaporated canned: Detected in 2/27 samples at levels @ 0.007 ppm.
- Pears, raw: Detected in 1/27 samples at levels @ 0.007 ppm.

PCP was not found in any other foods sampled, including all vegetables, fruit juices, and raw fruits other than pears.

When the results of FDA's regulatory monitoring data for FY 1985-94 are examined separately for each year, it can be seen that detection of PCP fell off dramatically after 1988. The highest PCP levels measured in 1987 and 1988 were 0.009 and 0.013 ppm, respectively, while in 1989-91 there was no PCP reported for any milk products sampled. The drop in detection is largely explained by the FDA's decision to limit reporting to PCP levels A 0.01 ppm for non-fat and low-fat items (including milk) and to PCP levels A 0.02 ppm for items containing > 20% fat (Bohannon, 1995). This change in reporting policy also explains the sudden drop-off of PCP levels in the Total Diet Study data collected through FY 1991. For example, in combination pork junior dinners (a bottled baby food item), PCP was detected at levels as high as 0.006 ppm in 1985, but none was detected from 1986 to 1991. Milk was the commodity with the highest detected PCP levels.

In food animal parts collected in Canada in 1980, Ryan *et al.* (1985) found PCP at levels above 0.01 ppm in 58/97 of chicken fat and 11/16 pork fat samples, with most detected values falling between 0.02 and 0.03 ppm. In the same study, PCP was above 0.01 ppm in 7/26 chicken liver and 5/5 pork liver samples, with detected values of 0.01-0.15 ppm and 0.07-0.34 ppm, respectively.

The 1985-1991 FDA surveys of foods eaten by infants and children revealed that PCP levels in non-milk foods are insignificant compared to PCP levels in milk. Because of the expectation that PCP levels in non-milk, adult foods are much lower than PCP levels in milk, the FDA does not monitor PCP levels in any non-milk, adult food. In the absence of recent data on PCP levels in adult, non-milk foods consumed by adults, DPR based the acute and chronic (annual) dietary risk assessment on milk consumption.

Table IV-B-5 shows the acute (95th percentile) daily PCP exposure levels in population subgroups, calculated using EX4 (TAS, 1993) with a PCP concentration set at 0.013 ppm (the maximum level detected by the FDA in 1987-88) in whole milk consumed in any form. Table IV-B-5 also shows the chronic (annual average) daily exposure levels for the same population subgroups; chronic exposure was calculated using program EX1 (TAS, 1993) with a default PCP concentration set at 0.005 ppm (half the FDA reporting cut-off since 1989) in whole milk consumed in any form.

Hattemer-Frey and Travis (1989) used three different methods to estimate the average daily intake of PCP in the United States. They concluded that 99.9% of human exposure is *via* the food chain, while drinking water is only a minor source of exposure. The most direct method relied on measured background concentrations of PCP in the environment and yielded an estimate of 16.6 µg/day. Application of a pharmacokinetic model to background PCP levels in human adipose tissue resulted in an estimate of 23 µg/day. Finally, application of a model developed by Crosby (1981) which relates human exposure and urinary PCP levels resulted in an estimate of 11 µg/day. Each of these estimates is in general agreement with an earlier estimate of 19 µg/day by Geyer *et al.* (1987) based on the bioconcentration of PCP in various human tissues. Based on the Hattemer-Frey and Travis (1989) estimate of average daily PCP intake (16.6 µg/day), the daily dose per unit body weight for young children, adult females, and adult males with body weights of 20, 60, and 70 kg are 0.83, 0.28, and 0.24 µg/kg-day, respectively. It is noteworthy that the exposure values obtained by Hattemer-Frey and Travis (1989) are in good agreement with the TAS-derived AADDs based on milk consumption shown in Table IV-B-5.

Table IV-B-5. Estimated Dietary Exposure to PCP

Population Subgroup	95th Percentile Daily Dose (µg/kg-day)[b]	Annual Average Daily Dose (µg/kg-day)[c]
Non-nursing Infants	1.19	0.11
Children, 1-6 yrs	0.88	0.12
Children, 7-12 yrs	0.48	0.070
Males, 13-19 yrs	0.26	0.038
Females, 13-19 yrs[a]	0.25	0.029
Males, 20+ yrs	0.15	0.018
Females, 20+ yrs[a]	0.14	0.017

[a] Not pregnant, not nursing.

[b] Acute exposure analysis based on the 95th percentile daily consumption profiles for whole milk consumed in any form, derived using program EX4 of TAS (1993). Milk was assumed to contain PCP at 0.013 ppm (the maximum level detected by the FDA in 1987-88).

[c] Chronic exposure analysis based on the annual average daily consumption profiles for whole milk consumed in any form, derived using program EX1 of TAS (1993). Milk was assumed to contain PCP at 0.005 ppm (half the FDA reporting cut-off since 1989).

C. RISK CHARACTERIZATION

1. Acute Exposure

Summary. Margins of exposure (MOEs) for acute occupational exposures (pressure-treatment work), residential exposures (residence in PCP-treated log homes), and dietary exposures (ingestion of products derived from incidentally contaminated animals) were calculated using the ratio of the critical NOEL (5.8 mg/kg) and the acute exposure value (ADD) from Tables IV-B-3, IV-B-4 and IV-B-5. All MOEs were greater than 100, a value generally considered to be sufficiently protective of human health for non-oncogenic effects observed in animal studies (Tables IV-C-1 to IV-C-3). The lowest MOE for acute occupational exposure was 590 (based on the 95% upper confidence limit on exposure for tank mixer/loaders who perform long-term retort maintenance). The MOE for acute residential exposure of male adults (the only subpopulation for which an exposure assessment has been developed) was 8,200. The lowest MOE for the upper 95th percentile of daily dietary exposure was 4,900. MOEs for combined acute occupational/dietary exposures (of male adults performing the jobs associated with the greatest exposure) and residential/dietary exposures (of male adults) are shown in Table IV-C-4. The lowest acute MOE identified was 577, for combined occupational/dietary exposure.

Table IV-C-1. Acute Margins of Exposure for Pressure-Treatment Workers[a]

Job Classification	ADD[c] (µg/kg)	MOE[d] (Mean)	MOE[d] (95% UCL)
(1) Tank mixing/loading	1.8 ± 1.6	3,200	1,200
(2) Retort loading or unloading	1.2 ± 1.0	4,800	1,800
(3) Long-term retort maintenance	2.5 ± 1.4	2,300	1,100
(3') Long-term retort maintenance[b]	2.3 ± 1.3	-	-
(1) + (3')	4.1 ± 2.9	1,400	590
(2) + (3')	3.5 ± 2.4	1,700	700
(4) Short-term retort maintenance	1.4 ± 0.82	4,100	1,900
(4') Short-term retort maintenance[b]	1.2 ± 0.67	-	-
(1) + (4')	2.9 ± 2.3	2,000	770
(2) + (4')	2.3 ± 1.7	2,500	1,000

[a] *Abbreviations:* ADD, (average) absorbed daily dosage; MOE, margin of exposure; UCL, upper confidence limit.

[b] Exposure within the retort only.

[c] Mean ADD ± standard deviation (SD) adapted from WH&S (1995), as described in Table IV-B-3.

[d] Mean MOE = acute NOEL/ADD, where the acute NOEL (no-observed-effect level) = 5,800 µg/kg. The 95% UCL on the MOE = acute NOEL/(ADD + 2SD), where the parameter (ADD + 2SD) approximates the 95% UCL on the ADD. Rounded to two significant digits.

Table IV-C-2. Acute Margins of Exposure for Residents of PCP-Treated Log Homes[a]

Population Subgroup	ADD[b] (µg/kg-day)	MOE[c]
Adult Males	0.71	8,200

[a] *Abbreviations:* ADD, (average) absorbed daily dosage; MOE, margin of exposure.
[b] Exposure dosage estimated by WH&S (1995), as described in Table IV-B-4.
[c] MOE = acute NOEL/ADD, where the acute NOEL (no-observed-effect level) = 5,800 µg/kg. Rounded to two significant digits.

Table IV-C-3. Margins of Exposure for Acute Dietary Exposures to PCP

Population Subgroup	95th Percentile Daily Dosage (µg/kg-day)[a]	MOE[b]
Non-nursing Infants	1.19	4,900
Children, 1-6 yrs	0.88	6,600
Children, 7-12 yrs	0.48	12,000
Males, 13-19 yrs	0.26	22,000
Females, 13-19 yrs	0.25	23,000
Males, 20+ yrs	0.15	39,000
Females, 20+ yrs	0.14	42,000

[a] Exposure analysis generated using EX4 of TAS (1993) as described in Table IV-B-5.
[b] MOE = acute NOEL/(95th percentile daily dosage), where the acute NOEL (no-observed-effect level) = 5,800 µg/kg. Rounded to two significant digits.

Table IV-C-4. Margins of Exposure for Combined Acute Occupational/Dietary and Residential/Dietary Exposures to PCP

Population Subgroup	Acute Dosage (µg/kg-day)			MOE[d]
	Occupational *or* Residential	Dietary[c]	Combined	
Occupational: Adult Male Pressure-treatment Workers (tank mixer/loaders who perform long-term retort maintenance)	9.9[a]	0.15	10.1	577
Residential: Adult Males	0.71[b]	0.15	0.86	6,700

[a] Sum of the (average) absorbed daily dosage (ADD) + twice the standard deviation (SD) for the jobs resulting in the highest calculated acute exposure [(1) + (3') in Table IV-C-1].

[b] The residential ADD calculated for adult males (from Table IV-C-2).

[c] The dietary 95th-percentile daily dosage for adult males (from Table IV-C-3).

[D] MOE = acute NOEL/(combined acute dosage), where the acute NOEL (no-observed-effect level) = 5,800 µg/kg. Rounded to two significant digits.

2. Chronic Exposure

Summary. MOEs for chronic occupational, residential, and dietary exposures were developed (Tables IV-C-5 to IV-C-7) from the critical, estimated no-effect level (NEL) for chronic exposure, 0.15 mg/kg (Table IV-A-1). The lowest MOE for chronic occupational exposure was 171 for workers who load or unload the retort and also perform long-term retort maintenance. The MOE for chronic residential exposure of male adults (the only subpopulation for which an exposure assessment has been developed) was 221. The lowest MOE for chronic dietary exposure was 1,300 for Children, 1-6 years. Because chronic dietary exposure was insignificant in comparison to chronic occupational exposure, no MOE was calculated for combined chronic occupational/dietary exposures. The MOE for combined chronic residential/dietary exposures (adult males)) was 206 (Table IV-C-8).

Table IV-C-5. Chronic Margins of Exposure for Pressure-Treatment Workers[a]

Job Classification	AADD[c] (µg/kg-day)	MOE[d]
(1) Tank mixing/loading	0.24 ± 0.21	625
(2) Retort loading/unloading	0.80 ± 0.70	188
(3') Long-term retort maintenance[b]	0.076 ± 0.043	-
(1) + (3')	0.32 ± 0.24	469
(2) + (3')	0.88 ± 0.74	171
(4') Short-term retort maintenance[b]	0.040 ± 0.022	-
(1) + (4')	0.28 ± 0.23	536
(2) + (4')	0.84 ± 0.72	179

[a] *Abbreviations:* AADD, annual average daily dosage; MOE, margin of exposure; UCL, upper confidence limit.

[b] Exposure within the retort only.

[c] Mean AADD ± standard deviation (SD) adapted from WH&S (1995), as described in Table IV-B-3.

[d] The mean MOE = estimated chronic NEL/AADD, where the estimated chronic NEL (no-effect level) = 150 µg/kg-day.

Table IV-C-6. Chronic Margins of Exposure for Residents of PCP-Treated Log Homes[a]

Population Subgroup	AADD[b] (µg/kg-day)	MOE[c]
Adult Males	0.68	221

[a] *Abbreviations:* AADD, annual average daily dosage; MOE , margin of exposure.
[b] AADD estimated by WH&S (1995), as described in Table IV-B-4.
[c] MOE = estimated chronic NEL/AADD, where the estimated chronic NEL (no-effect level) = 150 µg/kg-day.

Table IV-C-7. Margins of Exposure for Chronic Dietary Exposures to PCP

Population Subgroup	AADD (µg/kg-day)[a]	MOE[b]
Non-nursing Infants	0.11	1,400
Children, 1-6 yrs	0.12	1,300
Children, 7-12 yrs	0.070	2,100
Males, 13-19 yrs	0.038	3,900
Females, 13-19 yrs	0.029	5,200
Males, 20+ yrs	0.018	8,300
Females, 20+ yrs	0.017	8,800

[a] AADD (annual average daily dosage) generated using EX1 of TAS (1993), as described in Table IV-B-6.
[b] MOE = estimated chronic NEL/AADD, where the estimated chronic NEL (no-effect level) = 150 µg/kg. Rounded to two significant digits.

Table IV-C-8. Margins of Exposure for Combined Chronic Residential/Dietary Exposures to PCP

Population Subgroup	Chronic Dosage (µg/kg-day)			MOE[c]
	Residential[a]	Dietary[b]	Combined	
Adult Males	0.71	0.018	0.73	206

[a] The residential annual average daily dosage calculated for adult males (from Table IV-C-6).
[b] The dietary annual average daily dosage calculated for adult males (from Table IV-C-7).
[c] MOE = estimated chronic NEL/(combined chronic dosage), where the estimated chronic NEL (no-effect level) = 150 µg/kg-day.

3. Oncogenicity

Summary. The best-fit (MLE) of the initial slope and the 95% upper confidence limit on the MLE were derived from the dose response for hemangiosarcoma incidence in female mice and scaled to humans (Table IV-A-2). Based on the MLE and 95% UCL slopes, the excess cancer risk due to PCP exposure was calculated for occupational, residential, and dietary exposures (Tables IV-C-9 to IV-C-11) and combined occupational/dietary and residential/dietary exposures (Table IV-C-12). The highest 95% UCL occupational excess cancer risk was 7.7×10^{-6} (for workers who load or unload the retort and also perform long-term retort maintenance). The 95% UCL residential excess cancer risk for adult males (the only subpopulation for which an exposure assessment has been developed) was 1.5×10^{-6}. The highest 95% UCL dietary excess cancer risk was 5.7×10^{-7}. The combined 95% UCL occupational/dietary excess cancer risk was 8.3×10^{-6} and the combined residential/dietary excess cancer risk was 2.1×10^{-6}.

Table IV-C-9. Estimated Excess Cancer Risk of Lifetime Exposures to PCP in Pressure-Treatment Workers[a]

Job Classification	Mean LADD[c] (µg/kg-day)	Estimated Excess Human Cancer Risk	
		Based on the MLE[d]	Based on the 95% UCL[e]
(1) Tank mixing/loading	0.13	1.4×10^{-6}	2.1×10^{-6}
(2) Retort loading or unloading	0.43	4.6×10^{-6}	7.1×10^{-6}
(3') Long-term retort maintenance[b]	0.040	-	-
(1) + (3')	0.17	1.8×10^{-6}	2.8×10^{-6}
(2) + (3')	0.47	5.0×10^{-6}	7.7×10^{-6}
(4') Short-term retort maintenance[b]	0.021	-	-
(1) + (4')	0.15	1.6×10^{-6}	2.5×10^{-6}
(2) + (4')	0.45	4.8×10^{-6}	7.4×10^{-6}

[a] *Abbreviations:* LADD, lifetime average (absorbed) daily dosage; MLE, maximum likelihood estimate; UCL, upper confidence limit on the MLE.

[b] Exposure within the retort only.

[c] Mean LADD adapted from WH&S (1995), as described in Table IV-B-3.

[d] Estimated excess cancer risk = MLE × LADD, where MLE = 1.06×10^{-2} $(mg/kg\text{-}day)^{-1}$.

[e] Estimated excess cancer risk = 95% UCL × LADD, where 95% UCL = 1.64×10^{-2} $(mg/kg\text{-}day)^{-1}$.

Table IV-C-10. Estimated Excess Cancer Risk of Lifetime Exposures to PCP in Residents of PCP-Treated Log Homes[a]

Population Subgroup	Mean LADD[b] (µg/kg-day)	Estimated Excess Human Cancer Risk	
		Based on the MLE[c]	Based on the 95% UCL[d]
Adult Males	0.090	9.5×10^{-7}	1.5×10^{-6}

[a] *Abbreviations:* LADD, lifetime average daily dosage; MLE, maximum likelihood estimate; UCL, upper confidence limit on the MLE.

[b] Mean LADD adapted from WH&S (1995), as described in Table IV-B-4.

[c] Estimated excess cancer risk = MLE × LADD, where MLE = 1.06×10^{-2} $(mg/kg\text{-}day)^{-1}$.

[d] Estimated excess cancer risk = 95% UCL × LADD, where 95% UCL = 1.64×10^{-2} $(mg/kg\text{-}day)^{-1}$.

Table IV-C-11. Estimated Excess Cancer Risk of Lifetime Dietary Exposures to PCP[a]

Population Subgroup	LADD[b] (µg/kg-day)	Estimated Excess Cancer Risk	
		Based on the MLE[c]	Based on the 95% UCL[d]
Males	0.035	3.7×10^{-7}	5.7×10^{-7}
Females	0.031	3.3×10^{-7}	5.1×10^{-7}

[a] *Abbreviations:* LADD, lifetime average daily dosage; MLE, maximum likelihood estimate; UCL, upper confidence limit on the MLE.

[b] Average annual daily dosage (AADD) generated using EX1 of TAS (1993), as described in Table IV-B-6. LADD calculated as a weighted 70-yr average over age-specific AADD values: 1 yr for non-nursing infants, 6 yrs for children 1-6 yrs old, 6 yrs for children 7-12 yrs old, 7 yrs for males (or females) 13-19 yrs old, and 50 yrs for males (or females) 20+ yrs old.

[c] Estimated excess cancer risk = MLE × AADD, where MLE = 1.06×10^{-2} $(mg/kg\text{-}day)^{-1}$.

[d] Estimated excess cancer risk = 95% UCL × AADD, where 95% UCL = 1.64×10^{-2} $(mg/kg\text{-}day)^{-1}$.

Table IV-C-12. Estimated Excess Cancer Risk of Lifetime Combined Occupational/Dietary and Residential/Dietary Exposures to PCP[a]

	Lifetime Average Daily Dosage (µg/kg-day)			Estimated Excess Human Cancer Risk	
Population Subgroup	**Occupational *or* Residential**	**Dietary[d]**	**Combined**	**Based on the MLE[e]**	**Based on the 95% UCL[f]**
Occupational: Adult Male Pressure-treatment Workers (who perform retort loading or unloading and long-term retort maintenance)	0.47[b]	0.035	0.505	5.4×10^{-6}	8.3×10^{-6}
Residential: Adult Males	0.090[c]	0.035	0.125	1.3×10^{-6}	2.1×10^{-6}

[a] *Abbreviations:* MLE, maximum likelihood estimate; UCL, upper confidence limit on the MLE.

[b] Mean lifetime average (absorbed) daily dosage (LADD) for the jobs resulting in the highest calculated lifetime exposure [(2) + (3') in Table IV-C-9].

[c] The residential mean LADD calculated for adult males (from Table IV-C-10).

[d] The dietary LADD calculated for adult males (from Table IV-C-11).

[e] Estimated excess cancer risk = MLE × combined LADD, where MLE = 1.06×10^{-2} $(mg/kg\text{-}day)^{-1}$.

[f] Estimated excess cancer risk = 95% UCL × combined LADD, where 95% UCL = 1.64×10^{-2} $(mg/kg\text{-}day)^{-1}$.

V. RISK APPRAISAL

This Risk Characterization Document (RCD) addresses potential human health risks due to PCP exposure within the State of California. The exposure scenarios considered include occupational exposure during pressure treatment of lumber and logs, residential exposure in PCP-treated log homes (a use prohibited by the U.S. EPA since 1984), and dietary exposure *via* contaminated milk and meat products (diminishing due to restrictions on PCP use implemented by the U.S. EPA in 1984).

The risk assessment process is used to evaluate the potential for human exposure to a given substance and the likelihood that actual or expected exposures will produce adverse effects in humans. Every risk assessment is inherently limited in that the process generally entails extrapolation of experimental data in animals to potential health risks of exposure in humans. The assumptions that underlie these extrapolations occur at the hazard identification and dose-response assessment stages. In addition, risk assessment depends on the particular set of assumptions made at the exposure assessment stage. The risk characterization process integrates the three stages, thereby incorporating their assumptions and attendant uncertainties. Qualitatively similar uncertainties occur in the risk assessment process for all chemical exposures. However, the magnitude and importance of the uncertainties can vary with the availability and quality of the animal toxicity data, the availability of comparative toxicological and pharmacokinetic data for the test species and humans, and the degree to which human exposures have been adequately characterized. Uncertainties specific to the risk assessment for PCP are delineated in the following sections.

A. TOXICOLOGY ASSUMPTIONS/UNCERTAINTIES

1. Human Cancer Risk

Rodents metabolize a significant proportion of ingested PCP to form tetrachloro-1,4-hydroquinone (TeCHQ), whereas humans and monkeys apparently do not. TeCHQ has been demonstrated to be mutagenic and otherwise genotoxic in numerous short-term tests, whereas PCP has yielded largely negative or equivocal results in *in vitro* genotoxicity tests performed in the absence of rat liver microsomes. Therefore, the possibility should be considered that all or part of the rodent carcinogenicity of PCP depends upon the metabolism to TeCHQ. If so, then the oncogenicity demonstrated in rodents may not be an appropriate model for human cancer risk assessment.

Evidence from epidemiological studies is equivocal regarding the potential for PCP to produce cancer in humans. One case-control study of soft-tissue sarcoma found an association with exposure to PCP and other chlorophenols while a second study found no such link. A larger body of circumstantial evidence connects PCP exposure with hemotoxicity. Numerous case reports have described an association between short-term or occasional exposure to PCP in the course of wood treatment and hemotoxicity (aplastic anemia, thrombocytopenic purpura, or red cell aplasia); a few case reports have found a relationship with Hodgkin's diseaseand leukemia. Toxicity of hematopoietic tissues (spleen and/or bone marrow) is implied by the spectrum of hematologic effects (aplastic anemia and red cell aplasia) seen in individual cases of illness following PCP exposure. These reports provided little or no information on the purity of the PCP; however, it is reasonable to assume that most or all of the

exposures were to technical grade PCP. Given that polychlorodibenzo-*p*-dioxins (pCDDs) and polychlorodibenzofurans (pCDFs) are implicated in similar blood disorders and are commonly found as contaminants of technical grade PCP sold throughout the world, it seems likely that pCDDs and/or pCDFs played some role in the observed hemotoxicity. It is not known if either pure PCP or the technical grade PCP sold in California (which contains lower levels of the most toxic pCDDs and pCDFs than technical grades of PCP sold earlier or available outside the U.S.) would produce the same toxic effects to the human hematopoietic system.

The human cancer risk estimate derived in the Risk Assessment (Section IV) was based on the production of hemangiosarcoma in female mice given partially purified PCP in the diet. Hemangiosarcoma, a rare tumor of the circulatory system, was also produced in all dose groups of male mice given the same formulation, but the effect was not dose-related. All dose groups of male and female mice given a technical grade composite of PCP (with higher pCDD and pCDF contaminant levels than the partially purified formulation) also had elevated incidences of hemangiosarcoma. Based on the similarity of the results in animals treated with the two PCP formulations, the National Toxicology Program (NTP) pathologists who directed the study concluded that the hemangiosarcomas arose as a consequence of exposure to PCP itself and not to the contaminants found at higher concentrations in the technical grade composite. Most of the hemangiosarcomas were located in the spleen and may have been related to the diffuse hematopoietic cell proliferation found in all groups of treated mice. The possible relationship between splenic hematopoietic lesions and hemangiosarcomas in mice cannot be ignored in light of the isolated cases of hemotoxicity (and implicit hematopoietic damage) that have been reported in persons with unprotected, short-term exposure to PCP.

Although some questions remain concerning the role of the pCDD and pCDF contaminants in producing hemotoxicity in humans, the evidence from the NTP chronic study in mice supports the view that exposure to PCP alone (or PCP plus impurities present in the partially purified test material) is responsible for producing splenic hematopoietic lesions and hemangiosarcomas. Furthermore, the contaminant profile of the partially purified formulation (Dowicide EC-7) is similar to that of the PCP formulation currently registered for use in California. Given the present state of knowledge, it is reasonable to assume that the hematopoietic alterations and hemangiosarcomas produced in the spleens of mice treated with partially purified PCP in the NTP study are relevant to the potential of the formulation currently registered in California to produce similar neoplastic effects in humans. Additional data on the mechanism(s) by which PCP exposure leads to splenic toxicity in humans and mice would be useful to any future reevaluation of the relevance of rodent results to the potential human carcinogenicity of PCP. In addition, the results of a chronic study of pure PCP in rats may assist in determining if PCP is able to produce splenic hematopoietic toxicity in the absence of pCDD and pCDF impurities.

Comparison with U.S. EPA's cancer risk estimate. As noted in Section II-B, an upper-bound human cancer potency estimate (referred to as the cancer slope factor) of 1.2×10^{M1} appears in IRIS (U.S. EPA's on-line Integrated Risk Information System). This value is to be compared with the human cancer potency estimate of 1.6×10^{M2} (based on the 95% upper confidence limit) derived in Section IV-C-3. Thus, the U.S. EPA's estimate of the cancer potency is 7.5-fold larger than that calculated by DPR in spite of the fact that both values were based on results in female mice obtained in the same study (NTP, 1989). The reason for the discrepancy is that *(a)* U.S. EPA used the pooled incidence of tumors at three sites (including benign and malignant forms of each) whereas DPR used only hemangiosarcoma incidence, as recommended by U.S. EPA's Science Advisory Board (1991) and *(b)* U.S. EPA took the

geometric mean of the pooled incidence rates obtained with the two PCP test materials (technical grade composite and Dowicide EC-7) whereas DPR used data only from the groups receiving Dowicide EC-7. Because Dowicide EC-7, which is a partially purified formulation, is closer in impurity composition to the product registered in California , DPR made the determination that human cancer risk would more appropriately be based on the oncogenicity of Dowicide EC-7 than on that of the more highly contaminated technical grade composite.

B. EXPOSURE ASSUMPTIONS/UNCERTAINTIES

1. Occupational Exposure

It has been shown that urinary excretion of PCP is in equilibrium with steady-state exposures (Crosby, 1981). The relationship can be approximated by Equation V-1:

$$Absorbed Dose\,(mg/kg\text{-}day) = \frac{Urine Level\,(mg/L)\,x\,Urinary Output\,(L/day)}{Body\ Weight\ (kg)\ x\ 0.86} \qquad \text{V-1}$$

This relationship was originally developed in terms of the amount of PCP ingested (oral exposure dose), which is almost the same as the oral absorbed dose, since oral absorption is nearly 100%. Inhalation exposure likewise results in 100% absorption, and so the relationship is equally valid for inhalation exposure regardless of whether it is expressed in terms of exposure dose or absorbed dose. Expressing the relationship in terms of the absorbed dose (essentially equivalent to the AADD) rather than the exposure dose allows the equation to be applied when all or part of the exposure is *via* the dermal route, which can be corrected for the incompleteness of dermal absorption.

The usefulness of Equation V-1 in predicting background human exposure levels has been validated by Hattemer-Frey and Travis (1989). Note that the absorbed dose calculated by Equation V-1 is essentially equivalent to the AADD (see Section IV-B). It is of interest to use Equation V-1 to calculate the absorbed dose based on a urinary PCP level measured in pressure-treatment workers. Mean urinary PCP values of 1,240 µg/L (Arsenault, 1976), 300 µg/L (Wyllie *et al.*, 1975), 270 µg/L (Klemmer *et al.*, 1980), and 110 µg/L (inhalation + dermal; Embree *et al.*, 1984) have been reported in such workers. Taking the most recent measurement, 110 µg/L, and assuming that the urinary output of a 70-kg adult male is 1.4 L/day (ICRP, 1975), then a mean AADD value of 2.6 µg/kg-day is predicted.

There is precedent for using urinary PCP as a means of quantifying occupational exposure (Jorens and Schepens, 1993). Biological monitoring of workers in the pressure treatment industry may be helpful in assessing the reliability of the exposure assumptions used in this document. At the present time occupational exposure to PCP in California is limited to less than 12 male workers in the pressure treatment industry; therefore, wide-spread and variable exposure scenarios are not potential areas of uncertainty.

2. Residential Exposure

PCP is a restricted use pesticide and is not longer used in the treatment of logs for residential building (U.S. EPA, 1984a). For persons living in PCP-treated log homes built prior to federal restriction, any current or potential airborne levels of PCP would be expected to be declining over time.

In older homes where airborne PCP is below a level of concern for inhalation exposure, textiles in the residence may remain contaminated, resulting in potential dermal absorption (Gebefügi, 1989). The nature of the materials present in the home and the habits of the residents will determine the extent of dermal exposure. There is some evidence that toddlers living in PCP-treated log homes have substantially higher urinary PCP levels than their older siblings or parents (Hernandez and Strassman-Sundy, 1980). This suggests that hand-to-mouth exposure may be of importance in toddlers. The residential exposure in this document assumed that all exposure occurs *via* inhalation and was based on an air concentration of 5 $\mu g/m^3$. There is little evidence to suggest that actual residential exposure would occur primarily *via* the inhalation route; thus, this assumption would tend to underestimate risk. On the other hand, the air concentration selected (5 $\mu g/m^3$) is likely to be too high, tending to overestimate risk. For example, in a two-story home constructed from PCP-treated logs, air samples taken 5 years later had PCP concentrations of 0.20-0.38 $\mu g/m^3$ (Hernandez and Strassman-Sundy, 1980.

If a cistern is used for water storage in a PCP-treated log home, drinking water may be contaminated with PCP (Hosenfeld, 1986).

"Background" urinary PCP levels have been measured in several studies. Mean urinary levels of 6.9 µg/L were reported for adult Germans (N = 17, Grimm *et al.*, 1984) and, more recently, 1.6 µg/L for Canadians of various ages (N = 87, Thompson and Treble, 1994). A median level of 14 µg/L was found for children living in Arkansas (N = 197, Hill *et al.*, 1989). Other studies have reported values in approximately the same range (ICPS, 1987).

PCP levels in the urine of residentially exposed persons reflects their chronic exposure to PCP. In the most recent study of persons living in PCP-treated log homes, Cline *et al.* (1989) found urinary PCP levels ranging from 1-340 µg/L (mean, 69 µg/L) in 118 residents of unspecified age in nine States.

3. Dietary Exposure

There are no established tolerances for PCP on food commodities. Any dietary exposure to PCP would result from contaminated milk and meat products derived from animals inadvertently exposed to PCP in wood-treated animal dwellings (*e.g.* barns) . It would be expected that contamination of animals *via* direct or indirect contact with PCP-treated structures has been diminishing since such use was prohibited in the mid-1980s; therefore, dietary exposure values in this document would tend to over estimate risk to PCP.

VI. CONCLUSIONS

A. EXPOSURE

Occupational exposures in California affect less than one dozen male workers employed in the pressure treatment industry. Biological monitoring of urinary PCP levels in this occupational population would decrease the uncertainty associated with non-biological means of assessing exposure in this population. Residential exposures affect families living in PCP-treated log homes. PCP treatment of logs for residential construction has been prohibited by federal law since 1986; therefore, exposures to residents of existing PCP-treated log homes continue to diminish over time as airborne PCP levels decline. Dietary exposures are unlikely but may occur if contaminated animal products are consumed. Farm animals become contaminated primarily through contact with PCP-treated wood structures. Federal laws enacted in the mid-1980s prohibit PCP treatment of wood for structures which come into contact with food animals. As PCP contamination of food animals continues to decline, so will human dietary exposures to PCP. There are no established tolerances for PCP on food commodities; therefore, direct dietary exposure from the consumption of fruits and vegetables is considered in this document.

B. NON-CANCER RISK

Based on animal toxicity and human exposure data, margins of exposure (MOEs) were calculated for acute and chronic occupational (pressure-treatment of utility poles), residential (living in a PCP-treated log home), and dietary (consumption of PCP-containing animal products) exposures to PCP. Combined occupational/dietary and residential/dietary scenarios were also considered. For all acute and chronic exposure scenarios, MOEs were greater than 100, a value generally considered to be sufficiently protective of human health for non-oncogenic effects observed in animal studies.

C. CANCER RISK

Based on a linearized multistage model of tumor risk for malignant vascular tumors in female mice, the 95% upper confidence limit (UCL) lifetime cancer risk due to PCP was estimated to be as high as 7.7×10^{-6} for average exposure of the most highly exposed pressure-treatment workers, 1.5×10^{-6} for average exposure in PCP-treated log homes, 5.7×10^{-7} for average dietary intake, 8.3×10^{-6} for combined occupational and dietary exposure, and 2.1×10^{-6} for combined residential and dietary exposure.

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Estimation of Exposure of Persons in California to Pesticide Products Containing Pentachlorophenol

by

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Abstract

Pentachlorophenol is a pesticide used to protect wood products against microbial degradation and insect infestation. A dermal absorption value of 29.2% was obtained from a study using monkeys. A default inhalation absorption of 100% was used in the estimation of absorbed dosages. Elimination of PCP in humans is primarily by urinary excretion of free and glucuronide-conjugated pentachlorophenol. Total (acid hydrolyzed) urinary pentachlorophenol can be used for biological monitoring. Attributed to protein binding or enterohepatic recirculation, is a lag of a day or more in maximal pentachlorophenol urinary elimination following absorption. Following a single oral dose in human the half-lives for urinary elimination of PCP ranged from one to 20 days. Pentachlorophenol exposure in pressure-treating facilities is estimated by the Worker Health and Safety Branch as resulting in an absorbed daily dosage (ADD) of 1.2 μg/kg/day when loading/unloading retorts. Long maintenance work for retorts is estimated as leading to an ADD of 2.5 μg/kg/day, and mixing and loading to 1.8 μg/kg/day. The ADD for a worker performing mixing/loading and short maintenance work is 2.9 μg/kg/day and that for a worker performing retort loading/unloading and short maintenance work is 2.3 μg/kg/day.

This report was prepared as part of the Department's risk characterization document on pentachlorophenol pursuant to SB 950 and Proposition 65. Possible adverse effects associated with pentachlorophenol exposure in animals include oncogenicity in mice and immunotoxicity in mice and rats. The U.S. EPA has classified PCP as a B2 probable human carcinogen.

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APPENDIX B

California Department of Pesticide Regulation
Worker Health and Safety Branch

Human Exposure Assessment

PENTACHLOROPHENOL

April 1, 1991
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INTRODUCTION

This Appendix B is being prepared as part of the ongoing California Department of Pesticide Regulation evaluation of pesticides pursuant to the Birth Defect Prevention Act of 1984 (SB 950) and the Safe Drinking Water Enforcement Act of 1986 (Proposition 65).

Information for pentachlorophenol will be presented in this exposure assessment document. In this review, PCP will be used when the context of the discussion refers to pentachlorophenol. "Na-PCP" will be used to refer specifically to sodium pentachlorophenate. Other names will be used for any specific formulations of chlorophenols.

PHYSICAL AND CHEMICAL PROPERTIES

The empirical formula for PCP is C_6HCl_5O and its molecular weight is 266.35. Analytical grade PCP is a colorless to white crystalline or flaked solid (IARC, 1986). The melting point of PCP is 191 ^oC and its boiling point is 310 ^oC (Verschueren, 1983). PCP has a relatively low vapor pressure, $1.1x10^{-4}$ mm Hg at 20 ^oC (Verschueren, 1983). Its solubility in water is 14 ppm at 20 ^oC, and it is soluble in most organic solvents.

Technical grades of PCP contains tetra- and trichlorophenols and higher chlorinated phenoxy-phenol impurities. Representative concentrations of the principal active ingredient (a.i.) and impurities are shown in Table 1. Depending on the manufacturing process used, a variety of polychlorinated dibenzo-p-dioxins, dibenzofurans, and chlorobenzenes are also present as contaminants following production (IARC, 1986). Contaminants are found at different levels in each lot of PCP. Maximal values of some contaminants from representative samples are also shown in Table 1. TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) was not found as a contaminant of pentachlorophenol in the production process in the United States from 1991 to 1993 (Vulcan Chemical, 1993). The detection limit of TCDD was 1 part per billion.

Table 1. Active ingredient and impurities in technical grade pentachlorophenol[a].

Chemical	PCP % or ppm	Na-PCP % or ppm
pentachlorophenol	85%	82%
tetrachlorophenols	10%	4.5%
trichlorophenols	0.01%	0.01%
other chlorophenols	0.7%	0.02%
hexachloro-dibenzo-p-dioxin	35	20
heptachloro-dibenzo-p-dioxin	180	10
octachloro-dibenzo-p-dioxin	3600	3.8
tetradibenzofurans	0.45	0.02
pentadibenzofurans	0.25	0.20
hexadibenzofurans	36	39
heptadibenzofurans	320	280
octadibenzofurans	210	230

[a] Upper limit of range reported for contaminants as ppm (μg/g) or % (IARC, 1986). Contaminants are process dependent.

EPA STATUS

The United States Environmental Protection Agency (U.S. EPA) has published four Special Reviews of PCP-containing products (U.S. EPA, 1978, 1981, 1984, and 1986). Several action notices of Intent to Cancel Registration, Amended Cancellation, and a Final Determination have been published for wood preservative and/or non-wood uses (Federal Register, 1984, 1986, 1987a, 1987b, and 1988).

These reviews concluded that a number of uses should be canceled and that PCP products should be classified as "restricted use." Limitations were placed on interior wood uses and all non-wood uses were canceled except for microbiological control in dry paper mill, cooling tower, and oil well drilling applications. Canceled non-wood uses include: product preservative; herbicide; antimicrobial; disinfectant; mossicide; and defoliant applications.

These reviews instituted more rigorous protective and training measures and additional product composition requirements. These requirements also phased in a reduction of hexachlorodibenzo-p-dioxin in manufacturing and end use products to 1 ppm. This phase-in was scheduled to occur between 1987 and 1989. Limits were also imposed on hexachlorobenzene and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) contaminants in PCP.

USAGE

As of 1989 use of all PCP formulations is federally restricted to purchase and application by certified applicators. PCP is used to protect wood products against microbial degradation and insect infestation. In 1992, 107,946 lbs of PCP and 12,555 lbs of other related PCP products were used in California (DPR, 1992a). The amount of PCP sold in California in 1992 totaled 297,380 lbs a.i. and that for related PCP was 34,579 lbs a.i. (DPR, 1992b). There were three registrants in 1992. As of September, 1994, there is only one registrant of products sold in California.

FORMULATIONS

As of March 1995, Vulcan Glazd® Penta is the only PCP product registered for use in California. This product contains 86% pentachlorophenol and 10% other phenols and related compounds. The intended usages are: wood preservation; formulation of fungicidal and insecticidal solutions; and for incorporation into other manufactured pesticide products. This product is a Category I Pesticide that has a signal word "DANGER".

LABEL PRECAUTIONS

Vulcan Glazd® Penta is a restricted use pesticide. It is for retail sale to and use only by certified applicators or persons under their direct supervision. The U.S. EPA has determined that PCP can produce defects in the offspring of laboratory animals and that human exposure during pregnancy should be avoided.

Applicators must wear gloves (e.g., polyvinyl acetate, polyvinyl chloride, nitrile, NBR [Buna-N], or neoprene) impervious to the wood treatment formulation in all situations where dermal exposure is expected (including handling of freshly treated wood and manually opening cylinder doors). Individuals who manually open cylinder doors must wear gloves and a respirator. All workers must wear a long-sleeved shirt and long pants. Individuals who enter, clean or repair pressure treatment cylinders, vats, tanks, and other contaminated equipment with wood treatment formulation must wear a respirator approved for organic vapors and acid gases by the Mine Safety and Health Administration/the National Institute for Occupational Safety and Health (MSHA/NIOSH), goggles, and protective clothing (including overalls, jackets, gloves, boots) impervious to the wood treatment formulation.

Persons exposed to PCP should also be warned that PCP is harmful or fatal if swallowed and that it can be readily absorbed through the skin. PCP causes eye and skin irritation. If inhaled, remove the victim to fresh air. Exposed eyes should be flushed for 15 minutes with an excess of water and exposed skin should be thoroughly washed with soap and water. If ingested, dilute with several glasses of water and induce vomiting. Do not induce vomiting or give anything by mouth to an unconscious person. Immediate medical attention is essential for the proper treatment of PCP poisoning.

WORKER ILLNESS/INJURY

Worker illness/injury attributed to PCP products in California between 1984 and 1992 are mostly eye irritation injuries, and about half as many skin or systemic illness (Table 2). Eighteen cases were due to PCP exposure alone; 15 were combined mixes or formulations with a second active ingredient (Edmiston, 1990; Mehler, 1994). Half of all cases involved inappropriate or lack of personal protective clothing. Eight cases were due to cross-contamination from the hand. Three cases were due to misuse of the product, and three were vapor exposures (Edmiston, 1990; Mehler, 1994).

Table 2. California illness/injury associated with PCP exposure.

	Illness/injury			
year	eye	skin	systemic	total
1984	6	1	1	8
1985	3	3	2	8
1986	2	1	2	5
1987	3	1	1	5
1988	1	0	1	2
1989	2	0	0	2
1990	1	1	0	2
1991	0	1	0	1
1992	0	0	0	0
total	18	8	7	33

DERMAL AND INHALATION TOXICITY

Technical PCP is extremely toxic (Category I) by oral ingestion (LD_{50} = 50 mg/kg in rats). It is less toxic (Category II) by dermal route. Dermal toxicity tests using various formulations on New Zealand rabbits have shown that the dermal LD_{50} of PCP is greater than 200 mg/kg (Adamik, 1984; Myers, 1983; and Terrell, 1982a and 1982d). Inhalation toxicity tests on rats have shown that the LD_{50} of PCP is 11.7 mg/kg for an aerosol (Hoben *et al.*, 1976a).

IRRITATION AND SENSITIZATION

PCP is an eye irritant. The severity of eye irritation varies with the formulation between severe and mild (Gabriel, 1975 and 1982; Myers, 1983; and Terrell, 1982b and 1982c). No specific information on dermal sensitization due to PCP is available, although chloracne has been reported following exposure to products with high dioxin levels (Cole *et al.*, 1986).

PHARMACOKINETICS

This section presents information on biotransformation, distribution and elimination of PCP in animals and humans.

1. Biotransformation

Summary. A comparison of urinary excretion profiles indicates that the metabolism of PCP in rodents is qualitatively and quantitatively dissimilar to its metabolism in monkeys and humans. In mice and rats, a substantial, dose-dependent fraction (16-48%) of ingested PCP is excreted in the urine as tetrachloro-1,4-hydroquinone (TeCHQ), a compound known to be genotoxic. Humans and monkeys do not appear to metabolize PCP to TeCHQ, although there has been some controversy surrounding this question. Some recent *in vitro* studies indicated that PCP can be metabolized to TeCHQ in experimental systems containing human cytochrome P-450 enzymes. The potential influence of exposure route on the biotransformation of PCP has not been studied methodically; however, there is no evidence to suggest route-dependence of either rates or pathways. Experimentally observed urinary excretion profiles of PCP and TeCHQ following single-dose administration of PCP are summarized in Table 3.

Methodological issues. Exposure of mammals to PCP results in urinary excretion of free[1] and conjugated PCP and in some species, free and conjugated TeCHQ; the conjugated species have been identified as glucuronides and sulfates. All studies of PCP metabolism have reported some effort to hydrolyze the conjugates in question in order to quantify the various chemical species present. However, in the earlier studies, the methods of hydrolysis employed may have been inadequate. The work of Ahlborg *et al.* (1978) and of Edgerton and Moseman (1979) revealed the importance of insuring complete hydrolysis of urinary conjugates; subsequent work by others utilized their methods.

a. Mouse

Jakobson and Yllner (1971) looked for PCP and its metabolic products in the urine of female NMRI mice exposed i.p. to PCP at 7.4-8.2 mg/kg or 15-37 mg/kg. Similar results were obtained for one animal injected subcutaneously. Ahlborg *et al.* (1974) injected NMRI mice (unspecified sex) i.p. with PCP at 10-25 mg/kg. Reigner *et al.* (1992a) quantified the 48-hour urinary excretion of PCP and metabolites following a single gavage dose of PCP at 15 mg/kg in male $B6C3F_1$ mice. Between 80% and 90% of the conjugated species were sulfates (PCP-S and TeCHQ-S) while the remainder were glucuronides (PCP-G and TeCHQ-G). The results of the metabolism studies in the mouse are given in Table 3.

A study by Lin *et al.*, (1997) was conducted to investigate the dosimetry of chlorinated quinones arising from metabolism of PCP in the livers of male Sprague-Dawley rats and B6C3F1 mice by measuring the cysteinyl protein adducts and estimating the second-order reaction rate constants between the quinones and the proteins. Male B6C3F1 mice (30-36 g) were divided into ten groups of three mice and male Sprague-Dawley rats (320-375 g) (14-20 weeks old) were divided into eight groups of three rats. Nine mouse and seven rat groups were given a single dosage of

[1]Here,"free" is used to connote unconjugated to glucuronide or sulfate. This use is not meant to reflect protein binding status.

PCP at 20 mg/kg body wt (about 10% of the reported LD_{50}) by gavage. Previous studies demonstrated that metabolism of PCP proceeds primarily through the quinols, tetrachlorohydroquinone (Cl_4HQ) and tetrachlorocatechol (Cl_4CAT), which can then be oxidized to the corresponding quinones [tetrachloro-1,4-benzoquinone (Cl_4-1,4-BQ) and tetrachloro-1,2-benzoquinone (Cl_4-1,2-BQ)] via semiquinone intermediates [i.e., tetrachloro-1,2-benzosemiquinone (Cl_4-1,2-SQ) and tetrachloro-1,4-benzosemiquinone (Cl_4-1,4-SQ)]. Both the quinones and the semiquinones are capable of binding to macromolecules such as liver microsomal proteins, calf thymus DNA, blood proteins, and liver cytosolic and nuclear proteins. Lin *et al.* (1996) previously demonstrated that Cl_4-1,4-BQ and Cl_4-1,2-SQ were the major producers of liver-protein adducts in Sprague-Dawley rats to which PCP had been administered. This study repeated similar experiments with B6C3F1 mice to determine whether the types and quantities of adducts differed between the two species. The results indicate that Cl_4-1,2-BQ and Cl_4-1,4-BQ were the major producers of liver-protein adducts in B6C3F1 mice to which PCP had been administered. The adducts of Cl_4-1,2-BQ were observed in the livers of mice dosed with PCP, but not in the livers of rats, suggesting species specificity for production of Cl_4-1,2-BQ. The time course of adduct production in both species indicates that all quinone adducts reached their maximum values earlier in mice (0.5-4 hr) than in rats (8-24 hr), suggesting to more rapid PCP metabolism in the mouse. The estimated tissue doses of the quinones to liver cytosol decreased in the order rat Cl_4-1,4-BQ > mouse Cl_4-1,4-BQ > mouse Cl_4-1,2-BQ and to liver nuclei in the order mouse Cl_4-1,2-BQ > mouse Cl_4-1,4-BQ > rat Cl_4-1,4-BQ. The corresponding doses of Cl_4-1,2-SQ could not be determined because of an inability to estimate the second-order rate constants. After aggregating the estimated contributions of all quinone species, mice had a 4-fold greater dose to liver nuclei than rats, whereas rats had a three-fold greater dose to liver cytosol. The increased nuclear dose to mouse liver compared to that of the rat suggests that the mouse is at greater risk to hepatic DNA damage from PCP-derived quinones and that Cl_4-1,2-BQ may play a critical role in PCP carcinogenesis.

b. Rat

Ahlborg *et al.* (1978) analyzed metabolites in urine following i.p. administration of PCP at 10 mg/kg to rats (unspecified sex and strain); results are shown in Table 3. All conjugated species were glucuronides. These investigators also reported that pretreatment of rats with phenobarbital prior to oral PCP administration increased the rate of TeCHQ formation *in vivo* and in isolated liver microsomes. They concluded that the dechlorination of PCP is mediated by microsomal enzymes inducible by phenobarbital.

Braun *et al.* (1977) identified the compounds excreted in urine following a single gavage dose of PCP at 100 mg/kg to male and female Sprague-Dawley rats (Table 3); again, all conjugated species were glucuronides. In rats given a 10 mg/kg dose, both plasma and urine were analyzed. No TeCHQ was detected in the plasma. PCP-G was present in the plasma, although the ratio of PCP-G to PCP was much lower than in the urine. At 12 hrs post-exposure PCP-G represented, on average, 4-6% of the recovered dose in plasma, while after 6 days the percentage had increased to 11-16%.

Engst *et al.* (1976) analyzed the urine of male Wistar rats pooled during the final week of administering PCP at 8 mg/kg-day by gavage for 19 days. The investigators identified PCP, much

smaller amounts of 2,3,4,5-tetrachlorophenol (2,3,4,5-TeCP), and still smaller amounts of two other TeCP isomers and 2,3,4-trichlorophenol (TCP). TeCHQ was not reported.

Renner (1989) measured the concentrations of free and conjugated PCP and TeCHQ in the urine of 24 female Sprague-Dawley rats treated by gavage with PCP at 53 mg/kg-day for 28 days. In the 7-day urine samples collected during each week of the treatment period, the excreted PCP was 36-58% unconjugated while the excreted TeCHQ was 10-19% unconjugated. The relative proportions of PCP and TeCHQ were not reported.

Renner and Hopfer (1990) measured urinary metabolites in what seems to have been urine from the same treated animals described by Renner (1989). Apparently, the 7-day urine samples collected during exposure and for 2 weeks post-exposure were combined and analyzed as one lot. Based on their data the investigators suggested that the main degradative pathway for PCP leads via 2,3,5,6-tetrachlorophenol (2,3,5,6-TeCP) to TeCHQ and a minor pathway leads via 2,3,4,6-TeCP and 2,3,4,5-TeCP to trichlorohydroquinone (TCH). In addition, they reported finding small amounts of the oxidation products of both hydroquinones: trichloro-1,4-benzoquinone and tetrachloro-1,4-benzoquinone.

c. Monkey

In two male and two female rhesus monkeys given ^{14}C-labeled PCP at 10 mg/kg by nasogastric intubation, all radioactivity recovered in the urine occurred as unchanged PCP (Braun and Sauerhoff, 1976). Thus, the pattern of PCP metabolism in rhesus monkeys is unlike rodents in that PCP conjugate (PCP-c), TeCHQ, and TeCHQ conjugate (TeCHQ-c) are not found in the monkeys' urine following PCP treatment.

d. Human

Braun *et al.* (1979) failed to find TeCHQ in the urine of 4 human male volunteers exposed orally to PCP at a dose of 0.1 mg/kg. The portion of the dose recovered in the 7-day urine consisted entirely of unchanged PCP (86%) and PCP-G (14%).

Uhll *et al.* (1986) found no trace of [^{13}C]-isotopes of TeCHQ, 2,3,4,5-TeCP, or 2,3,4,6-TeCP. In a separate ingestion experiment, Uhl *et al.* (1986) followed the percentage of urinary PCP-G excreted by a subject given 0.31 mg/kg PCP of normal isotopic composition. The percentage of total urinary PCP (free plus conjugated) present as the glucuronide was found to increase from a value of approximately 29% on day one after exposure to 60-65% on day 28, after which the value remained stable throughout the remaining ten days of measurement. This "baseline" level of 60-65% is in agreement with the percentage present as the glucuronide conjugate (range, 61-70%) found by these investigators in the urine of 13 untreated volunteers.

In contrast to the finding of no TeCHQ in the urine of PCP-exposed human volunteers by Uhl *et al.* (1986) and Braun *et al.* (1979), both TeCHQ and PCP were identified (without quantification) in the urine of two occupationally exposed male pesticide applicators by Ahlborg *et al.* (1974). However, these investigators did not obtain complete exposure profiles for the applicators; therefore, one cannot rule out the possibility of co-exposure to another pesticide, such as lindane. Lindane (γ-hexachlorocyclohexane) undergoes hydroxylation followed by aromatization

(Gopalaswamy and Aiyar, 1986) to form 2,3,4,6- and 2,3,5,6-TeCP as major metabolites in the rat (Engst *et al.*, 1976), while TeCHQ is the primary metabolite of 2,3,5,6-TeCP administered to rats (Ahlborg *et al*., 1978). This pathway does not entail formation of PCP. Furthermore, TeCP is a contaminant of technical grade PCP; for example, TeCP was present at 3.8% and 9.4%, respectively, in the two PCP formulations tested in the NTP mouse carcinogenicity bioassay.

Another finding which is in apparent conflict with the *in vivo* observations of no PCP metabolism to TeCHQ is the *in vitro* result of Juhl *et al.* (1985), who found that a microsomal extract (S-9 fraction) from the liver of a 61-year-old woman converted PCP to TeCHQ at a rate comparable to that of a rat liver microsomal extract. Additionally, more recent *in vitro* evidence using human cytochrome P-450 3A4 expressed in *Saccharomyces cerevisiae* and a microsomal fraction from the whole yeast cells showed the formation of TeCHQ from hexachlorobenzene, pentachlorobenzene and PCP (Mehmood *et al*., 1996). These investigators indicated that the rates of metabolism in all instances were low. Therefore, the apparent *in vivo* differences between rodents and humans to biotransform PCP to TeCHQ may be more quantitative (i.e., rate dependent) than qualitative.

Reigner *et al.* (1992b) suggested that the inability of some investigators to detect TeCHQ in the urine of humans exposed to PCP may reflect the instability of this compound in urine. However, it is not clear why the breakdown product(s) would not then be detected, especially in the [^{13}C]PCP experiment of Uhl *et al.* (1986).

2. Distribution and Elimination

Summary. There is good agreement in the published literature on plasma half-lives of PCP in various experimental animals. Following oral or i.v. administration, mean half-lives of 5-6 hrs in mice, 2-11 hrs in rats, and 72-84 hrs in monkeys have been calculated based on a first-order model representing the major portion of plasma PCP. Urinary excretion rates are similar to the corresponding plasma distribution rates, with estimated mean half-lives of 13 hrs in rats and 41-92 hrs in monkeys. In rats, excretion by combined urinary and fecal routes has also been measured; the major portion of dose is excreted with an estimated mean half-life of 13-27 hrs. The single human study to examine the rate of decline of PCP in plasma reported a mean half-life of 30 hrs, nearly identical to the urinary excretion mean half-life found in the same study (33 hrs). The other human studies of urinary excretion reported much longer half-lives (128-480 hrs). Interindividual variability may account for the nearly 4-fold variation in the upper range, while the difference in ranges between the two studies is unexplained. The kinetics of plasma distribution and excretion kinetics are summarized in Tables 4 and 5.

a. Oral Exposure

a.1 Mouse

Reigner *et al.* (1992a) drew sequential tail vein blood samples from B6C3F$_1$ mice following a single gavage or i.v. dose of PCP at 15 mg/kg. The mean (± SD), monophasic, elimination half-lives for PCP (measured by chemical analysis) were 5.8 ± 0.6 hrs for the oral route and 5.2 ± 0.6 hrs for the i.v. route. Urinary excretion accounted for over 90% of the dose removed from the body during the first 48 hrs.

a.2 Rat

Braun *et al.* (1977) administered a single gavage dose of ^{14}C-labeled PCP at 10 mg/kg to Sprague-Dawley rats. Plasma radioactivity was measured in animals sacrificed sequentially, 2 of each sex per time point. The decline in plasma ^{14}C was biphasic. DPR estimated half-lives for the rapid (alpha) phase as 6.9 and 11 hrs for males and females, respectively.

Braun *et al.* (1977) also followed the level of radioactivity over time in excreta of Sprague-Dawley rats given a single gavage dose of ^{14}C-labeled PCP at 10 or 100 mg/kg. The mean (± SD) half-life for the rapid, initial phase of the combined urinary and fecal excretion was 17.4 ± 1.7 hrs in males and 13.4 ± 2.3 hrs in females given 10 mg/kg and 12.8 ± 1.1 in males given 100 mg/kg. In all dose groups, 90% of the dose was excreted in the urine or feces within the first 3 days, indicating that the rapid, initial phase was far more important than the slow phase.

Reigner *et al.* (1991) drew sequential jugular vein blood samples from male Sprague-Dawley rats following a single gavage or i.v. dose of PCP at 2.5 mg/kg. For the oral route, the mean (± SD), monophasic, elimination half-life for PCP (measured chemically) was 7.5 ± 0.4 hrs. For i.v. administration, the half-life for the major portion of the dose was similar (7.1 ± 0.87 hrs), but in addition there was an initial, short-lived, extremely rapid drop (half-life, 0.7 ± 0.5 hrs) which accounted for approximately one-fourth of the decline.

Yuan *et al.* (1994) took orbital blood from male and female F344 rats (3 animals per time point, two time points per animal) following a single i.v. dose of PCP at 5 mg/kg. Plasma PCP (measured by chemical analysis) declined in a biphasic fashion. The investigators estimated that the half-life for the slow phase was 5.6 hrs in the males and 9.5 hrs in the females.

Meerman *et al.* (1983) drew aortal blood from male Wistar rats (2 animals per time point) following a single i.v. dose of PCP at 10.7 mg/kg. Plasma PCP (measured by chemical analysis) declined in two phases. Approximately half the dose was eliminated with a mean rapid-phase half-life of 2.2 hrs, while the slow-phase half-life was 7.2 hrs.

a.3 Monkey

Braun and Sauerhoff (1976) administered a single 10 mg/kg dose of [^{14}C]-labeled PCP by nasogastric intubation to three male and three female monkeys. Radioactive counting of ^{14}C was combined with chemical analysis of PCP. The mean half-life in plasma was 72 hrs for males and 84 hrs for females. Excretion from urine had a mean half-life of 41 hrs for males and 92 hrs for females.

a.4 Human

Braun *et al.* (1979) gave single oral doses of PCP at 0.1 mg/kg to 4 male subjects and measured levels in plasma and urine for 6 days by chemical analysis. Using an open one-compartment model, they calculated a mean (± SD) plasma elimination half-life of 30.2 ± 4.0 hrs. In the urine, about one-sixth of the initial PCP dose is excreted as the glucuronide with a half-life of 12.7 ± 5.4 hrs; the remainder is excreted as unmetabolized PCP with a half-life of 33.1 ± 5.5 hrs.

Table 3. Relative amounts of unchanged and metabolized PCP in urine following single exposure[a].

Study	Species	Sex	Route	Collection period	Dose (mg/kg)	Percentage of urinary excretion (Mean)			
						PCP	PCP-c	TeCHQ	TeCHQ-c
Jakobson & Yllner, 1971	mouse	F	i.p.	24 hrs	7.4-8.2	54%[b]		44%[b]	
" " "	mouse	F	i.p.	24 hrs	15-37	53%	15%	33, 48%[b,c]	
Ahlborg *et al.*, 1974	mouse	n.s.	i.p.	24 hrs	10-25	41%	13%	24%	22%
Reigner *et al.*, 1992a	mouse	M	gav.	48 hrs	15	8%	51%	5%	47%
Ahlborg *et al.*, 1978	rat	n.s.	i.p.	24 hrs	10	60%	9-16%	7%	22%
Braun *et al.*, 1977	rat	M/F	gav.	8 days	100	75%	9%	16%	-
Braun & Sauerhoff, 1976	monkey	M/F	n.g.	7-15 days	10	100%	-	-	-
Braun *et al.*, 1979	human	M	oral	7 days	0.1	86%	14%	-	-
Uhl *et al.*, 1986	human	M	oral	24 hrs[d]	0.31	71%	29%	-	-

[a] Abbreviations: PCP-c, PCP conjugate; TeCHQ, tetrachloro-1,4-hydroquinone; TeCHQ-c, TeCHQ-conjugate; n.s., not specified; i.p., intraperitoneal; n.g., nasogastric; gav., gavage.

[b] The percentages of conjugated and unconjugated compound were not reported separately.

[c] Not mean values. Percentages shown are for two individual animals.

[d] Single sample collected 24 hrs after dosing.

In a study performed by Uhl *et al.* (1986), three male volunteers participated in a total of six, single-dose ingestion experiments in which the dosages tested were 0.033-0.31 mg/kg for PCP of normal isotopic composition and 0.016 mg/kg for [^{13}C]PCP. The kinetics of urinary excretion were calculated only for two experiments on one volunteer. This subject ingested PCP of normal isotopic composition at 0.31 mg/kg on one occasion and later, [^{13}C]PCP at 0.016 mg/kg. The results yielded similar half-lives for free PCP in urine: 480 ± 82 hrs and 432 ± 58 hrs, respectively. A half-life in plasma of 384 ± 60 hrs was measured in the ^{13}C experiment. Further experiments indicated possible shorter half-lives which were closer to those seen by Braun *et al.* (1979).

Barbieri *et al.* (1995) used chemical analysis to investigate the urinary excretion of PCP in four workers in Northern Italy (two at a wood-working factory and two at a tannery). Urinary PCP concentrations were from 86 to 470 μg/L in the wood-workers and from 601 to 2,063 μg/L in the tannery workers. PCP levels in morning samples were approximately 2-fold higher than those collected in the evening. The half-life of urinary PCP levels throughout a 4-week holiday period was estimated as 240 hrs.

Young and Haley (1978) developed a pharmacokinetic model based on a case study of intentional PCP ingestion. The patient was a 71-year old male who had ingested an estimated 4-8 ounces of weed killer containing 12% PCP and 1.5% other chlorinated phenols (Haley, 1977). Plasma and urinary PCP levels were measured by chemical analysis. The model was fitted to blood and urine measurements beginning about 2.5 hrs after ingestion. Although the patient was treated with a diuretic during a well-defined portion of his recovery, the observed elimination could be modeled so as to predict the underlying rates of elimination in the absence of the diuretic. The underlying half-life for overall elimination from the body was predicted by this model to be 116 hrs; for urinary elimination alone, the model yielded a half-life of 128 hrs.

Table 4. Half-lives in mouse, rat, monkey, and human plasma following a single dose of PCP[a].

Study	Route	Species	Sex	No.	Dose (mg/kg)	Collection period	Analytical method	Half-Life in plasma (hrs)
Reigner *et al.*, 1992a	oral	mouse	M	6	15	36 hrs	Chem.	5.8[c]
" " "	i.v.	mouse	M	6	15	36 hrs	Chem.	5.2[c]
Braun *et al.*, 1977	oral	rat	M	2[d]	10	6 days	^{14}C	6.9, (24)[b,e]
" " "	oral	rat	F	2[d]	10	6 days	^{14}C	11, (30)[b,e]
Reigner *et al.*, 1991	oral	rat	M	5	2.5	48 hrs	Chem.	7.5[c]
" " "	i.v.	rat	M	5	2.5	48 hrs	Chem.	(0.7), 7.1[e]
" " "	i.v.	rat	M	1	20	96 hrs	Chem.	4.1, (36)
" " "	i.v.	rat	M	1	20	96 hrs	^{14}C	4.5, (45)
Yuan *et al.*, 1994	oral	rat	M	3[d]	9.5	40 hrs	Chem.	8.6[c]
" " "	oral	rat	M	3[d]	38	60 hrs	Chem.	6.3[c]
" " "	i.v.	rat	M	3[d]	5	20 hrs	Chem.	< 3[f], 5.6[e]
" " "	i.v.	rat	F	3[d]	5	20 hrs	Chem.	< 4[f], 9.5[e]
Meerman *et al.*, 1983	i.v.	rat	M	2[d]	10.7	36 hrs	Chem.	2.2, 7.2[e]
Braun & Sauerhoff, 1976	n.g.	monkey	M	3	10	7 days	^{14}C/Chem.	72[c]
" " "	n.g.	monkey	F	3	10	7 days	^{14}C/Chem.	84[c]
Braun *et al.*, 1979	oral	human	M	4	0.1	6 days	Chem.	30[c]

[a] Half-lives given are mean values. A*bbreviations:* n.g., nasogastric; Chem., chemical analysis; ^{14}C, radioactive counts.
[b] Value estimated by DPR using linear extrapolation from data in Figure 2 of the citation.
[c] Monophasic model.
[d] Number of animals sacrificed or sampled per time point.
[e] Biphasic model. Half-lives accounting for only a minor portion of PCP are in parentheses.
[f] Upper limit of initial-phase half-life estimated by DPR from inspection of data in Figure 1 of the citation.

Table 5. Half-lives in rat, monkey, and human excreta following a single dose of PCP[a].

Study	Route	Species	No.	Sex	Dose (mg/kg)	Collection period	Analytical method	Half-Life in excreta[b] (hrs)	Half-Life in urine (hrs)
Braun *et al.*, 1977	oral	rat	3	M	10	9 d	^{14}C	17.4, (40.2)[c]	-
" " "	oral	rat	3	F	10	9 d	^{14}C	13.4, (32.5)[c]	-
" " "	oral	rat	3	M	100	8 d	^{14}C	12.8, (121)[c]	-
" " "	oral	rat	3	F	100	8 d	^{14}C	27.2[d]	-
" " "	oral	rat	3	n.s.	100	8 d	^{14}C	-	13, (31)[c,e]
Braun & Sauerhoff, 1976	n.g.	monkey	3	M	10	7 d	^{14}C/Chem.	-	41[d]
" " "	n.g.	monkey	3	F	10	7 d	^{14}C/Chem.	-	92[d]
Braun *et al.*, 1979	oral	human	4	M	0.1	6 d	Chem.	-	33[d]
Uhl *et al.*, 1986	oral	human	1	M	0.016	53 d	^{13}C	-	432[d]
" " "	oral	human	1	M	0.31	70 d	Chem.	-	480[d]
" " "	oral	human	3	M	0.055-0.15	6-14 d	Chem.	-	≤ 144[d,f]
Young & Haley, 1978	oral	human	1	M	≥ 2,400[g]	7 d	Chem.	116[d]	128[d]

[a] Half-lives given are mean values. *Abbreviations:* n.g., nasogastric; Chem., chemical analysis; ^{14}C, radioactive counts; ^{13}C, isotopic substitution.

[b] Combined urinary and fecal excretion.

[c] Biphasic model. Half-lives accounting for only a minor portion of PCP are in parentheses.

[d] Monophasic model.

[e] Values estimated by DPR using linear extrapolation from data in Figure 4 of the citation. Sex not specified (n.s.)

[f] Estimated from Figure 1 of the citation.

[g] Accidental poisoning case study.

DERMAL ABSORPTION

The U.S. EPA (1984) has used the ratio between oral and dermal toxicities to estimate dermal absorption of PCP as 50%. A lower value (1%) has been estimated by U.S. EPA for Na-PCP based on its water solubility. The dermal absorption of PCP for use in this exposure assessment document was estimated from a study conducted by Wester *et al*. (1993). Four female Rhesus monkeys were used in the *in vivo* study. An abdominal skin area of 12 cm^2 was lightly clipper shaved to remove hair but did not abrade the skin. Monkeys were restrained in metabolic chairs during the first 24 hours. Doses of ^{14}C-labeled PCP were prepared either in acetone or in soil for topical administration. For a dose in soil, a Yolo county soil sample was used in the study. Soil used in this study was composed of 26% clay, 48% silt and 9% organic. Soil was passed through 10, 20, and 48-mesh sieves; soil retained by 80-mesh was used to prepare the dose.

The soil sample was premoistened before adding ^{14}C-labeled PCP. Labeled PCP (37 mCi/mmol and 98.6% pure) was prepared in 7:3 (v/v) hexane:methylene chloride. Soil was mixed well by hand. PCP was also prepared in acetone for topical administration. The administered doses of PCP on skin were 0.7 $\mu g/cm^2$ in soil and 0.8 $\mu g/cm^2$ in acetone A dose of PCP was applied to a premeasured 12 cm^2 area of shaved abdominal skin. After the application, the treated sites were covered with non-occlusive covers to stop soil from falling off the skin. The protective cover was made of two standard human aluminum eye patches with large holes permeating the surface. A sheet of water-vapor-permeating membrane was sandwiched between the eye patches. This allowed free passage of moisture, but retained the soil at the treated skin site. Monkeys were restrained in the metabolic chairs during the first 24 hours and then transferred to metabolic cages thereafter. Urine was collected the first 24 hours after treatment in the pan under the metabolic chair. The cover of the treated skin site was removed and all visible soil was collected. The treated skin sites were then washed with soap and water and the animals transferred to metabolic cages for continued daily urine collection for 14 days. To correct for incomplete urinary excretion of an absorbed dose, PCP in propylene glycol (1 μCi ^{14}C-PCP) was administered intravenously (i.v.) to 4 other monkeys and urine collected from the animals in metabolic cages.

The percutaneous absorption value (%) was determined as follows: (^{14}C urinary excretion from topical administration x 100/^{14}C urinary excretion from i.v. administration). The *in vivo* percutaneous absorption value of PCP was determined to be 24.4 ± 6.4% for applied dose from soil and 29.2 ± 5.8% for applied dose from the acetone formulation. It is appropriate to use the percent dermal absorption result obtained from the dose prepared in acetone rather than from the dose prepared in soil because exposure of handlers was not the result of contacting PCP-contaminated soil. A mean dermal absorption value of 29.2 percent was used in the estimation of absorbed dosage.

An *in vitro* dermal absorption study was conducted by Rossner (1986). This study used human skin to measure the absorption of Na-PCP and PCP. The recovery of PCP was only 38%, which was very low. Since *in vivo* dermal absorption is available as described above, dermal absorption *in vitro* will not be used for the estimation of absorbed dosages. Furthermore, *in vivo* percutaneous absorption values of some pesticides and other compounds obtained from studies using monkeys and humans are similar (Wester and Maibach, 1975, 1977).

INHALATION ABSORPTION

Studies are available in both rats and humans that can be used to estimate the absorption of PCP during inhalation exposure. These studies yield a similar estimate for inhalation absorption. Hoben *et al.* (1976b) have investigated the distribution and excretion of inhaled PCP in male Sprague Dawley rats. Rats were enclosed in bottles from which only their nares extended. They were exposed to an aerosol (unspecified diameter) of PCP in a chamber through which a constant flow rate of PCP was maintained. Rats were exposed for 20 minutes at a time for 1, 2, 3, 4, or 5 days. Exposure was estimated as 5.2-5.9 mg/kg based on the concentration in the chamber and an inhalation rate of 80 mL of air/minute (1.6 L of air/20 minute exposure). Animals were sacrificed at 0, 5, 12, 24, 48 and 72 hours post-exposure to determine the distribution of PCP in the lungs, liver, and blood. Animals sacrificed at 24, 48, and 72 hours were housed in metabolism cages for the collection of urine. Tissue, blood and urine were acidified, extracted, alkylated, and run on a GC equipped with an electron capture detector to quantify PCP and metabolites.

Metabolism following inhalation exposure was similar to that following oral exposure. Elimination was primarily as PCP, but trace amounts of TeCHQ were also detected in the liver. This study did not test for glucuronide-conjugated PCP. Following multiple exposures there was no increase in PCP accumulation in blood, liver or lung tissue. Urinary elimination of PCP as a percent of non-cumulative daily dose increased through day 5 following multiple exposures. At least 50% of the dose was found to be excreted in the urine 24 hours post-dosing. This is less than that observed following i.p. dosing (70%, Ahlborg *et al.*, 1974), but more than recovered following oral dosing (40%, Ahlborg *et al.*, 1974; Braun *et al.*, 1977).

An estimate of absorption following inhalation exposure in rats can best be derived using the single-dose data. The authors found a total of about 80% of the estimated exposure dose had been recovered in the urine by 72 hours. At this time less than 2% of the dose remained in the liver, plasma, and lung. Braun *et al.* (1977) found that over 18% of an oral dose given to rats was eliminated in the feces. Feces samples were not collected for analysis. Assuming a similar elimination in the feces for the inhaled dose as that for the oral dose, it can be estimated that close to 100% of the inhaled dose is absorbed through the lungs and eliminated.

A study by Casarett *et al.* (1969) can be used to estimate human respiratory absorption. They followed excretion of PCP after an inhalation exposure to two workers. These workers had not been previously occupationally exposed. They spent 45 minutes in an enclosed area during a brush-on application of PCP. One worker operated the air sampling apparatus and measured respiration rates. Most of his exposure was via inhalation and some skin permeation. The second worker applied the PCP solution. The Worker Health and Safety Branch has excluded this worker from calculation of inhalation absorption because of the probability that he was also subject to significant dermal exposure. Midget impingers were used to collect air samples in the enclosed area. Total urine was collected for two days prior to exposure and 7 days after exposure. PCP in urine was determined using a GC equipped with an electron capture detector. Inhalation exposure was estimated based on the observed inhalation rate of the second worker, standard tidal volumes, and measured air concentrations. By 7 days post-exposure 88% of the estimated dose had been recovered from urine.

After 8 days Braun *et al.* (1979) found a similar percent (86%) excreted following a single oral dose to humans. Braun *et al.* (1979) also found 4% of the dose excreted in feces. The detection method of Casarett *et al.* (1969) measured only PCP, so recovery may have been higher. They also had no way of accounting for PCP still in the body at 7 days and did not measure PCP excreted in feces. Assuming that dermal exposure was minimal, some PCP was excreted in feces, and that some conjugated PCP was produced, The Worker Health and Safety Branch estimates that 88-100% of inhaled PCP was absorbed. Thus, similar results were obtained from both rat and human studies. For the purpose of human exposure assessment 100%, inhalation absorption will be used.

BIOLOGICAL MONITORING

There are extensive data measuring PCP in the urine of occupationally exposed workers and the general population. These data clearly show elevated levels of PCP in exposed workers (see Table 3), and also show that low levels of PCP are excreted in individuals not occupationally exposed to PCP. These low levels of PCP are believed to result primarily from the wide-spread distribution of PCP in the environment (Crosby, 1981) and to a lesser extent the metabolism of the fungicide and PCP contaminant hexachlorobenzene to PCP (Koss and Koransky, 1978; Renner and Mücke, 1986; van Ommen *et al*., 1985).

Urinary levels of PCP and metabolites are subject to a lag in elimination and to the variable half-life discussed above. Consequently, urinary PCP will prove a difficult biological monitor of short-term exposure, but can be used for repetitive (long-term) exposures. In generalizing from biological monitoring data the following caveats are considered: data are for different sites where workers may have used different protective measures and formulations; workers may have been exposed for different periods; data are for single samples not complete urines; worker exposures were not necessarily at steady state when samples were taken; and different methods were used to analyze and correct PCP levels. This latter point is important because determination of PCP values without complete hydrolysis can underestimate PCP levels (Ahlborg *et al*., 1978; Drummond *et al*., 1982; Edgerton and Moseman, 1979). Information concerning hydrolysis and normalization for specific gravity or creatinine content is shown in Table 6.

Urinary concentrations of PCP in occupational workers were measured before the current requirements for personal protection were in force. In general these urine data can be used to substantiate the designation of four exposure groups: direct dermal, indirect dermal, primarily inhalation, and background. A range of PCP levels occurs within each exposure group. The data presented in Table 6 are averages. Spray, dip, or brush treatments with PCP lead to the highest-urinary PCP concentration in exposed workers (mean = 876 ppb) and are likely to be the highest-exposure work tasks. These are all application tasks that have in common direct dermal exposure to the treatment solution. Tasks limited to indirect dermal contact via treated wood or contaminated surfaces lead to lower urine levels (mean = 229 ppb). These levels are found in formulators, workers in pressure treatment facilities, mixer/loaders, and sawmill workers. Airborne exposure is the most significant exposure route for occupants of log homes constructed

from PCP-treated logs. This chronic non-occupational exposure can lead to slightly elevated urine levels (mean = 69 ppb). Airborne levels for various exposures are shown in Table 7. Urine levels for these three exposures are above the background PCP levels in urine observed in the general U.S. population (3-40 ppb). A biological threshold value of 7,000 ppb has been suggested in Canada as an action level for exposure reduction (Drummond *et al.*, 1982). The American Conference of Governmental Industrial Hygienists (1986) has recommended a Biological Exposure Index of 2 ppm in urine and 5 ppm in plasma.

Biological monitoring data also support an extended elimination (excretion) half-life ($E_{1/2}$) for urinary PCP following long-term exposure. Kalman and Horstmanand (1983) and Kleinman *et al*. (1986) observed slow or minimal reductions in urinary PCP levels in groups of exposed mill workers during 2-week vacation periods. Begley *et al*. (1977) found a gradual decline in urinary PCP during a 20-day vacation in a group of exposed structural-control pesticide applicators. An $E_{1/2}$ of about 15.6 days has been calculated from their data by the Worker Health and Safety Branch. This half-life value is in the same range of $E_{1/2}$ discussed above on pharmacokinetics of PCP in humans.

Table 6. Average level of PCP determined in urine for various exposure groups.

Exposure task	Reference	PCP equivalent[a] (ppb)	Total/free PCP[b]	Correction applied
Mill spray applicator				
	Lindroos *et al*., 1987	2249[c]	total	SP
	Enarson *et al*., 1986	269	free	SP
	Bentley *et al*, 1989	207	total	None
	Kauppinen and Lindroos, 1985	170[c]	free	SP
Structural spray applicator				
	Bevenue *et al*., 1967	1802	free	NS
	Jones *et al*., 1986	748[d]	total	CR
	Gilbert *et al*., 1984	174	free	NS
Dip or brush applicator				
	Begley *et al*., 1977	1310	free	SP
	Kauppinen and Lindroos, 1985	952[c]	free	SP
Mill, "high" dermal contact				
	Fenske *et al*., 1987	1130	total	None
	Lindroos *et al*., 1987	404	total	SP
	Jones *et al*., 1986	202[d]	total	CR
	Kalman and Horstmanand, 1983	117	total	None
	Embree *et al*., 1984	105	free	SP
	Kleinman *et al*., 1986	81	total	None
Pressure treatment				
Cylinder worker	Wyllie *et al*., 1975	296	free	None
Maintenance	Wyllie *et al*., 1975	174	free	None
Outside labor	Wyllie *et al*., 1975	105	free	None
Mill, "low" dermal contact				
	Lindroos *et al*., 1987	260	total	SP
	Enarson *et al*., 1986	149	free	SP
	Embree *et al*., 1984	45	free	SP
Formulation				
Filling	Triebig *et al*., 1987	241	free	NS
Labor	Triebig *et al*., 1987	173	free	NS
Production	Triebig *et al*., 1987	154	free	NS
	Jones *et al*., 1986	108[d]	total	CR
Mill, mixer/loader				
	Kauppinen and Lindroos, 1985	147[c]	free	SP
Log-home occupant				
	Cline *et al*., 1989	69	total	None
General population				
	Kleinman *et al*., 1986	39	total	None
	Wyllie *et al*., 1975	26	free	None
	Hill *et al*., 1989	14	free	NS
	Kalman and Horstmanand, 1983	10	total	None
	Cline *et al*., 1989	3	total	None

[a] Other chlorophenates converted to equal PCP stoichiometric values.

[b] Total PCP values were determined following complete hydrolysis using acid and heat. Free PCP values were not completely hydrolyzed.

[c] Value is for tri, tetra and pentachlorophenol.

[d] Recalculated by WH&S from a molar concentration based on 1500 mg creatinine in 1.4 L of urine excreted daily.

SP=Normalized to a constant specific gravity.
CR=Normalized to a constant creatinine concentration.
NS=Not stated in reference.

WORKER EXPOSURE AND WORK ENVIRONMENT MONITORING

In California, worker exposures to PCP are primarily during the treatment of logs or lumber by pressure treatment. Dermal contact may occur by direct contact with the treatment solution or indirectly via contact with wet or dry wood. Several exposure situations are discussed below.

PCP is used in pressure treatment facilities where a single load of wood (charge) is chained to narrow-gauge railroad cars (trams). The tram is then pushed into long cylinders (retort) that can be pressurized. These trams are used only for wood treatment in these retorts. PCP is dissolved in either aromatic oil or butane/isopropyl ether. Mixing/loading of PCP is now done using closed systems. The retort is closed and filled with the PCP solution and pressurized to drive the solution into the wood. When the treatment is complete, the solution is pumped out, and the retort chamber and loaded tram are steamed, and then a vacuum is drawn to remove volatile residues. A forklift is typically used to pull the trams out of the chamber and to stack the wood outdoors. When finished wood is ready for transport, a forklift is again used for loading. The primary worker exposures during this process will occur during proximity to the treatment chamber or treated wood. Both airborne and dermal exposure can occur to persons loading or unloading the chamber and the treated wood. Maintenance workers might also be exposed in the chamber. No task-specific monitoring data are available for the dermal component of this exposure. Some airborne levels are available. Airborne exposure ranges from 0.2 - 197 $\mu g/m^3$ in the pressure treatment area, from <0.1 - 3.9 $\mu g/m^3$ in the rest of a pressure treatment plant, and from 1 - 15 $\mu g/m^3$ outside near stacks of treated wood (NIOSH, 1983; Vulcan, 1993; Wyllie *et al*., 1975; see Table 7).

Spray and dip applications are done primarily in sawmills after timber has been cut to lumber and milled products. These applications typically use water-soluble chlorophenol, which is often formulated with tetrachlorophenol (TCP). Automated spray booths are used in some mills and this reduces exposure. Spraying may be done inside a closed or semi-enclosed facility or in an outside yard. Consequently, reported airborne concentrations vary considerably (see Table 7). This type of treatment is no longer done in California (Brodberg, 1990).

Table 7. Level of airborne PCP equivalents at various exposure sites.

Exposure situation	Reference	PCP equivalents[a] $\mu g/m^3$ Mean	Range
Mill M/L	Kauppinen and Lindroos, 1985	66[b]	5-210
Dip	Kauppinen and Lindroos, 1985	48[b]	1-170
Formulation plant			
loading	Triebig *et al*., 1987	72	13-180
production	Triebig *et al*., 1987	27	5-44
filling	Triebig *et al*., 1987	4.5	0.3-8
Mill spray			
booth	Kauppinen and Lindroos, 1985	78.5[b]	57-100
open indoor	Kauppinen and Lindroos, 1985	24[b]	7-50
booth	Embree *et al*., 1984	6	--
booth	Kleinman *et al*., 1986	<0.5	--
Pressure treating			
retort area (n=45)	NIOSH, 83; Vulcan, 93	23.7 ± 40.8	1-197
retort area	Wyllie *et al*., 1975	3.9	0.2-15.3
outside stacks (n=8)	NIOSH, 83; Vulcan, 93	5.8 ± 3.6	1-15
general plant	Wyllie *et al*., 1975	0.3	<0.1-3.9

M/L=Mixer/loader

[a] Other chlorophenols converted to equal PCP stoichiometric values.
[b] Reported as penta- + tetra- + trichlorophenol. From 10 sites with different manufacturing facilities and practices.

Fenske *et al.* (1987) mixed a fluorescent tracer (4-methyl-7-diethylaminocoumarin, a whitening agent) with an aqueous formulation of 20% TCP and 3% PCP to monitor dermal exposure in a planing mill. The final formulation for wood treatment contained 1.1% tetrachlorophenol and 0.2% pentachlorophenol (Kleinman *et al*., 1986). Using their technique, the skin deposition of the tracer is visualized under UV-A illumination and measured using a video imaging system. The amount of tracer observed is related quantitatively to pesticide residues by a calibration factor (essentially a co-transfer factor) determined at the time of exposure. This study monitored seven workers exposed handling cut wood as it emerged from a closed spray booth. Only the upper body was monitored and dermal exposure values were reported for the hands and forearms only. Exposure to the face was noted and attributed to hand cross-contamination. The authors noted anecdotally that these workers also had frequent wood contact with the torso and upper

legs. Impervious gauntlet-type polyvinyl chloride gloves, which covered up to the mid-forearms (Thongsinthusak, 1994), and a vinyl apron were worn during the study. The apron provided no protection to the monitored sites (hands and forearms).

The rate of tetrachlorophenol deposition through protective clothing to the hands and forearms was 2.7 μg/hr and 15 μg/hr, respectively. Rates of PCP deposition calculated from these values are shown in Table 8. The hand and forearm exposures were corrected for the ratio of TCP and PCP, the ratio of final PCP concentration in pressure treatment and PCP used in the Fenske study, and protection provided by clothing. The mean (arithmetic) ± (standard deviation) for hand and forearm exposures are 0.080 ± 0.095 and 0.189 ± 0.044 μg/cm^2/hr, respectively (Table 8).

A correction factor of 27.5 (Table 8, footnote d) was based upon the assumption that dermal exposure is dependent on concentration or percent of active ingredient in the ready-to-use solution. This practice is generally accepted for extrapolation of worker exposure using surrogate data. For this extrapolation, percent of PCP in the ready-to-use solution for the pressure treatment was 5.5%, whereas for PCP used in the Fenske study it was 0.2%. Therefore, PCP dermal exposure derived from the Fenske study was increased by 27.5-fold (5.5%/0.2%) for retort workers.

Dermal exposure of maintenance workers was extrapolated as shown in Table 9. In making this extrapolation, all exposed regions were assumed to have at least as much exposure per unit area as the hands. Maintenance workers were assumed to contact PCP on most body regions. Workers were assumed to be wearing long-sleeved shirts, long pants, and clean, chemical-resistant protective clothing and gloves. The estimated dermal exposure was 156 ± 174 μg/hr.

A mixer/loader and retort loader were assumed to be wearing work clothing and chemical resistant gloves. The apron in the Fenske study was ignored since in the past this was not a clothing requirement. It was assumed that only some body surface areas would be exposed to PCP because mechanical transfer of a PCP block in a closed system occurs during mixing/loading, resulting in limited body contact to PCP and PCP-contaminated surfaces. Furthermore, PCP residues on hands and forearms were obtained from a study in timber mills where workers handled wet timber. These residues were used to estimate exposure of workers in a pressure treatment facility where most surfaces are dry. This method of extrapolation can overestimate exposure of workers in the pressure treatment facility. It is unlikely that some body regions of workers in a pressure wood treatment facility would contact contaminated surfaces as much as hands or forearms would in timber mills. It should be reasonable to estimate exposure based upon 50% of the surface areas of the head, chest, upper arms, and thighs and 100% to that of hands and forearms. Dermal exposure for mixer/loaders or retort loaders was estimated to be 696 ± 609 μg/hr (Table 10).

Table 8. Calculation of PCP dermal exposures of hands and forearms from mill spray application based on tetrachlorophenol[a].

Mean

Body site (n)	TCP dermal exposure (mean, μg/hr)	PCP dermal exposure (mean, μg/hr)[b]	Corrected PCP dermal exposure (mean, μg/hr)[c]	Correction factor[d]	Corrected PCP exposure (μg/hr)	SA (cm^2)[e]	PCP dermal exposure (μg/cm^2/hr)
Hands (7)	26.7	2.67	2.67	27.5	73.4	915	0.080
Forearms (7)	151	15.1	8.32	27.5	229	1211	0.189

SD

Body site (n)	TCP dermal exposure (SD, μg/hr)	PCP dermal exposure (SD, μg/hr)[b]	Corrected PCP dermal exposure (SD, μg/hr)[c]	Correction factor[d]	Corrected exposure (μg/hr)	SA (cm^2)[e]	PCP Dermal exposure (μg/cm^2/hr)
Hands (7)	31.7	3.17	3.17	27.5	87.2	915	0.095
Forearms (7)	35.4	3.54	1.95	27.5	53.5	1211	0.044

[a] Workers wore work clothing and polyvinyl chloride gloves.
[b] Ten-fold exposure reduction for TCP:PCP ratio (Tracer:TCP = 1:10; Tracer:PCP = 1:1. Therefore, TCP:PCP = 10:1).
[c] Gauntlet gloves used in the study covered up to the mid-forearms (Thongsinthusak, 1994). Fifty percent of forearm exposure is reduced 90% by glove protection. Calculation of forearm exposure: ((15.1/2) + (15.1/2 x 0.1)) = 8.32 μg/hr.
[d] Permatox 100® (20% TCP, 3% PCP) was diluted 18 to 20-fold with water prior to use (Kleinman, 1986, Thongsinthusak, 1994). PCP conc. = 3%/19 = 0.2%. Correction factor = 5.5% (% in pressure treatment)/0.2% (% in mill treatment) = 27.5.
[e] U.S. EPA (1985).

SA = surface area

NORMALIZED EXPOSURE ESTIMATES

Current worker exposure in California falls into two exposure scenarios, i.e., exposure during pressure treatment of logs or lumber and people residing in log homes where lumber was treated with PCP. As of September 1994, registration for other end-use products has not been renewed. There are no specific exposure studies available to estimate worker exposure for these scenarios; consequently, surrogate studies will be used. Exposure estimates will be adjusted for the amount of active ingredient in the final solution and current protective clothing requirements.

Exposure during pressure treatment is via airborne material and by dermal contact during the moving and unloading of treated wood. Airborne exposure is highest near the retort and lower in the general plant and yard area (see Table 7). Mixing and loading is done using closed systems. In the more common system one-ton solid Penta blocks are lifted into a mixing tank using a fork-lift or pulley system. The blocks are wrapped in plastic and lifted by a bar hook molded into the block. The plastic is removed as the block is lowered into the tank. Once the Penta is in the tank, the tank is closed, solvent is pumped in, and the mixture is heated until the Penta is dissolved. Large mixing tanks may hold 10,000 gallons. Solution from the mixing tank is piped to work tanks at the retort, where it is refilled as needed. Depending on treatment activity, fresh Penta may be mixed weekly or monthly.

In California, pressure treatments range in duration from 10 hours to 3 days depending on characteristics of the wood (Brodberg, 1990). Only one pressure-treating facility with two retorts (pressure cylinders) remains operational in the state (Baxter, 1994). If each retort is loaded and unloaded by the same worker, then a single worker's maximal exposure in a day will be during two retort cycles. Due to treatments requiring more than one day, the average number of charges is approximately 150 to 200 charges per retort per year (Baxter, 1994). In practice, retort loading and unloading is typically divided between two or more workers.

The data of Fenske *et al.* (1987) was used as a surrogate to estimate pressure-treatment exposure under current protective clothing requirements. Dermal exposure for maintenance workers, mixer/loaders or retort loader/unloaders was estimated and shown in Tables 9 and 10. Average respiratory exposure in several pressure-treatment facilities was measured as 23.7 ± 40.8 μg/m^3 at the retort area (see Table 7) or 19.9 ± 34.3 μg/hour for light activity (respiration rate of 0.84 m^3/hour (U.S. EPA, 1985). Mixer/loaders will be exposed for about 0.5 hours per day during high-inhalation and dermal exposure and 4.3 hours per day for low-inhalation exposure (Baxter, 1994). The estimated absorbed daily dosage for a mixer/loader is 1.8 μg/kg/day (Table 11). Retort loader/unloaders will be exposed for about 0.3 hours during high-inhalation and dermal exposure and 4.5 hours during low-inhalation exposure (Baxter, 1994). Treated lumber, as it comes out of the retort, is dry to the touch. This should reduce dermal transfer and exposure in comparison to the Fenske study in which workers handled wet wood. Worker exposure during most of the day will be by inhalation in areas of the facility with reduced airborne levels of PCP (e.g., the general plant and storage yard). Measured airborne levels for these regions were 5.8 ± 3.6 μg/m^3 (low-inhalation exposure) (see Table 7). The daily absorbed dosage of retort loader/unloaders (Table 11) was estimated to be 1.2 μg/kg/day, which is comparable to the U.S. EPA estimate of 2.0 μg/kg/day (U.S. EPA, 1984).

Table 9. Dermal exposure extrapolated by Worker Health and Safety for maintenance workers.

Body site	SA (cm^2)	Dermal exposure ($\mu g/cm^2/hr$)	Dermal exposure (regional, $\mu g/hr$)	Corrected Exposure[a] ($\mu g/hr$)
Face	630	0.080	50.4	25.2
Neck	253	0.080	20.2	1.01
Chest	3454	0.080	276	0.59
Back	3454	0.080	276	13.8
Upper arms	1479	0.080	118	5.92
Thighs	3663	0.080	293	14.7
Lower legs	2455	0.080	196	5.16
Feet	1256	0.080	101	5.02
Hands			73	73.0
Forearms			229	11.5
Dermal exposure (mean) of maintenance workers				156
Dermal exposure (SD) of maintenance workers				174[b]

[a] Maintenance workers must wear work clothing (long-sleeved shirt, long pants), goggles, protective clothing (including overalls, jackets, gloves, and boots) impervious to PCP formulation, and MSHA/NIOSH-approved half-face respirators. Default values for PCP protection provided by clothing and protective clothing and equipment were adopted from Thonsinthusak *et al*. (1993). Thus, overalls, jackets, gloves, and boots impervious to PCP formulation provide 95% protection. The assumed percentage of surface areas covered by clothing were: overalls - chest 85%, thighs 100%, lower legs 100%; jacket - neck 100%, chest 100%, back 100%, upper arms and forearms 100%, boots - lower legs 50%, feet 100%. It was assumed that goggles and a respirator reduced overall face exposure 50%.

[b] Similar calculation as that for mean values, but SD values were used instead of mean values.

Table 10. Dermal exposure extrapolated by Worker Health and Safety for PCP mixers/loaders and retort loaders[a].

Body site	SA (cm^2)	Exposed SA (cm^2)[b]	Dermal exposure ($\mu g/cm^2/hr$)	Dermal exposure ($\mu g/hr$)
Face	630	630	0.080	50.4
Chest	3454	1727	0.080	138
Upper arms	1479	740	0.080	59.2
Thighs	3663	1832	0.080	147
Hands	915	915	--	73.0
Forearms	1211	1211	--	229
Dermal exposure (mean) of mixers/loaders and retort loaders				696
Dermal exposure (SD) of mixers/loaders and retort loaders				609[c]

[a] M/Ls and retort loader/unloaders must wear work clothing and chemical-resistant gloves.

[b] Assumed exposed surface areas: 50% for head, chest, upper arms, and thighs; 100% for hands and forearms.

[c] Similar calculation as that for mean values, but SD values were used instead of mean values.

Table 11. Normalized absorbed dosages of pentachlorophenol for occupational and non-occupational exposure[a].

	Exposure		Normalized Dosage		
Work Task	Inhalation (μg/kg/day)	Dermal (μg/kg/day)	ADD (μg/kg/day)	AADD (μg/kg/day)	LADD (μg/kg/day)
Pressure Treatment					
1. Mixer/loader (M/L)[b]	0.41 ± 0.40	4.6 ± 4.0	1.8 ± 1.6	0.24 ± 0.21	0.13 ± 0.11
2. Retort loader/unloader (RL/UL)[c]	0.37 ± 0.31	2.8 ± 2.4	1.2 ± 1.0	0.80 ± 0.70	0.43 ± 0.37
3. Long Maintenance (LM)[d]	1.3	4.1 ± 4.6	2.5	----	----
4. Short Maintenance (SM)[e]	0.80	2.1 ± 2.3	1.4	----	----
5. Combined (SM + LM)[f]	----	----	----	0.07	0.04
6. M/L + SM[g]	0.96	6.6 ± 6.3	2.9	0.28	0.15
7. RL/UL + SM[g]	0.92	4.8 ± 4.7	2.3	0.84	0.45
Log home[h]	0.71	-	0.71	0.68	0.09

[a] Daily dosages reported here include both absorbed dermal and inhaled dosages, and are based on a 75.9 kg adult male worker (U.S. EPA, 1985). Results represent mean (arithmetic) ± SD (standard deviation), except for maintenance activities where SD values could not be calculated. This is because the TLV/TWA of 500 μg/m^3 was used to estimate the high inhalation exposure; the SD value was not available.

[b] Exposure is based on workers wearing long-sleeved shirt, long pants, and chemical-resistant gloves. Absorbed daily dosage (ADD) is based on 0.5 hours of high inhalation and dermal exposure and 4.3 hours of low inhalation exposure at a light inhalation rate of 0.84 m^3/hr (U.S. EPA, 1985); 100% inhalation absorption; and 29.2% dermal absorption. Annual Average Daily Dosage (AADD) is based on 50 daily exposures per year. Lifetime Average Daily Dosage (LADD) is based on 40 working years in a 75-year life-span (Bureau of the Census, 1991).

[c] Exposure is based on workers wearing long-sleeved shirt, long pants, and chemical-resistant gloves. ADD is based on 0.3 hours of simultaneous high inhalation and dermal exposure and 4.5 hours of lower inhalation exposure at a light inhalation rate (0.84 m^3/hr); AADD is based on 250 daily exposures per year. LADD is based on 40 working years in a 75-year life-span.

[d] Exposure is based on workers wearing clothing and protective clothing as those listed in “a” (Table 9). ADD is based on two hours of simultaneous high inhalation and dermal exposure and 2.8 hours of lower inhalation exposure at a light respiration rate (0.84 m^3/hr). Surface areas covered by overalls are: chest/stomach (85%), thighs and lower legs (100%) and none for other body regions. A jacket is assumed to protect upper arms, forearms, neck, chest/stomach, and back. Goggles and a respirator are assumed to cover 50% of the face area.

[e] Exposure is based on workers wearing the same protective clothing as in "d" above. ADD is based on one hour of simultaneous high inhalation and dermal exposure and 3.8 hours of low inhalation exposure at a light inhalation rate (0.84 m^3/hr).

[f] Exposure is based on workers wearing the same protective clothing as in "d" above. No combined short and long maintenance exposures are expected in the same day, so no ADD is given. AADD is based on 4 daily long exposures and 12 daily short exposures per year. LADD is based on 40 working years in a 75-year life-span.

[g] A mixer/loader or a retort loader/unloader may spend one hour per month on maintenance work (Vulcan, 1992). Therefore, exposure from short-term maintenance work (one hour high inhalation and dermal exposure) is added to either exposure of a mixer/loader or retort loader/unloader.

[h] Exposure in a log home is based on an unprotected adult male occupant. ADD is based on 15 hours of inhalation at a low activity level of 0.72 m^3/hr. AADD is based on 347 exposure days per year. LADD is based on 10 residence years per 75 year life-span.

Notes: Calculation procedures for ADD, AADD, and LADD are as follows:

ADD = [(daily dermal exposure x % dermal absorption) + (daily inhalation exposure x % inhalation absorption)] ÷ adult male body weight (75.9 kg)
AADD = (ADD x days exposed/year) ÷ 365 days/year
LADD = (AADD x years worked) ÷ 75-year lifetime

Maintenance workers in pressure-treatment facilities will be exposed to PCP when repairing the retorts. At the end of a normal treatment cycle (after the treatment solution is pumped out) the interior of a retort is steamed or heated and subjected to a vacuum for 1-2 hours to remove volatiles. This cleans and dries both the treated wood and the retort interior. Prior to workers entering retorts, the retorts are aired even longer. No airborne levels of PCP inside retorts have been published. To estimate inhalation exposure in this case, the Threshold Limit Value/Time-Weighted Average of 500 $\mu g/m^3$ will be used as the level inside of the retort. Workers entering the retorts are required to wear MSHA/NIOSH-approved respirators and chemical-resistant protective clothing impervious to PCP formulation, which limits respiratory and dermal exposure. Repair or long-term maintenance activity is expected to result in dermal exposure for 2 hours/day. Maintenance of this duration is not a daily activity, but might occur once in three months (Brodberg, 1990). These workers would also be exposed for 2.8 hours to general plant airborne levels of PCP.

Additional exposure inside the retort might occur for short-term minor work or tram cleaning. Trams are cleaned with a high-pressure wash inside the retorts. This minor work might lead to retort level exposures of one hour on a monthly basis, followed by general plant airborne level exposure for another 3.8 hours. Clothing protection is factored in to the separate daily exposure. Dosages for both short and long maintenance work are shown in Table 11. Both long- and short-term exposures are combined in the maintenance work for yearly and lifetime dosages.

More than one of the pressure-treatment tasks (e.g., mixing/loading, retort loading/unloading, and maintenance) may be performed by the same worker during the course of a year. Since retorts are typically run by a 2-4 person crew it would be unrealistic to apply all of the maximal exposures to a single worker. Certain daily work combinations are not likely (e.g., long maintenance work is not compatible with completing two retort cycles in a day). However, short maintenance of equipment that may be needed once per month may be performed by the same worker who mixes/loads PCP or a worker who works as a retort loader/unloader (Vulcan Chemical, 1992). In this scenario, high inhalation and dermal exposure for a period of one hour will be added to exposure arising from working as a mixer/loader or a retort loader/unloader. Results are shown in Table 11. The results indicated that a retort loader performing short maintenance work receives the highest yearly (0.84 μg/kg/day) and lifetime dosages (0.45 μg/kg/day). A mixer/loader who also maintains equipment receives the highest absorbed daily dosage (2.9 μg/kg/day).

Non-occupational exposure to PCP is limited to airborne exposure in log homes constructed with PCP-treated logs. Since the use of PCP-treated logs for this purpose is now prohibited, new exposure cases should not arise. Interior brush-on treatment is also prohibited. Limited use of pre-treated wood is allowed only if it is coated with a sealer to prevent volatilization of PCP. Application of a sealer can also be used as a mitigation measure to reduce volatilization in a home built prior to these restrictions.

Exposure in pre-existing log homes constructed of pressure-treated logs is estimated from the mid-point of the range for these homes (0.5 - 10 $\mu g/m^3$) given in EPA Position Document 4 (U.S. EPA, 1984) as 5 $\mu g/m^3$. For a rest activity levels (respiration of 0.72 m^3/hr for a 75.9 kg male)

would result in a 15 hour exposure and a dosage of 0.71 μg/kg/day (Table 11). A 15 hour in home exposure is estimated for a working male. Using the Gjovik *et al.* (1981) equation, this would yield an additional 20 ppb PCP in urine. This level would be added to background or occupational exposure. This estimate is consistent with the levels shown in Table 6; e.g., for a background of 26 ppb + 20 ppb = 46 ppb, compared to a measured value of 69 ppb. It is not likely that combined occupational and non-occupational exposure will occur. PCP-treated log homes are scarce, and they are not located in urban areas where current PCP occupational exposures are centered. To normalize yearly log-home exposure, 14 vacation + 4 other days away from the home are assumed. For lifetime exposure, 10 residence years in the home are assumed. These assumptions should be conservative for California where people spend more time outdoors and move frequently. The estimate in Table 11 is also conservative because the PCP in home levels would decay with time.

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