DRAFT

Public Health Goal for
Pentachlorophenol
in Drinking Water

NOT A REGULATORY STANDARD

Prepared by

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

July 2008

LIST OF CONTRIBUTORS

PHG PROJECT MANAGEMENT	REPORT PREPARATION	SUPPORT
Project Director	***Authors***	***Administrative Support***
Anna Fan, Ph.D.	Charles Vidair, Ph.D.	Hermelinda Jimenez
		Michael Baes
		Janet Rennert
PHG Program Leader	***Primary Reviewer***	
Robert A. Howd, Ph.D.	David Morry, Ph.D.	***Library Support***
		Charleen Kubota, M.L.S.
Comment Coordinator	***Final Reviewers***	***Web site Posting***
Michael Baes	Anna Fan, Ph.D.	Laurie Monserrat
	George Alexeeff, Ph.D.	
	Robert Howd, Ph.D.	

PREFACE

Drinking Water Public Health Goals
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances that may cause chronic disease shall be based solely on health effects and shall be set at levels that OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider potential adverse effects on members of subgroups that comprise a meaningful proportion of the population, including but not limited to infants, children, pregnant women, the elderly, and individuals with a history of serious illness.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. OEHHA shall consider additive effects of exposure to contaminants in media other than drinking water, including food and air, and the resulting body burden.
7. In risk assessments that involve infants and children, OEHHA shall specifically assess exposure patterns, special susceptibility, multiple contaminants with toxic mechanisms in common, and the interactions of such contaminants.

8. In cases of insufficient data for OEHHA to determine a level that creates no significant risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
9. In cases where scientific evidence demonstrates that a safe dose response threshold for a contaminant exists, then the PHG should be set at that threshold.
10. The PHG may be set at zero if necessary to satisfy the requirements listed above in items seven and eight.
11. PHGs adopted by OEHHA shall be reviewed at least once every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Public Health (DPH) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations or technical feasibility, drinking water standards adopted by DPH are to consider economic factors and technical feasibility. Each primary drinking water standard adopted by DPH shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By state and federal law, MCLs established by DPH must be at least as stringent as the federal MCL, if one exists.

PHG documents are used to provide technical assistance to DPH, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not intended to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.

TABLE OF CONTENTS

LIST OF CONTRIBUTORS ..... **II**

PREFACE ..... **III**

TABLE OF CONTENTS ..... **V**

PUBLIC HEALTH GOAL FOR PENTACHLOROPHENOL IN DRINKING WATER **1**

SUMMARY **1**

INTRODUCTION **1**

CHEMICAL PROFILE **2**

ENVIRONMENTAL OCCURRENCE **3**

Air 3

Soil 3

Water 4

METABOLISM AND PHARMACOKINETICS **4**

Absorption 4

Distribution 5

Metabolism and Excretion 5

TOXICOLOGY **5**

Toxicological Effects in Animals 6

Acute Toxicity 6

Subchronic Toxicity 7

Chronic Toxicity 7

Liver 7

Kidneys 12

Respiratory System 13

Central Nervous System 13

Skin 14

Immune System 14

Cardiovascular and Hematologic Systems 15
Reproductive and Developmental Toxicity 15
Genetic Toxicity 17
Carcinogenicity 19
Toxicological Effects in Humans 24
Acute and Short-Term Toxicity 24
Chronic Toxicity 25
Liver 25
Kidneys 26
Heart 26
Hematopoietic System 27
Respiratory System 28
Central Nervous System 28
Immune System 28
Pancreas 29
Skin 29
Reproductive System 30
Developmental Toxicity 31
Genetic Toxicity 31
Carcinogenicity 31
Soft-tissue Sarcoma 32
Malignant Lymphoma 32
Nasal and Nasopharyngeal Cancer 33
Liver and Colon Cancer 33
Summary of Carcinogenic Effects in Humans 34
DOSE-RESPONSE ASSESSMENT 34
Noncarcinogenic Effects 34
Acute Studies 34
Subchronic Studies 34
Chronic Studies 36
Carcinogenic Effects 38
Animal Studies 38

Human Studies 39
CALCULATION OF PHG 39
Noncarcinogenic Effects 39
Carcinogenic Effects 41
Linearized Multi-Stage Model 41
LED_{10} Model 43
RISK CHARACTERIZATION 43
OTHER STANDARDS 45
REFERENCES 46

PUBLIC HEALTH GOAL FOR PENTACHLOROPHENOL IN DRINKING WATER

SUMMARY

A revised Public Health Goal (PHG) of 0.3 parts per billion (ppb) is proposed for pentachlorophenol (PCP) in drinking water, based on carcinogenicity. The current PHG for PCP of 0.4 ppb, developed in 1997, is based on the same rodent carcinogenicity data and a cancer potency value identical to that used in this revised PHG. The 1997 calculation used a lower value for exposure to PCP through consumption of drinking water. The new calculation uses an upper 95th percentile value for consumption of domestic water supplies for the entire population, based on a U.S. Environmental Protection Agency (U.S. EPA, 2004b) assessment of data from the National Health and Nutrition Examination Survey (NHANES).

PCP is a chlorinated aromatic organic chemical with low volatility which has been used as a wide-spectrum biocide; its main application is as a wood preservative, although it is no longer registered for sale in California. Because it was so widely used and is persistent in the environment, it can be detected at many locations in soil or other environmental samples but is not often found in California drinking water.

PCP has both noncarcinogenic and carcinogenic health effects. PCP is a proven carcinogen in rodent studies and there is some epidemiological evidence that PCP is carcinogenic in humans. U.S. EPA has placed PCP in class B2, a probable human carcinogen, based on inadequate data in humans and adequate data in laboratory animals. The International Agency for Research on Cancer (IARC) has placed PCP in group 2B, possibly carcinogenic to humans, based on inadequate evidence in humans and sufficient evidence of carcinogenicity in experimental animals. The human data are inadequate for calculation of a cancer potency factor. Therefore, the calculation of the proposed PHG is based on carcinogenic effects (adenoma and carcinoma) in male mice in a 1989 National Toxicology Program (NTP) bioassay. Using these data, the Office of Environmental Health Hazard Assessment (OEHHA) calculated an upper bound cancer potency using the linearized multistage model of 8.34×10^{-2} (mg/kg-day)$^{-1}$ and a human equivalent oral cancer slope factor (CSF) of 8.11×10^{-2} (mg/kg-day)$^{-1}$. Assuming a drinking water consumption rate of 0.044 L/kg-day and a *de minimis* theoretical excess individual lifetime cancer risk level of one in one million, OEHHA proposes a PHG of 0.0003 mg/L (0.3 ppb) for PCP in drinking water. The U.S. EPA's Maximum Contaminant Level (MCL) and Maximum Contaminant Level Goal (MCLG) for PCP in drinking water are 1 ppb and zero, respectively.

INTRODUCTION

PCP is a broad spectrum pesticide which had past use in a wide variety of applications including as a disinfectant and as a wood preservative. Today it is restricted to use as a

wood preservative in specified outdoor applications such as utility poles. The only registered application method is by heat and pressure treatment. PCP is no longer registered as a pesticide in California. It rarely occurs as a water contaminant in California. The toxicology of PCP has been thoroughly studied, and has been reviewed by U.S. EPA (2004a), by IARC (1991), and by the Agency for Toxic Substances and Disease Registry (ATSDR, 2001). A toxicological review and health risk assessment was prepared for OEHHA, formerly within the California Department of Health Services, now the Department of Public Health (DPH), by the University of California, Davis (Hsieh, 1990), and the toxicological data were again reviewed and evaluated by OEHHA in preparation of the existing PHG (OEHHA, 1997). The current review is carried out under the mandate of the California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365) to conduct regular re-reviews and updates of all regulated chemicals in drinking water.

All of the toxicity studies and evaluations considered together make it clear that PCP is a highly toxic material that can have serious health consequences, both as a carcinogen and in terms of noncarcinogenic health effects. Exposure to PCP may occur by inhalation, ingestion or dermal absorption.

CHEMICAL PROFILE

Pentachlorophenol has the structure shown in Figure 1 below. Pure PCP exists as colorless crystals, with little odor at room temperature. Impure PCP is dark gray to brown in color. There are two common forms of PCP, pentachlorophenol and its sodium salt. The sodium salt dissolves easily in water whereas pentachlorophenol does not. Commercial grade PCP contains polychlorinated phenols, polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans as contaminants. This will be designated throughout this report as tech-PCP.

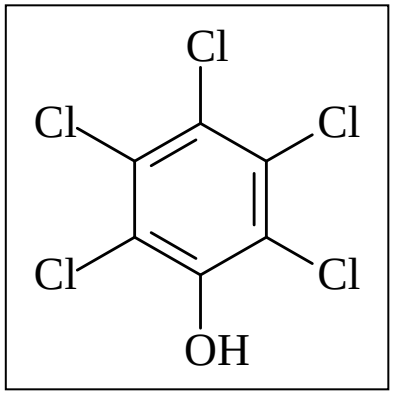

Figure 1. Pentachlorophenol structure

The CAS Registry Number for PCP is 87-86-5. Common synonyms are chlorophen; PCP; penchloropol; penta; pentachlorofenol; pentachlorofenolo; pentachlorophenol;

2,3,4,5,6-pentachlorophenol. Trade names that have been used for this chemical include: Acutox; Chem-Penta; Chem-Tol; Cryptogilol; Dowicide 7; Dowicide EC-7; Dow Pentachlorophenol DP-2 Antimicrobial; Durotox; EP 30; Fungifen; Fungol; Glazed Penta; Grundier Arbezol; Lauxtol; Lauxtol A; Liroprem; Moosuran; Pentacon; Penta-Kil; Pentasol; Penwar; Peratox; Permacide; Permagard; Permasan; Permatox; Priltox; Permite; Santophen; Santophen 20; Sinituho; Term-i-Trol; Thompson's Wood Fix; Weedone; Witophen P.

PCP is manufactured in the U.S. by chlorination of phenol at 100° to 180°C with catalysts such as $AlCl_3$, $FeCl_3$, activated carbon and quinoline. Hydrogen chloride (HCl) and chlorine gases from the primary reactor are further treated with phenol to form pure HCl gas and a mixture of chlorinated phenols. Crude PCP is purified by distillation under reduced pressure in the presence of 0.05 percent to 2 percent (by weight) amine or alkanolamine (Freiter, 1979).

PCP is used as a fungicide and insecticide for wood preservation. U.S. consumption of PCP for 1986 was reported to be 28 million pounds (Chemical Marketing Reporter, 1987) before federal use restrictions in 1987. U.S. production was estimated at 2 million pounds in 2002 (U.S. EPA, 2007a). Although no longer registered as a pesticide in California, in those states where it is registered it is permitted only for outdoor use as a wood preservative for specified applications such as utility poles. It must be applied by heat and pressure treatment in a lumber processing plant (U.S. EPA, 2007a).

ENVIRONMENTAL OCCURRENCE

PCP may be found in air, soil or water. Each of these media may be a source of human exposure to PCP.

Air

Little information is available on the fate of PCP in the atmosphere. In urban areas, PCP has been found in air at concentrations of 5.7 to 7.8 ng/m^3 (IARC, 1979). Recent measurements in France ranged from 0.11 to 1.29 ng/m^3 for urban, suburban and rural areas (Morville *et al.*, 2006). PCP is released directly into the atmosphere via volatilization from treated wood products, at an estimated rate of 760,000 pounds per year (Scow *et al.*, 1980). Thus, it is not surprising that in a recent study of the air surrounding a wood treatment facility in Georgia, concentrations of 2-4 $\mu g/m^3$ were detected at distances of one mile and greater downwind of the plant (ATSDR, 2004). These values exceeded the U.S. EPA risk-based value of 0.052 $\mu g/m^3$, associated with a cancer risk of 10^{-6} for a 70 year exposure.

Soil

Adsorption of PCP in soils is dependent on organic content of the soil, and on pH, being strongest in acidic soils and decreasing in neutral and basic soils. PCP in shallow surface waters can be degraded by light. PCP in soil is degraded by microorganisms. Anaerobic

conditions are generally unfavorable for biodegradation (Boyle *et al.*, 1980; Wong and Crosby, 1981). PCP has been detected in soil at the following concentrations in the following locations: 0.320-200 ppm at a Louisiana wood treatment plant, 3.4-654 ppm within 12 inches of utility poles, and up to 21 ppm at an inactive Florida landfill (ATSDR, 2001).

Water

PCP enters water as an effluent from manufacturing plants, by leaching from treated wood and by runoff after application as a herbicide, molluscicide or fungicide. Photolysis and biodegradation are believed to be the important transformation processes for PCP in aquatic systems. The rate of photolysis of PCP in aqueous solution is rapid, with total degradation within five to seven days. Photolysis in the environment would only occur close to the surface. Genetically adapted microorganisms transformed PCP in water much more rapidly under aerobic conditions than under anaerobic conditions (Liu *et al.*, 1981).

PCP was measured in water samples from five sites along the California aqueduct between 1974 and 1976 (Cirelli, 1978). Values ranging from 0.01 to 16 mg/L were reported for these water samples. PCP was not found in the 1986 survey of water contaminants in large water systems in California mandated by AB 1803. U.S. EPA's recent Reregistration Eligibility Decision (RED) for PCP used an exposure model to estimate the surface water concentrations of PCP (U.S. EPA, 2004a). The values relevant to risk assessment were 0.176 ppb for acute exposures and 0.014 ppb for chronic exposures.

METABOLISM AND PHARMACOKINETICS

Pharmacokinetics includes absorption, distribution, metabolism and excretion. An understanding of the pharmacokinetics of PCP is needed to extrapolate from animal exposures in experiments to human environmental exposures. The effective dose of a chemical is its concentration in the target tissues. These target tissue concentrations can only be predicted by modeling the pharmacokinetics of the compound based on available pharmacokinetic data from animal and human studies.

Absorption

PCP is readily absorbed following the inhalation, dermal and ingestion routes of exposure in animals and in humans. Human male volunteers who received oral doses of 0.1 mg/kg sodium pentachlorophenol reached the maximum plasma concentration (0.24 mg/mL) within four hours. The plasma half-life of PCP was calculated as 1.3 ± 0.4 hours (Braun *et al.*, 1979). Following oral administration, the time course of appearance in the plasma, as well as the final percentage absorbed, were similar in rats and humans (CDPR, 1998). Dermal absorption was 24 percent in rhesus monkeys and 40 percent in rats (U.S. EPA, 2004a).

Distribution

PCP is distributed to all tissues of the body. The levels in liver and kidney are particularly high, whereas those in fat, brain and muscle are relatively low (Larsen *et al.,* 1972; Braun *et al.,* 1977). The volume of distribution of PCP was 116 to 268 mL/kg in rats and 348 mL/kg in humans (U.S. EPA, 2004a).

Metabolism and Excretion

In rats, metabolism of PCP involves conjugation, reductive dechlorination, hydrolytic dechlorination and oxidation (Renner and Hopfer, 1990). Rat metabolism occurs via oxidation to tetrachlorohydroquinone (TCHQ) and to a lesser extent to trichlorohydroquinone, as well as by glucuronidation (Jacobson and Yllner, 1971; Ahlborg and Thunberg, 1980). In male volunteers, PCP given orally was eliminated as both the parent compound and the glucuronide. No other metabolites were observed in these experiments (Braun and Sauerhoff, 1976; Braun *et al.,* 1979; Uhl *et al.,* 1986). About 86 percent of the total dose was excreted in the urine, and 4 percent in the feces in the eight days following PCP administration (Braun *et al.,* 1979). The remaining 10 percent is either excreted later or remains in the organism. TCHQ is genotoxic in rodents (Dahlhaus *et al.,* 1994). While TCHQ has not been identified as an *in vivo* metabolite of PCP in humans, it was detected in a cell-free system containing human cytochrome P450 (Mehmood *et al.,* 1996).

The half-lives for urinary elimination of PCP and PCP glucuronide were approximately 33 hours and 13 hours, respectively. The slow urinary excretion rate was attributed to enterohepatic recirculation (Braun *et al.,* 1979).

The metabolism of PCP may be affected by diet and by the amount of body fat. The amount of body fat would influence the amount of PCP and fat-soluble metabolites in the liver where they are subjected to the action of liver enzymes (Umezaki *et al.,* 1993). The pharmacokinetics of the impurities in PCP are more complex. Some of them may affect the metabolism of PCP by stimulating mixed function oxidases (Goldstein *et al.,* 1977).

TOXICOLOGY

Toxicological data from human exposure is not adequate for a full assessment of the potential health effects of PCP on humans. Therefore, data from animals and other model systems must be used to estimate the potential health effects to humans. Many of the toxic effects of PCP are due to its effect as an uncoupler of oxidative phosphorylation. PCP acts as a protonophore and allows passage of protons across energy-generating membranes without coupling to the energy-generating system (Barstad *et al.,* 1993).

Toxicological Effects in Animals

Acute Toxicity

The acute oral LD_{50} is 130 mg/kg for mice and 184 mg/kg for rats (Demidenko, 1969). The dermal LD_{50} for rats is 96 mg/kg. The inhalation LD_{50} is 335 mg/m^3 for rats and 225 mg/m^3 for mice.

Deichmann *et al.* (1942) examined the effects of acute exposure to sodium salts of PCP in rats, guinea pigs, rabbits and dogs. The effects observed included elevated blood pressure, hyperglycemia, hyperperistalsis, glycosuria and motor weakness leading to asphyxial convulsive movements and immediate, profound rigor mortis. Borzelleca *et al.* (1984) exposed CD-1 ICR mice to single oral doses of PCP, resulting in central nervous system (CNS) depression, increased respiration, motor weakness, tremors and convulsions.

Table 1 below shows the acute toxicity, eye and dermal irritation, and dermal sensitization studies submitted for reregistration of PCP (U.S. EPA, 2004a). The inhalation study was waived and a category I assigned due to the difficulty in generating respirable atmospheres of PCP, and the requirement for workers to wear respirators. The U.S. EPA Reregistration Eligibility Document (RED) for PCP (U.S. EPA, 2004a) noted that these acute studies were performed with test material that was contaminated with other compounds such as hexachlorodioxin and hexachlorobenzene.

Table 1. Acute Toxicity, Eye Irritation, Dermal Irritation, and Dermal Sensitization Studies for Pentachlorophenol (U.S. EPA, 2004a)

Guideline No.	Study Type	Results	Toxicity Category
§81-1 (OPPTS 870.1100)	Acute Oral Toxicity	LD50=155 mg/kg (M); LD50=137 mg/kg (F)	II
§81.2 (OPPTS 870.1200)	Acute Dermal Toxicity	LD50>3980 mg/kg	IV
§81-3	Acute Inhalation Toxicity	Waiver granted	I
§81-4 (OPPTS 870.2400)	Primary Eye Irritation	Corneal involvement at day 7 post-instillation	II
§81-5 (OPPTS 870.2500)	Primary Dermal Irritation	Moderate irritation at 72 h post-application	III
§81-6 (OPPTS 870.2600)	Dermal Sensitization	No sensitization using Buehler method	Not applicable

Subchronic Toxicity

A number of investigators (Knudsen *et al.,* 1974; Goldstein *et al.,* 1977; Kimbrough and Linder, 1978; Schwetz *et al.,* 1978; NTP, 1989) consistently observed decreased body weight in rats and mice exposed subchronically or chronically to oral doses of technical grade PCP (tech-PCP) or purified PCP. Schwetz *et al.* (1978) exposed Sprague-Dawley rats to 1.0, 3.0, 10 or 30 mg/kg of tech-PCP in their feed continuously for 22 to 24 months and observed decreased weight gain only at the highest dose. Holstein cattle were exposed to PCP at doses of 0.2 to 2.0 mg/kg in their feed for 43 days (Hughes *et al.,* 1985). The cattle exhibited hyperthermia, diarrhea, rapid respiration and anorexia, along with decreased weight gain. Hyperthermia appears to be a consequence of the decoupling of oxidative phosphorylation. Decreased weight gain would be expected in animals that experienced these toxic effects.

Surveying the subchronic studies, decreased maternal bodyweight gain was observed in the recent rat and rabbit developmental toxicity studies (Bernard and Hoberman, 2001; Bernard *et al.,* 2001). Increased liver weight, increased liver enzymes, and histopathological changes to the liver in the subchronic rat and mouse studies suggest that liver was the target organ. Lastly, subchronic exposure of the rat via the dermal route yielded a markedly higher lowest observed effect level (LOEL) of 500 mg/kg-day, compared to comparable oral exposures (U.S. EPA, 2004a).

Chronic Toxicity

Prolonged exposure of laboratory animals to PCP appears to affect primarily the liver, kidneys, central nervous system and skin. These effects are summarized in Table 2.

Liver

Acute and chronic exposure of mice and rats to PCP has caused adverse liver effects (NTP, 1989; Nishimura *et al.,* 1982; Fleischer *et al.,* 1980; Kimbrough and Linder, 1978; Goldstein *et al.,* 1977; Knudsen *et al.,* 1974; Johnson *et al.,* 1973). Wistar rats exhibited increased liver weights after a single oral administration of 30, 60, 120 or 150 mg/kg PCP (Nishimura *et al.,* 1982). This effect was not observed at 10 mg/kg. Female Sherman rats orally exposed to 1, 6 or 30 mg/kg tech-PCP for eight months exhibited increased liver to body weight ratios (Kimbrough and Linder, 1978). When exposed to purified PCP for the same duration, a dose of 30 mg/kg was required to produce this effect (Goldstein *et al.,* 1977), indicating that the impurities in PCP probably contribute significantly to this observed liver toxicity.

Table 2. Noncarcinogenic No-Observed-Adverse-Effect-Levels (NOAELs) and Lowest-Observed-Adverse-Effect-Levels (LOAELs) for PCP in Animals

Species and strain	Route	Sex	N*	Dose Regimen	NOAEL	LOAEL	Endpoint	Reference
***Acute Studies*:**								
Rat, Wistar	gavage	male	4-18 (6)	single dose	10 mg/kg		increased hepatic glycogen	Nishimura *et al.* (1982)
Subchronic Studies:								
Rat, Sprague-Dawley	feed	NR	NR	90 day	3 mg/kg-day		Hepatocellular degeneration and necrosis	Johnson *et al.* (1973)
Rat, Sprague-Dawley	gavage	female	20 to 40	days 6-15 of gestation		5 mg/kg-day	fetal resorptions	Schwetz *et al.* (1974)
Rat, F344/N	feed	male, female	10 (6)	28 days	None	20 mg/kg-day	Increased absolute and relative liver weights	Chhabra *et al.* (1999)
Rat, Crl:CD BR VAF/plus	gavage	female	25 (4)	Days 6-15 of gestation	Maternal 30 mg/kg-day; Develop-mental 30 mg/kg-day	Maternal: 80 mg/kg-day; develop-mental: 80 mg/kg-day	Maternal: reduced body-weight gain Developmental: increased resorptions, skeletal malformations and variations, reduced fetal weight	Bernard and Hoberman (2001)
Rabbit, New Zealand White	gavage	female	20 (4)	Days 6-18 of gestation	Maternal 15 mg/kg-day; Develop-mental 30 mg/kg-day	Maternal: 30 mg/kg-day; Develop-mental: none	Maternal: reduced body-weight gain and food consumption; Developmental: none	Bernard *et al.* (2001)
Rat, Wistar	intra-peritoneal	male	NR	daily for 15 days		30 mg/kg-day	altered hepatic ultrastructure	Fleischer *et al.* (1980)
Rat, Wistar	feed	male, female	10 (4)	12 weeks	(m) 1.21 mg/kg-day, (f) 1.64 mg/kg-day		anemia, centrilobular vacuolization in liver	Knudsen *et al.* (1974)
Mice, C5751/6J	feed	male	NR	10-12 weeks		5 mg/kg-day	tumor growth susceptibility	Kerkvliet *et al.* (1982)

Species and strain	Route	Sex	N*	Dose Regimen	NOAEL	LOAEL	Endpoint	Reference
Rat, Wistar	gavage	female	8 (7)	28 days	None	3 mg/kg-day	Reduced serum and intrathyroidal levels of T_4 and T_3; reduced serum TSH	Jekat *et al.*, 1994
Mouse, $B6C3F_1$	feed	male, female	5-19 (6)	30 days	2.8-4.3 mg/kg-day	24-102 mg/kg-day	Liver lesions and histopathology, increased serum liver enzymes	Review of NTP (1989) mouse study as presented in CDPR (1998)
Mouse, $B6C3F_1$	feed	male, female	10 (4)	6 months	None	43-54 mg/kg-day	Liver lesions and histopathology, urinary bladder changes, immune suppression	Review of NTP (1989) mouse study as presented in CDPR (1998)
Pigs	oral capsule	NR	6 (4)	daily for 30 days	5 mg/kg-day		leucopenia	Greichus *et al.* (1979)
Rat, Sprague-Dawley	dermal occlusion	male, female	10 (4)	6 hr/day and 5 day/week for 90 days	100 mg/kg-day	500 mg/kg-day	Enzyme induction, mild hepatocellular degeneration and chronic inflammation	U.S. EPA (2004a)
Chronic Studies:								
Rat, Sherman	feed	female	6 (4)	daily for 8 months	6 mg/kg-day		increased hepatic enzymes and porphyrin	Goldstein *et al.* (1977)
Rat, Sprague-Dawley	feed	male, female	10M, 20F (3) (repro-ductive study)	From 62 days before mating to day 21 post weaning	3 mg/kg-day		embryolethality	Schwetz *et al.* (1978)
Rat, Sprague-Dawley	feed	male, female	25 (5) (chronic toxicity study)	22 months (males), 24 months (females)	10 mg/kg-day (males), 3 mg/kg-day (females)		Increased liver enzyme activity, increased liver and kidney pigmentation	Schwetz *et al.* (1978)

Species and strain	Route	Sex	N*	Dose Regimen	NOAEL	LOAEL	Endpoint	Reference
Rat, Sprague-Dawley	gavage	male, female	30 (4)	70 days before mating, during gestation and lactation (F1 and F2)	Reproductive 10 mg/kg-day; Systemic none	Reproductive: 30 mg/kg-day; Systemic: 10 mg/kg-day	Reproductive: decreased litter weights and body weights in F1 pups Systemic: hepatocellular hypertrophy and vacuolation in all adults and F2 weanlings, increased kidney weight in males, epididymal mononuclear cell infiltration in F1 males	Bernard *et al.* (2002)
Rat, F344/N	feed	male, female	50 (5)	52 or 105 weeks	10 mg/kg-day	20 mg/kg-day	Decreased body-weight, hepatocyte cystic degeneration	NTP (1999)
Mouse, $B6C3F_1$	feed	male, female	35-50 (2 or 3)	2 years	None	17 mg/kg-day	Liver lesions, spleenic extra-medullary hematopoiesis	NTP (1989)
Dog, beagles	capsule	male, female	4 (4)	52 weeks	None	1.5 mg/kg-day	Histopathology: pigment accumulation, cytoplasmic vacuolation, centrilobular hypertrophy of hepatocytes	U.S. EPA (2004a)
Sheep	feed	female	6 or 13 (2)	Conception to 67 weeks old	None	1.0 mg/kg-day	Reduced serum T_4; reduced T_4 and T_3 response to TSH	Beard and Rawlings (1999)
Mink	feed	male, female	6-10 (2)	3 weeks before mating through lactation (F_2 and F_3)	None	1.0 mg/kg-day	Reduced serum thyroxine (T_4) in both male generations and in F_3 females	Beard and Rawlings (1998)

***** Number of animals per sex per group. The number of dose groups including control is given in parentheses.
NR = not reported.

B6C3F$_1$ mice administered 1,250 mg/kg tech-PCP, Dowicide EC-7 (91 percent purity) or purified PCP in the feed for 30 days showed increased liver weight and increased liver to body weight ratio (NTP, 1989). These two grades of PCP contain polychlorinated phenols, polychlorinated dibenzo-p-dioxins, and polychlorinated dibenzofurans as contaminants. However, in a six month experiment in which male and female mice were administered tech-PCP and purified PCP, increased absolute and relative liver weights were observed in both male and female mice at lower doses with tech-PCP and at higher doses with purified PCP. Details are provided in Table 3.

Table 3. PCP Doses that Altered Absolute and Relative Liver Weights in Male and Female B6C3F$_1$ Mice (NTP, 1989).

Test Animal	Grade of PCP	Effective Doses (mg/kg)
Male mice	tech-PCP	28.5, 85.4, 256.3
Female mice	tech-PCP	36.4, 109.1, 327.3
Male mice	purified PCP	85.4, 213.6
Female mice	purified PCP	109.1, 272.7

Histological changes including centrilobular cytomegaly, vacuolization of the cytoplasm, focal hepatocellular degeneration and necrosis and accumulation of yellow to brown pigment in macrophages and Kupffer cells were observed in the livers of rats and mice exposed chronically or subchronically to tech-PCP or purified PCP (Johnson *et al.*, 1973; Knudsen *et al.*, 1974; Kimbrough and Linder, 1978; Fleischer *et al.*, 1980; NTP, 1989). Hepatocellular degeneration and necrosis were seen in Sprague-Dawley rats exposed for 90 days to 30 mg/kg tech-PCP in their feed; however, when the exposure was to purified PCP for the same period, no histopathological changes were reported (Johnson *et al.*, 1973). Enlarged liver was also observed in Holstein cows given 0.2 mg/kg PCP in their feed for 84 days and 2 mg/kg for the following 60 days (Kinzell *et al.*, 1981).

Male Wistar rats administered 2.43 to 9.36 mg/kg PCP and female rats administered 3.14 or 13.12 mg/kg PCP for 12 weeks in their feed exhibited hepatic centrilobular vacuolization (Knudsen *et al.*, 1974). Hepatic centrilobular cytomegaly and cytoplasmic eosinophilic inclusions of Wistar rats fed 1 to 30 mg/kg tech-PCP were more pronounced than in Wistar rats fed 30 mg/kg purified PCP (Kimbrough and Linder, 1978). In an NTP study, B6C3F$_1$ mice were fed 23.0 to 327.3 mg/kg tech-PCP, Dowicide EC-7, DP-2 or purified PCP for 30 days in their feed for two years, resulting in karyomegaly, nuclear atypia and bile duct hyperplasia with periportal fibrosis (NTP, 1989). The lesions were more diffuse and more severe in mice exposed to tech-PCP than in mice exposed to other grades of PCP.

Chickens exposed to 10 to 100 mg/kg PCP in feed for eight weeks, beginning at six weeks of age, showed proliferative changes in bile duct and fatty degeneration of the liver (Stedman *et al.,* 1980).

Investigators observed ultrastructural changes in livers of rats fed PCP, including proliferation of smooth endoplasmic reticulum (SER), the presence of lipid vacuoles and small pleomorphic mitochondria (Fleischer *et al.,* 1980; Kimbrough and Linder, 1978). Fleischer *et al.* (1980) observed enlarged sinusoids, multinucleated hepatocytes and increased heterochromatin to euchromatin ratio in rats exposed to 30 mg/kg PCP for 15 days.

Rats administered 1 to 1,250 mg of PCP in their diet developed histochemical changes and elevated total liver porphyrin and cytochrome P_{450}, serum glutamic pyruvic transaminase (SGPT), glutamic pyruvic transaminase (GPT), serum glutamic oxaloacetic transaminase (SGOT), aryl hydrocarbon hydroxylase (AHH) and glucuronyl transferase (NTP, 1989; Kimbrough and Linder, 1978; Goldstein *et al.,* 1977). Wistar rats given single doses of 120 or 150 mg/kg of PCP had increased hepatic glycogen and lactate (Nishimura *et al.,* 1982). Rats administered 1, 6 or 30 mg/kg tech-PCP or purified PCP in their feed for eight months had increased cytochrome P_{450}, glucuronyl transferase and AHH (Goldstein *et al.,* 1977). The effects were much greater when tech-PCP was used as compared to purified PCP.

Mice administered 4.8 to 1,250 mg/kg tech-PCP or purified PCP had increased mean cholesterol, serum alkaline phosphatase (SAP) and SGPT (NTP, 1989). The greatest changes in SGPT were seen in the higher dose groups of tech-PCP. Rats administered 45 to 90 mg/kg tech-PCP in their feed for six months exhibited increased porphyrin excretion in their urine (Wainstok de Calmanovici and San Martin de Viale, 1980). When purified PCP was used there was no increase in porphyrin excretion. The authors interpreted this difference as evidence that the impurities in tech-PCP were mainly responsible for the toxic effects.

The two most recent chronic studies in the rat (NTP, 1999; Bernard *et al.,* 2002) identified histopathological changes to the liver at the lowest observed adverse effect level (LOAEL) (10-20 mg/kg-day), including hepatocyte hypertrophy, vacuolation, and cystic degeneration. In the mouse, the liver, as well as the spleen, exhibited adverse changes at the study (LOAEL) (17 mg/kg-day; NTP, 1989). Dogs were more sensitive (U.S. EPA, 2004a), with a study LOAEL of 1.5 mg/kg-day based on hepatocyte alterations including pigment accumulation, cytoplasmic vacuolation and centrilobular hypertrophy.

Kidneys

The predominant gross change associated with acute or chronic exposure of laboratory animals to PCP is increased kidney weight (Hughes *et al.,* 1985; Kinzell *et al.,* 1981; Stedman *et al.,* 1980; Kimbrough and Linder, 1978; Johnson *et al.,* 1973; Blevins, 1965; Bernard *et al.,* 2002). Swine exposed to lumber treated with 5 percent tech-PCP exhibited hemorrhages, subcapsular fluid and a spongy texture of the kidney (Blevins, 1965; Schipper, 1961).

Mice administered one dose of 148 to 1,250 mg/kg PCP in their diet had darkening of the urine (NTP, 1989). Rats exhibited accumulation of pigment in the kidneys and increased specific gravity of the urine after receiving 10 to 30 mg/kg PCP in their diet for two years (Schwetz *et al.*, 1978).

Rabbits that were administered 1.3, 7.5, 27.5 or 70 mg/kg PCP subcutaneously, or 15 mg/kg intraperitoneally, exhibited hemorrhage, congestion, lymphocytic infiltration of the cortex and albuminous or fatty degeneration of the kidneys (McGavach *et al.*, 1941). A cow which accidentally ingested 5 percent PCP in kerosene had extensive necrosis of the convoluted tubules (Spencer, 1957).

Holstein bulls administered 1 to 10 mg/kg PCP in their diet for 43 days had functional impairment of the kidneys (Hughes *et al.*, 1985). Cattle administered 0.2 mg/kg PCP in their feed for 75 to 84 days then 2 mg/kg for 50 to 60 days exhibited interstitial nephritis and thickened Bowman's capsule (Kinzell *et al.*, 1981).

Chickens administered 100 to 1,000 mg/kg of PCP in their feed exhibited increased kidney weight (increasing from a mean of 12.4 for the controls, up to 15.9 and 18.3 grams for the two top doses), however there was no effect when they received 1 to 10 mg/kg (Stedman, *et al.*, 1980). The kidney was the organ with the highest accumulation of PCP in these chickens.

Respiratory System

Sprague-Dawley rats exposed to a single dose of 31 or 449 mg/kg of tech-PCP evinced rapid respiration after 25 minutes (St. Omer and Gadusek, 1987). Similar effects have been reported in rabbits, mice and pigs (McGavack *et al.*, 1941). Piglets in contact with wooden crates that had been treated with PCP developed necrosis of the external nares (Schipper, 1961).

Cattle had increased lung weight resulting from exposure to 15 to 20 mg/kg PCP in feed for 160 days (McConnell *et al.*, 1980). Mice administered 28.5 to 327.3 mg/kg PCP for six months were observed to have histopathological lesions, including metaplasia of the nasal mucosa (NTP, 1989). Rabbits administered daily subcutaneous or intraperitoneal injections of PCP suffered partial collapse of their lungs (McGavack *et al.*, 1941). Pigs exposed to 5 percent PCP on wood pens for 1 to 12 days developed congestion and emphysema (Blevins, 1965; Schipper, 1961). A cow that accidentally ingested 5 percent PCP in kerosene developed signs of internal tissue bleeding in the tracheal mucosa and ulcerations of the mucosa of the pharynx and larynx (Spencer, 1957).

Central Nervous System

Mice injected intraperitoneally with one dose of 65 to 252 mg/kg purified PCP exhibited depression of the central nervous system (CNS) (Borzelleca *et al.*, 1984). Rabbits acutely exposed by subcutaneous or intraperitoneal injections of 50 to 700 mg/kg of PCP exhibited no gross changes in the brain or spinal cord. Likewise, dogs injected subcutaneously with 125 to 175 mg/kg of PCP exhibited no changes in CNS function (McGavack *et al.*, 1941).

Exposure of rabbits to 13.7, 27.5 or 70 mg/kg of PCP by subcutaneous injection or to 15 mg/kg of PCP by intraperitoneal injection daily for 60 days resulted in listlessness, frequent defecation and slight motor weakness. Convulsive seizures resulting in death as well as histopathological changes were observed in rabbits exposed to 450 mg/kg (McGavack *et al.,* 1941).

Skin

Rabbits exposed to one cutaneous application of 60 to 600 mg/kg PCP exhibited edema, inflammation and desquamation as well as tanning of the skin (McGavack *et al.,* 1941). Rabbits administered 60 to 600 mg/kg of PCP for four to seven days exhibited hyperkeratinization of the epidermis and hypertrophy of the hair follicles (McGavack *et al.,* 1941).

Deichmann *et al.* (1942) reported no wrinkling of the skin or hair loss in rabbits administered 40 mg/kg dermally each day for 100 days. Cattle administered 20 mg/kg tech-PCP in their feed for 160 days exhibited dilation and mild to moderate hyperkeratosis of the ductal lining of the meibomian glands in the eyelids (McConnell *et al.,* 1980).

Immune System

Splenic antibody production and serum antibody titers were suppressed in mice administered 5 to 50 mg/kg of tech-PCP in feed for 10 to 12 weeks. No response was seen with purified PCP. However, mice exposed to purified PCP exhibited enhanced development of splenic tumors resulting from challenge with Moloney sarcoma virus-induced tumor cells (Kerkvliet *et al.,* 1982).

Rats administered 100 mg/kg tech-PCP in their feed for 14 days exhibited suppressed complement activity. Mice administered the same dose exhibited suppressed IgM antibody response to sheep red blood cells. Mice exposed to purified PCP exhibited neither of these responses (Holsapple *et al.,* 1987).

Mice administered tech-PCP by gavage for 30 days or six months exhibited increased thymus and spleen weight (NTP, 1989). Decreased lymphocyte populations were observed in mice administered tech-PCP in the diet for 30 days. Tech-PCP but not purified PCP caused decreases in plaque-forming cell response in mice (NTP, 1989).

More recently, adult male rats were treated by gavage with PCP at 2.0 mg/kg-day, twice weekly, for four weeks (Blakley *et al.,* 1998). The chemical stimulated rather than inhibited T- and B-cell blastogenesis. Work carried out with cultured cells suggests that PCP also can inhibit some aspects of immune system function. Cultured human natural killer (NK) cells treated with PCP exhibited decreased tumor cell lysis (Taylor *et al.,* 2005). Such an effect *in vivo* could negatively impact immune surveillance of potential tumor cells. A mouse macrophage cell line treated with PCP exhibited decreased activation of the transcription factor NF-κB in response to bacterial components (Igarashi *et al*., 2006). Whether these effects observed in cultured cells also occur *in vivo* is not known.

Cardiovascular and Hematologic Systems

Rabbits administered 50 to 700 mg/kg PCP subcutaneously, intraperitoneally or orally evinced a marked drop in blood pressure followed by a sharp rise and then another drop (McGavack *et al.,* 1941). Dogs exhibited cardiac arrest when administered 125 to 175 mg/kg PCP (McGavack *et al.,* 1941).

Tech-PCP but not purified PCP caused reduced red blood cell count and hemoglobin as well as reduced cell volume in Sprague-Dawley rats administered 30 mg/kg-day in the diet for 90 days (Johnson *et al.,* 1973). Anemia in rats was also observed by Knudsen *et al*. (1974). Rabbits exhibited leukopenia, with relative lymphocytosis and decreased hemoglobin when injected subcutaneously with 27.5 mg/kg of PCP per day for 60 days (McGavack *et al.,* 1941). Likewise, pigs experienced transient leukopenia when administered 5, 10 or 15 mg/kg PCP in the diet for 30 days (Hillam and Greichus, 1983).

Male mice exposed to doses ranging from 4.8 to 1,250 mg/kg PCP and female mice exposed to doses ranging from 6.3 to 1,250 mg/kg PCP in their feed for 30 days exhibited lymphopenia, leukopenia, monocytosis and thrombocytosis (NTP, 1989).

Rabbits administered 13.7 to 70 mg/kg PCP for 160 days exhibited dilation of the right side of the heart and usually contraction of the left side (McGavack *et al.,* 1941). Sprague-Dawley rats administered 3, 10 or 30 mg/kg-day of tech-PCP in the diet for 90 days exhibited increased serum alkaline phosphatase (SAP), as did mice receiving PCP for 30 days. The mice also showed increased cholesterol levels (NTP, 1989). In a study by Johnson *et al.* (1973), rats administered tech-PCP for 30 days exhibited decreased serum albumin.

Reproductive and Developmental Toxicity

Both purified PCP and tech-PCP have been studied in rodents and swine by a number of investigators. Decreased fetal body weight on days 9 and 10 of gestation as well as malformations such as dwarfism, exencephaly, macrophthalmia and absence of tail were observed in Charles River rats administered one dose of 60 mg/kg of purified PCP on day 8, 9, 10, 11 or 12 of gestation (Larsen *et al.,* 1975). Larsen *et al*. (1975) studied the teratogenic effects and placental transfer of PCP in CD rats, by administered single oral doses of 60 mg/kg on days 8, 9, 10, 11, 12 or 13 of gestation. This dose was chosen as 75 percent of the LD_{50}. The PCP was administered to the rats by gavage in olive oil. Fetuses were removed and examined on day 20 of gestation. Fetuses were examined for viability, cutaneous reflex, weight and gross external malformations and half were checked for skeletal abnormalities.

Fetal weights were lower than the controls when the PCP was administered on day 9 or 10. One dwarf was found among the fetuses from day eight administration. The day nine treatment produced three malformations in three different rat fetuses. These malformations were exencephaly, macrophthalmia and absence of tail. There were also a number of resorption sites. No malformations were found in the control groups.

^{14}C-labeled PCP was used to study placental transfer. Less than 0.2 percent of the labeled PCP entered the fetus. The investigators concluded that transfer of PCP across

the placenta was "negligible." This leads to the possibility that malformations observed in the fetuses are an indirect effect, or are caused by extremely low concentrations of PCP in fetal tissue.

Schwetz *et al.* investigated both purified PCP and tech-PCP in Sprague-Dawley rats. The only effects reported due to purified PCP exposure were decreased fetal weight and decreased crown-to-rump length, resulting from a dose of 30 mg/kg purified PCP. A wider variety of toxic effects was reported for tech-PCP, including significant decrease in maternal body weight, increased fetal resorptions, altered sex ratios and decreased fetal body weight (Schwetz *et al.*, 1974).

Increased conception rate, increased number of stillbirths and decreased body weight were observed in Sprague-Dawley rats exposed continuously for 10 weeks to 0.5, 5 and 50 mg/kg (Exon and Koller, 1982). Male and female Sprague-Dawley rats administered 60, 200 or 600 ppm purified PCP in their feed (4, 13 or 43 mg/kg) for 181 days prior to mating and during gestation showed a dose-related decrease in fetal body weight, embryolethality (43 mg/kg), increased fetal resorptions, decreased crown-to-rump length and increased fetal skeletal variations (13 mg/kg) (Welsh *et al.*, 1987).

Golden Syrian hamsters exhibited fetal death and resorption when exposed orally to 1.25 to 20 mg/kg of PCP during days 5 to 10 of gestation (Hinkle, 1973). An increased number of stillbirths and postpartum deaths occurred to swine exposed to PCP-treated pens for an unspecified number of days prior to giving birth (Schipper, 1961). Reduction in fetal body weight (at 75 mg/kg) and decreased maternal body weight gain (at 40 mg/kg) as well as increased fetal resorption (at 40 mg/kg) were observed in rats exposed to tech-PCP or purified PCP by intraperitoneal injection (Courtney *et al.*, 1976; Chou and Cook, 1979).

A more recent developmental toxicity study was performed in the rat by Bernard and Hoberman (2001). A no observed adverse effect level (NOAEL) of 30 mg/kg-day was determined for both maternal (reduced bodyweight gain) and developmental (increased resorptions, skeletal anomalies, reduced fetal weight) effects. The most recent developmental toxicity study in the rabbit (Bernard *et al.*, 2001) identified a maternal NOAEL at 15 mg/kg-day based on reduced bodyweight gain, with no developmental effects at the highest dose tested (30 mg/kg-day). The most recent reproductive toxicity study was performed in the rat by Bernard *et al.* (2002). There was no NOAEL for systemic, parental toxicity, with effects to the liver, kidneys and epididymis at the lowest dose tested (10 mg/kg-day). The NOAEL for effects to offspring was 10 mg/kg-day, based on decreased litter and pup weights at 30 mg/kg-day. The three studies described in this paragraph were considered acceptable by both U.S. EPA and the California Department of Pesticide Regulation for registration purposes. Thus, in contrast to some of the earlier studies described above, none of these three more recent studies showed any increased fetal or offspring sensitivity to PCP compared to maternal/parental sensitivity.

Testing for possible endocrine effects of PCP, Beard and Rawlings (1999) fed breeding ewes a diet containing 1.0 mg/kg-day of PCP for five weeks prior to mating, through pregnancy and through lactation. All reproductive parameters were unaffected including ovulation rate, follicle and corpus luteum size, gestation length, pregnancy rate, lambing rate and lamb birth weight. The only effect of PCP was a significant reduction in the

concentration of the thyroid hormone thyroxine (T_4) in the blood. The authors speculated that such a reduction could have long-term consequences for reproduction.

The same researchers also performed a multigenerational study with PCP in mink (Beard and Rawlings, 1998). A single dose level of 1.0 mg/kg-day was used in addition to control. Animals were dosed via feed from three weeks prior to mating, during gestation and lactation (F_2), repeating the above schedule for the F_3 generation. Exposed males of both the F_2 and F_3 generations and exposed females of the F_3 generation exhibited significant decreases (approximately 17-19 percent, $p<0.05$) in serum thyroxine (T_4). Guinea pigs have also been tested for reproductive/estrogenic effects in response to PCP (Danzo *et al.*, 2002). Adult females were treated for 14 days via subcutaneous injection at 40 mg/kg-day. No estrogenic effects were observed in the reproductive tracts of castrated females, and no obvious anti-estrogenic effects were observed in normal females.

When cultured human breast cancer cells (MCF-7) carrying a 17β-estradiol reporter gene were treated with PCP, transcription was inhibited, possibly due to competitive inhibition of estradiol binding to the estrogen receptor by PCP (Jung *et al.*, 2004). Similarly, PCP inhibited estradiol binding to estrogen receptor α in HeLa cell lines containing estrogen-sensitive reporter genes (Lemaire *et al.*, 2006). Anti-estrogenic activity of PCP was also detected in cultures of juvenile goldfish hepatocytes (Zhao *et al.*, 2006). In apparent contrast to the above results indicating anti-estrogenic activity of PCP, MCF-7 human breast cancer cells were used to screen for estrogen-responsive genes measured by DNA microarray analysis (Terasaka *et al.*, 2006); in this assay PCP stimulated estrogenic-sensitive gene expression suggesting it was estrogenic.

The possible androgenic activity of PCP was recently tested in cultured monkey cells (CV-1) containing an androgen receptor-mediated reporter gene (Sun *et al.*, 2006). Neither agonist nor antagonist activity was detected. Whether the estrogenic effects of PCP in cultured cells described above also occur when exposure is *in vivo* is unknown.

In summary, based on earlier studies, both tech-PCP and purified PCP appear to be embryotoxic and teratogenic in rodents. However, tech-PCP appears to be more potent than purified PCP, indicating that the impurities probably contribute significantly to the developmental toxicity of this material. In more recent studies, PCP was only embryotoxic and teratogenic at maternally toxic dose levels.

Genetic Toxicity

For the most part, PCP has not manifested significant genotoxic activity in those *in vitro* or *in vivo* systems in which it has been tested (NTP, 1989; Hattula and Knuutinene, 1985; Borzelleca *et al.*, 1984; Legator *et al.*, 1982; Lawlor and Haworth, 1979; Simmon *et al.*, 1977; Mattern, 1975; Vogel and Chandler, 1974). Technical grade PCP was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 at doses up to 30 mg/plate with or without S9 enzyme activation (NTP, 1989). More recently, PCP tested in the presence of S9 was mutagenic in the Ames test (U.S. EPA, 2004a).

PCP exhibited weak activity in sister-chromatid exchange (SCE) and chromosome aberration assays in Chinese hamster ovary (CHO) cells. In the chromosome aberration assay, PCP was weakly positive only with S9 activation. Statistically significant increases in abnormal metaphases were observed at 80 or 100 mg/mL PCP. A weakly positive SCE response was observed in the absence of S9 at 3.0 to 30 mg/mL PCP. However, no SCE induction was observed in the presence of Aroclor-induced rat liver S9 at the same dosages (NTP, 1989). Purified PCP (99 percent pure) at 400 mg/L was observed to induce forward mutations and intragenic recombinations, but not intergenic recombinations, in *Saccharomyces cerevisiae* (Fahrig *et al.*, 1978). PCP at 240-300 µg/ml induced chromosome aberrations in CHO cells, while cultured human lymphocytes were negative for aberrations at concentrations of PCP up to 90 µg/ml (U.S. EPA, 2004a).

Tech-PCP caused DNA damage in prokaryotes and eukaryotes (Waters *et al.*, 1982). Tech-PCP was positive in the *Bacillus subtilis* strain 45 recA differential toxicity assay and in the *S. cerevisiae* D3 assay (Waters *et al.*, 1982).

Fahrig *et al.* (1978) tested purified PCP for mutagenicity in the mammalian spot test to detect somatic cell mutations *in vivo*. They bred female C57BL/6JHan mice (homozygous recessive at one coat color locus; otherwise wild type) to males of the "T-stock" (homozygous recessive at five coat color loci), yielding embryos that were heterozygous at four different recessive coat-color loci. The dams were administered a single intraperitoneal injection of either 50 or 100 mg/kg purified PCP on day 10 of gestation. The pups were examined for color spots twice weekly from two to five weeks postpartum. Nine of the 473 pups exhibited color spots on their fur, four of which were judged to be definite mutations. A single gray spot and a single light brown spot were observed in the 50 mg/kg dose group. One light gray and one gray spot were observed in the 100 mg/kg dose group. Only one of the 967 control pups had a color spot that definitely was a result of mutation. The authors concluded that this experiment indicated that purified PCP was unequivocally but weakly mutagenic (Fahrig *et al.*, 1978).

The ability of PCP to induce chromosome aberrations was tested *in vivo* by treating CD-1 mice and harvesting bone marrow cells 24-72 hours later (U.S. EPA, 2004a). Despite dose levels that caused lethality in some of the animals, there was no significant increase in micronucleated polychromatic erythrocytes, suggesting that chromosome aberrations had not been induced.

Tetrachlorohydroquinone (TCHQ), the major metabolite of PCP, is more toxic to CHO cells than PCP itself, and causes DNA single-strand breaks and alkali-labile sites at concentrations of 2 to 10 mg/mL as demonstrated by the alkaline elution technique (Ehrlich, 1990). TCHQ induced thioguanine-resistant mutants in V79 Chinese hamster cells, indicating that TCHQ may be at least partly responsible for the genotoxic activity of PCP (Jansson and Jansson, 1991). It also induced micronuclei in V79 cells at 1.3 to 5.3 µg/ml (Jansson and Jansson, 1992).

Carcinogenicity

In March 1989, NTP published the results of a two-year bioassay of PCP on male and female $B6C3F_1$ mice. The data from this experiment are summarized in Table 4. Mice were exposed to two different grades of PCP: tech-PCP (90.4 percent pure) and Dowicide EC-7 (91 percent pure). These two grades of PCP contain polychlorinated phenols, polychlorinated dibenzo-*p*-dioxins and poly-chlorinated dibenzofurans as contaminants. The test material was mixed with the animals' feed at concentrations of 0, 100, 200 and 600 ppm. There was no 600 ppm exposure group for tech-PCP, because this material was too toxic at this level. Based on food consumption and the weights of the mice, the doses were calculated in mg/kg-day for each exposure group. The 100 and 200 ppm exposure levels corresponded to doses of 17 to 18 and 34 to 37 mg/kg-day, respectively. The highest exposure level, 600 ppm, corresponded to 114 mg/kg-day in female mice and to 116 mg/kg-day in male mice.

Increases in non-neoplastic and neoplastic lesions were produced by both grades of PCP in both sexes of mouse. Tech-PCP produced higher tumor incidences than EC-7, presumably because of greater contamination with carcinogens such as dioxins and furans. Hepatocellular adenomas and carcinomas were increased in a dose-related manner in male mice exposed to either tech-PCP or EC-7; the increase in incidence was less marked in female mice.

Incidence of pheochromocytoma, a usually non-malignant tumor of the adrenal medulla, was significantly increased over controls in male mice for both tech-PCP and EC-7. Pheochromocytomas were also increased in female mice exposed to EC-7 at the highest dose but not in those exposed to tech-PCP. Hyperplasia of the adrenal medulla occurred with increased incidence in male or female mice exposed to either tech-PCP or EC-7.

High-dose female mice that received either tech-PCP or EC-7 had significantly greater incidences of hemangiosarcomas in the spleen and liver. Compound-related non-neoplastic lesions were also observed in the livers, spleens and noses of male and female mice exposed to either tech-PCP or EC-7.

Table 4. Carcinogenicity Bioassay of Pentachlorophenol in B6C3F$_1$ Mice (NTP, 1989)

	Tumor incidences				q1* human (mg/kg-d)$^{-1}$	CSF human (mg/kg-d)$^{-1}$	Upper-bound cancer risk level based on q_1* (ppb)	Upper-bound cancer risk level based on CSF (ppb)
Technical Grade (tech-PCP)								
	Dose (mg/kg-day)							
Male Mice	**0**	**18**	**35**					
pheochromocytoma	0/31	10/45	23/45		1.55E-01	1.47E-01	0.15	0.15
hepatocellular adenoma	5/32	20/47	33/48		2.38E-01	2.25E-01	0.10	0.10
hepatocellular carcinoma	2/32	10/47	12/48		8.13E-02	7.72E-02	0.28	0.29
hepatocellular adenoma and carcinoma	7/32	26/47	37/48		3.13E-01	2.97E-01	0.07	0.08
	Dose (mg/kg-day)							
Female Mice	**0**	**17**	**35**					
hemangiosarcoma	0/35	3/50	6/50		4.17E-02	3.98E-02	0.55	0.57
Dowicide EC-7								
	Dose (mg/kg-day)							
Male Mice	**0**	**18**	**37**	**116**				
pheochromocytoma	0/34	4/48	21/48	44/49	9.10E-02	8.54E-02	0.25	0.27
benign & malignant pheochromocytoma	1/34	4/48	21/48	45/49	9.66E-02	7.47E-02	0.24	0.30

hepatocellular adenoma	5/35	13/48	17/46	32/49	7.65E-02	7.16E-02	0.30	0.32
hepatocellular carcinoma	1/35	7/48	7/49	8/49	1.19E-02	2.55E-02	1.91	0.89
hepatocellular adenoma & carcinoma	6/35	19/48	21/48	34/49	8.34E-02	8.11E-02	0.27	0.28
	Dose (mg/kg-day)							
Female Mice	**0**	**17**	**34**	**114**				
pheochromocytoma	0/35	1/49	2/46	38/49	1.59E-02	8.70E-03	1.43	2.61
benign & malignant pheochromocytoma	0/35	2/49	2/46	38/49	2.15E-02	1.22E-02	1.06	1.86
hepatocellular adenoma	1/34	3/50	6/49	30/48	3.63E-02	2.99E-02	0.63	0.76
hepatocellular adenoma & carcinoma	1/34	4/50	6/49	31/48	3.57E-02	3.39E-02	0.64	0.67
hemangiosarcoma	0/35	1/50	3/50	8/49	1.70E-02	1.58E-02	1.34	1.44
hemangioma & hemangiosarcoma	0/35	1/50	3/50	9/49	1.83E-02	1.73E-02	1.24	1.31

All data sets in this table passed the test for goodness of fit (i.e, had p values for the Monte Carlo test greater than 0.05). The test material was mixed with animal feed at 0, 100, 200 and 600 ppm (600 ppm dose omitted for tech-PCP because of toxicity). Dose calculated in mg/kg-day based on body weight and food consumption.

q_1* = the 95 percent upper confidence limit on the slope of the linearized multistage dose-response curve.

CSF = the cancer slope factor as defined below in the section on the LED_{10} model.

NTP evaluated the data from this study and concluded that there was clear evidence of carcinogenicity[1] of tech-PCP in male mice based on adrenal medullary and hepatocellular neoplasms, and some evidence of carcinogenicity[2] of this test material in female mice based on hemangiosarcomas and hepatocellular neoplasms. EC-7 showed clear evidence of carcinogenicity in both male and female mice based on adrenal medullary and hepatocellular neoplasms. These conclusions are summarized in Table 5.

Table 5. National Toxicology Program Bioassay Conclusions (NTP, 1989)

Test Material	Sex and Species	NTP "Level of Evidence"	Tumor Types
Tech-PCP	male mice	"clear"	adrenal medullary and hepatocellular neoplasms
	female mice	"some"	hemangiosarcomas and hepatocellular neoplasms
Dowicide EC-7	male mice	"clear"	adrenal medullary and hepatocellular neoplasms
	female mice	"clear"	adrenal medullary and hepatocellular neoplasms

As can be seen in Table 4, there was a high background incidence of hepatocellular neoplasms (adenomas and carcinomas) in the male $B6C3F_1$ mice. This strain of mice frequently exhibits a high background rate of hepatocellular neoplasms, raising some doubt as to their relevance to human carcinogenicity. However, the positive trend for this data set was highly significant, based on both Monte Carlo and Chi-square tests.

In April 1999 the NTP published their second carcinogenicity study with PCP, this time performed in the rat (NTP, 1999). In one part of the study, 50 animals/sex/dose level were fed PCP (99 percent pure) in their diet for two years at 200, 400 or 600 ppm, yielding intake levels of about 10, 20 or 30 mg/kg-day. In another part of the study, 60 animals/sex/dose level received 1,000 ppm for one year, corresponding to 60 mg/kg-day, followed by one year of feed without added test article (stop-exposure group). The third part of the study consisted of 10 animals/sex/dose level fed the test article at 1,000 ppm for seven months. After seven months or two years the animals were sacrificed and subjected to pathological examination.

---

[1] Clear evidence of carcinogenic activity means the studies show a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms, if there is an indication from this or other studies of the ability of such tumors to progress to malignancy (NTP, 1989).

[2] Some evidence of carcinogenic activity means the studies show a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence (NTP, 1989).

Nonneoplastic findings at seven months in the 1,000 ppm groups included increased incidences of centrilobular hepatocyte hypertrophy in males and females and increased incidences of hepatocyte vacuolization in males. At two years, all exposed males exhibited increased incidences of hepatodiaphragmatic nodules and hepatocytic cystic degeneration, while 1,000 ppm males also had increased incidences of basophilic foci in liver.

As shown in Table 6, neoplastic changes were observed in high dose males of the stop-exposure group. Two different tumor types were increased relative to controls. The increase in malignant mesotheliomas to 9/50 (18 percent) was statistically significant as well as outside the historical control range (0-8 percent). While the incidence of nasal squamous cell carcinoma was not statistically significant (5/50 = 10 percent), it was outside the historical control range (0-4 percent). The NTP considered these findings "some evidence" for carcinogenicity of PCP in the high dose males. The high dose males had increased survival compared to the control group (Table 6). There was "no evidence" of carcinogenicity for high dose females or for any other dose group.

The positive carcinogenicity findings of the NTP rat study can be contrasted with those of Schwetz *et al.* (1978), who found no evidence of carcinogenicity in rats fed PCP at up to 30 mg/kg-day for 22-24 months. In comparing the two NTP studies performed with PCP in the mouse (NTP, 1989) and rat (NTP, 1999), the compound caused much more liver toxicity in the mouse, both for neoplastic and nonneoplastic endpoints.

Table 6. Summary of 2 Year Rat Carcinogenicity Study with PCP (NTP, 1999).

Exposure for two years		
	Males	**Females**
Doses in feed	0, 200, 400, 600 ppm	0, 200, 400, 600 ppm
Body weights	NOAEL = 200 ppm	NOAEL = 200 ppm
Survival	12/50, 16/50, 21/50, 31/50	28/50, 33/50, 34/50, 28/50
Neoplastic effects	None	None
Level of evidence of carcinogenicity	None	None
Exposure for one year followed by one year unexposed		
	Males	**Females**
Doses in feed	1,000 ppm	1,000 ppm
Body weights	Less than controls during year 1, similar to controls during year 2	
Survival	27/50	28/50
Neoplastic effects	Malignant mesothelioma of the *tunica vaginalis* (1/50, 9/50); nasal squamous cell carcinoma (1/50, 5/50)	None
Level of evidence of carcinogenicity	Some evidence	No evidence

Toxicological Effects in Humans

Most of the information about the health effects of PCP in humans comes from occupational settings where workers are exposed to high levels of the chemical. The workers who are exposed to these high levels are those who work in the production of PCP, or in its application in wood treatment plants, as well as those who handle treated wood and use it in fabricating cooling towers and other outdoor structures. Very little information is available on the long-term effects of low level exposures to PCP.

Acute and Short-Term Toxicity

Irritation of the skin, the nasal and respiratory tracts and the eyes result from nonfatal exposures to PCP (U.S. EPA, 1985). Repeated skin exposure to sodium pentachlorophenate caused dermatitis, and occasionally an allergic response (Dow Chemical Co., 1969). Corneal damage leading to permanent impairment of vision was also observed when PCP came into contact with the eyes. Koppers Company conducted a retrospective study of its 1,670 employees who were occupationally exposed to PCP in wood preservative plants (American Wood Preservers Institute, 1977). Twenty-six cases of PCP-related health problems were reported in this study. The most frequent symptoms were conjunctivitis, allergies, dermatitis and skin burn (American Wood Preservers Institute, 1977).

Fatal exposures of humans to PCP cause profuse sweating, fatigue, intense thirst, nausea, vomiting, general weakness, anorexia, abdominal pain, hyperpyrexia, tachycardia, tachypnea, severe terminal spasms, progressive coma and death within 3 to 30 hours of the onset of these symptoms (Menon, 1958; Bergner *et al.,* 1965; Chapman and Robson, 1965; Mason *et al.,* 1965; Robson *et al.,* 1969; Wood *et al.,* 1983). These symptoms are consistent with the mechanism of action of PCP as an uncoupler of oxidative phosphorylation (Proudfoot, 2003). In fatal cases, an intense form of rigor mortis is often observed.

Twenty newborn infants became ill and two died after brief exposures to PCP from nursery linens laundered in an antimicrobial neutralizer containing 22.9 percent sodium pentachlorophenate. Two neonates developed characteristic signs of PCP poisoning including excessive sweating, fever, tachycardia, tachypnea, hepatomegaly and metabolic acidosis (Armstrong *et al.,* 1969; Robson *et al.,* 1969).

A drinking water well contaminated with 12.5 ppm PCP caused illnesses in approximately twelve people who used water from the well for drinking and bathing. All of the exposed individuals had irritated throats, fever and increased pulse and respiratory rates and were flushed (Uede *et al.,* 1962; Chapman and Robson, 1965). Two children who were exposed were intermittently delirious and excitable, but recovered completely after a week of no exposure (Chapman and Robson, 1965). The health of the other exposed individuals improved after two or three days of no exposure (Uede *et al.,* 1962).

Fifteen members of three families were exposed to PCP in the air in their homes. The maximum air concentrations were 0.4, 0.95 and 1.2 mg/m^3 (Sangster *et al.,* 1982). Symptoms reported for these exposed individuals were painful burning sensations of the

skin of the face and hands, erythema, dryness and scaling of the skin, drowsiness, nausea, decreased appetite, fatigue, pain upon breathing deeply and swelling of the eyelids. These symptoms gradually disappeared after exposure ceased.

Chronic Toxicity

Adverse health effects associated with chronic exposure to PCP include fatigue, neuropsychiatric disorders, skin infections, respiratory symptoms, neuralgic leg pain, impaired fertility and hypothyroidism, the latter two being due to endocrine disruption (Proudfoot, 2003).

Occupational exposure of lumber mill workers to a wood preservative containing PCP was the subject of a two-year study (Kleinman *et al.,* 1986). Ten workers in the PCP production department of a manufacturing plant had histories of severe skin eruptions, and all but one had extensive acne more than a year after production was suspended. Eight of the workers reported neuralgia of the legs and feet. Four complained of persistent bronchitis. Also reported were palpitations of the heart, disturbances of the libido, bursitis of the elbow, acute upper respiratory irritation and lacrimation (Baader and Bauer, 1951). Dermal exposure of one worker to PCP for approximately one year resulted in fatal aplastic anemia (Roberts, 1963).

Data from occupational exposure usually involves the inhalation route of exposure, and is usually long-term. The underlying mechanism that accounts for most of the clinical observations is an increase in the metabolic rate to compensate for loss of energy from uncoupling of oxidative phosphorylation (Williams, 1982).

Sawmill workers in New Zealand were surveyed for personal health concerns (Walls *et al.,* 1998). A significant dose-response was detected between PCP exposure and the following self-reported symptoms in 127 workers: fever/sweating, weight loss, fatigue, nausea and specific responses to a neuropsychological questionnaire. The authors found that these results were similar to their clinical experiences treating sawmill workers, and therefore recommended larger studies to test the associations between PCP exposure and adverse health effects.

Liver

PCP exposure causes gross, histological and biochemical alterations of the liver. Enlargement and fatty degeneration of the liver have been caused by both occupational and accidental exposures (Gorski *et al.,* 1984; Wood *et al.,* 1983). Two infants who died following PCP poisoning exhibited swollen hepatocytes with numerous small cytoplasmic vacuoles (Robson *et al.,* 1969). These infants also exhibited fatty metamorphosis of the liver.

Three male PCP factory workers, and another male who accidentally drank a wood preservative containing 5.2 percent PCP in a kerosene/naphtha mixture, all exhibited severe centrilobular congestion of the liver with numerous fat droplets in hepatocytes (Gray *et al.,* 1985; Mason *et al.,* 1965; Stevens and Richardson, 1979).

One hundred and twenty workers from a PCP manufacturing plant were found to have increased levels of triglycerides and decreased levels of total serum cholesterol, lactate dehydrogenase (LDH) and total bilirubin (Baxter, 1984). However, these changes were not statistically significant, and there was no discernible change in other liver enzymes such as SGPT, SGOT and GGT. These workers were exposed to 0.5 to 16.5 mg/m^3 PCP for periods of three months to over 20 years.

A woman was chronically exposed to PCP in her wooden house that had been extensively treated with chlorophenol preservatives. She exhibited liver damage together with increased activity of SGPT, SGOT, GGT, LDH and glutamate dehydrogenase (GLDH) (Brandt *et al.,* 1977).

Kidneys

A six-day-old girl and a twelve-day-old boy who died within 3 and 46 hours, respectively, of the first signs of PCP intoxication, exhibited kidneys that were pale with fat vacuoles in the cytoplasm of epithelial cells of the proximal convoluted tubules (Robson *et al.,* 1969). These effects were attributed to percutaneous absorption of PCP used in laundering of the infants' diapers and linens. The laundry product contained 23 percent NaPCP, 4 percent 3,4,4-trichlorocarbanilide, 3.2 percent sodium salts of other chlorophenols and inert ingredients.

Other PCP poisoning cases have involved hydropic and fatty degeneration of the renal tubules, or slight congestion of the kidney (Bergner *et al.,* 1965; Wood *et al.,* 1983; Gray *et al.,* 1985; Mason *et al.,* 1965; Stevens and Richardson, 1979). Elevated blood urea nitrogen (BUN), proteinuria, ketonuria and acidosis have been characteristic of PCP poisoning cases (Chapman and Robson, 1965; Robson *et al.,* 1969; Gray *et al.,* 1985).

A four-year-old child who was poisoned (via a contaminated water supply) with an insecticide mixture containing PCP was found to have generalized aminoaciduria in addition to the usual biochemical abnormalities mentioned above (Chapman and Robson, 1965). The insecticide mixture also contained b-naphthol and dieldrin in an oily solvent. The child had washed and bathed in the contaminated water for 13 days. Forty hours after hospitalization the concentration of PCP in the urine was 6 mg/100 mL, but no dieldrin was detected.

Evidence of reversible renal dysfunction was observed in 18 workers at a wood treatment plant (Begley *et al.,* 1977). Creatinine clearance and phosphorus resorption values were depressed prior to a 20-day vacation period but showed significant improvement during vacation, suggesting that PCP exposure transiently reduced both the glomerular filtration rate and tubular function (Begley *et al.,* 1977).

Heart

Fatalities due to PCP poisoning have sometimes been attributed to cardiac arrest (Bergner *et al.,* 1965; Stevens and Richardson, 1979; Ahlborg and Thunberg, 1980; Wood *et al.,* 1983); however, few cardiac abnormalities have been reported following nonlethal poisoning. One fatality resulting from occupational exposure was a 58-year-old man

whose cardiac rhythm was irregular because of episodes of sinus arrest and nodal premature beats (Bergner *et al.,* 1965). Cardiac dilation and fatty degeneration of the heart have been commonly observed during pathological examination of industrial fatalities (Truhaut *et al.,* 1952; Menon, 1958; Bergner *et al.,* 1965; Mason *et al.,* 1965; Robson *et al.,* 1969; Wood *et al.,* 1983; Gray *et al.,* 1985). Pallor of the myocardium and cardiomegaly has also been reported (Robson *et al.,* 1969).

A 16-year-old male who had sprayed a 1 percent solution of NaPCP as a herbicide in an Australian pineapple plantation for three hours per day, two days per week for four weeks, developed hyperpyrexia, hyperpnea, general flaccidity and a slight neck stiffness (Gordon, 1956). This individual, who had worn no protective clothing, died 21 hours after the onset of the symptoms. A post-mortem examination revealed fragmentation of some muscle fibers of the heart, as well as degeneration of intravascular leukocytes.

In a similar incident, a 14-year-old male, who had prepared a 2.5 percent NaPCP solution and sprayed it for several hours per day for an unspecified number of weeks, died without medical attention within 18 hours of a final full-day exposure to the solution. Autopsy of this individual revealed scattered hemorrhages in the subpericardial fatty tissues (Gordon, 1956).

Hematopoietic System

A woman exposed to PCP in an insecticide she used to clean furniture developed intravascular hemolytic anemia (Hassan *et al.,* 1985). Laboratory examination of a blood sample collected from the patient revealed decreased hemoglobin, decreased white blood cell count and up to 30 percent reticulocytosis. Microcytosis, spherocytosis and anisocytosis were observed in peripheral blood smears. The investigators' interpretation was that PCP causes hemolysis by blocking formation of ATP (Hassan *et al.,* 1985).

A man who handled wet lumber processed with a product containing 3 percent PCP and 1.5 percent tetrachlorophenol died from aplastic anemia. The same preparation caused aplastic anemia in three patients, and red cell aplasia in two others (Roberts, 1981; Roberts, 1983). One of the patients with red cell aplasia later developed acute leukemia (Schmid *et al.,* 1963), and another had Hodgkin's disease in the left cervical nodes (Roberts, 1983).

Five workers were discovered to have leukemia after working at an army depot where high concentrations of PCP were found in the ambient air from PCP-treated lumber (Roberts, 1983). A construction worker regularly exposed to PCP presented with severe aplastic anemia, and later developed Hodgkin's disease in the left supraclavicular nodes (Louwagie *et al.,* 1978). These findings suggest that PCP may simultaneously damage the bone marrow and initiate lymphoproliferation. Klemmer *et al.* (1980) found a significant association ($p < 0.005$, ANOVA) between PCP exposure and the occurrence of increased immature band neutrophils and basophils, along with increased alkaline phosphatase concentrations.

Enlarged spleens were reported in two cases of chronic PCP exposure: a 14-year-old female with granulocytopenia, lymphocytosis and hepatomegaly (Gorski *et al.,* 1984); and a 22-year-old man with accompanying edema of the brain and lungs (Menon, 1958).

The investigator suggested that the toxic effects of PCP exposure may be increased in individuals in tropical countries who consume rice diets with little protein, and that there may be racial differences in susceptibility to PCP toxicity. Two of nine infants who were exposed to toxic amounts of PCP in a nursery exhibited splenomegaly (Robson *et al.,* 1969).

Respiratory System

The clinical effects of occupational and accidental exposure to PCP on the respiratory tract have been reported as nasal stuffiness, mucosal irritation of the upper airways, tachypnea, respiratory distress and intercostal retractions, and bilateral basal crepitations on auscultation (Chapman and Robson, 1965; Baader and Bauer, 1951; Robson *et al.,* 1969; Cooper and Macauley, 1982). Post-mortems of patients who died from inhalation of PCP have revealed gross congestion of the lungs and acute edema (Menon, 1958; Mason *et al.,* 1965; Stevens and Richardson, 1979; Wood *et al.,* 1983; Gray *et al.,* 1985). No other pulmonary lesions were mentioned in the available literature.

Central Nervous System

Children who were bathed in PCP-contaminated water (PCP/b-naphthol/dieldrin) exhibited nose and eye irritation, fever and intermittent delirium and rigors following periods of excitability (Chapman and Robson, 1965). Another fatal case also involved delirium and convulsions (Wood *et al.,* 1983). Acute exposure to PCP has been shown to cause depression and progressive neuromuscular weakness (Ahlborg and Thunberg, 1980).

Transient cases of sciatic neuralgia among men shoveling PCP in a manufacturing plant were described by Barnes (1953). Seven cases of polyneuritis were reported in men and women, aged 36 to 61 years, who had used insecticides containing PCP (Campbell, 1952). Peripheral neuritis was found in five of these cases, and retrobulbar neuritis was found in three. Neuralgic pain in the lower extremities was reported by workers exposed to PCP (Baader and Bauer, 1951). These workers also experienced weakness of the lower limbs, paresthesia and severe pain of the gluteal and femoral regions and along the sciatic nerve. Significantly decreased sensory nerve conduction velocities were measured in 18 workers exposed for 12 years in a PCP processing factory (Triebig *et al.,* 1981).

Pathological findings related to central nervous system effects of PCP exposure include focal neuronal degeneration as well as cerebral edema with focal swelling of the myelin sheaths in the white matter (Gordon, 1956; Bergner *et al.,* 1965; Robson *et al.,* 1969; Wood *et al.,* 1983; Gray *et al.,* 1985).

Immune System

Significant increases in immunoglobulins occurred among occupationally exposed individuals, whose plasma levels of PCP ranged from 0.2 to 2.4 mg/mL (Zober *et al.,* 1981). Workers exposed to PCP were found to have conjunctivitis, chronic sinusitis and upper respiratory infections (Klemmer *et al.,* 1980). A highly significant ($p < 0.005$)

association was found between PCP exposure and an increased number of band neutrophils (immature leukocytes) after controlling for age and ethnicity (Klemmer *et al.*, 1980).

In a more recent study (Daniel *et al*, 2001), a group of patients (n=190) exposed to PCP for longer than six months also reported high incidences of respiratory infections and general fatigue. The levels of PCP in their blood were measured and correlated with a variety of markers of immune function. The following immune parameters were negatively correlated with serum PCP concentration: total lymphocyte counts, CD4/CD8 ratios, absolute counts of CD3+, CD4+, CD16+, CD25+, DR+, CD8+/56+ and CD19+ cells, plasma levels of interleukin-2, soluble IL-2R, IL-6, interferon-gamma, tumor necrosis factor-alpha, transforming-growth factor-beta$_2$, soluble IL-1 receptor antagonist, soluble intercellular adhesion molecule-1 and immunoglobulin M-anti-Fab type autoantibodies. The authors suggested that some of these signs of immunosuppression might be responsible for the frequent respiratory infections and high incidence of fatigue reported by this group of patients. In a smaller group of subjects (n=32) exposed to PCP through work at a wood treatment plant (Colosio *et al.*, 1993), the peripheral blood mononuclear cells of subjects with the highest urine and plasma levels of PCP exhibited a significantly reduced proliferative response to phytohemagglutinin compared to the lower exposed subjects and to controls. In contrast to this possible adverse effect of long-term PCP exposure on immune function, other parameters such as circulating levels of various lymphocyte subsets and immunoglobulin classes were unaffected.

Pancreas

Two cases of PCP poisoning involved pancreatic effects. The first case, a 51-year-old man occupationally exposed to "Cuprinol Clear" wood preservative containing PCP and zinc naphthenate, initially manifested abdominal pain, anorexia, vomiting and dark-colored urine (Cooper and Macaulay, 1982). This individual was found to have pancreatitis, together with increased levels of serum bilirubin, aspartate transaminase, alanine transferase, gamma-glutamyltranspeptidase and amylase. The authors judged that PCP was "highly likely to have been the cause of the pancreatitis."

The second case involved another 51-year-old man who accidentally drank 53 mL of wood preservative containing 5.2 percent PCP (2.8 g of PCP) and upon pathological examination exhibited gross congestion of the pancreas (Stevens and Richardson, 1979). The pancreas, kidneys and intestines of this individual showed greater than normal epithelial autolysis.

Skin

Many incidents of human exposure to PCP result from direct dermal contact during industrial or home use. An adult male who immersed his hands for 10 minutes in a 0.4 percent solution of PCP had reddening and pain in his hands that persisted for two hours. Urinary PCP levels had returned to background levels one month after the episode (Bevenue *et al.*, 1967). A man whose job involved scooping PCP into a pail had chronic diffuse urticaria and angioedema of the hands (Kentor, 1986). Two cases of *pemphigus*

vulgaris (skin eruptions characterized by large vesicles, usually 2 cm or more in diameter) occurred in individuals who were exposed to PCP in a nonoccupational setting (Lambert *et al.,* 1986). Chronic urticaria was observed in a case with increased anti-skin antibodies. In each of these cases the symptoms correlated well with serum PCP levels, ranging from 15 mg/L to 143 mg/L (Lambert *et al.,* 1986).

Many studies have reported an association between commercial PCP and chloracne, which is characterized by folliculitis and comedones with secondary infection (U.S. EPA, 2004a; Hryhorczuk *et al.,* 1998). However, the occurrence of chloracne in PCP workers may be caused by the chlorinated dioxin and dibenzofuran contaminants in PCP (Johnson *et al.,* 1973; Cole *et al.,* 1986). The recent finding of high levels of dioxin in the blood of PCP workers (mean 313 ppt in exposed compared to 68 ppt in controls) supports this view (Collins *et al.,* 2006).

Rashes and skin irritations commonly result from acute or chronic exposure to PCP (Klemmer *et al.,* 1980; Sangster *et al.,* 1982; Kleinman *et al.,* 1986). Three patients experienced burning sensations, erythema, dryness and scaling caused by exposure to PCP in the air (Sangster *et al.,* 1982).

Reproductive System

The available evidence on the effect of PCP on the human reproductive system is sketchy and inconclusive. Four of 10 workers chronically exposed to PCP complained of "disturbances of libido" (Baader and Bauer, 1951). Exposure was not quantitated in this study, but it was sufficient to cause a range of symptoms, including severe acne, eye irritation and neuralgic pain of the lower extremities.

A 25-year-old woman reported headache, dizziness and fatigue approximately one month after moving with her family into a restored house that had been treated with a 5.5 percent solution of PCP in white spirit followed by linseed oil (Sangster *et al.,* 1982). The concentration of PCP in the house air during the second month of exposure was 0.7 mg/m^3. The woman experienced a spontaneous abortion after three months of residence in the house. No physical or biochemical abnormalities were found during clinical examination of this woman (Sangster *et al.,* 1982). There is no evidence that establishes a causal relationship between the PCP exposure and the spontaneous abortion.

A large study of the progeny of male sawmill workers was conducted in British Columbia, Canada (Dimich-Ward *et al.,* 1996). Workers were exposed to chlorophenates (tetrachlorophenol and/or PCP) for at least one year prior to fathering a child. The medical records of 19,675 of the workers' children born between 1952 and 1988 were examined for birth defects. The children of highly exposed sawmill workers had significantly higher rates of congenital anomalies of the eye and genital organs, and increased risks of developing anencephaly or spina bifida compared to workers with lower exposures. These adverse reproductive outcomes may have resulted from paternal exposure to either chlorophenate or to the dioxin contaminant in the chlorophenate preparations.

In a more recent study by Gerhard *et al*. (1998), German women with repeated miscarriages had higher concentrations of chlorinated hydrocarbons (PCP and others)

than the reference group, suggesting a possible adverse effect of chlorinated hydrocarbons on female reproduction. A related study (Gerhard *et al.*, 1999) examined PCP levels in a group of German women with gynecological problems, including infertility. Compared to matched controls, this group had higher blood levels of PCP and lower blood levels of follicle-stimulating hormone, triiodothyronine, and a number of adrenal hormones, suggesting that PCP caused endocrine disruption in women.

Developmental Toxicity

The birth outcomes of 737 wives of employees of a chemical company in Michigan were investigated by means of an interviewer-administered questionnaire (Townsend *et al.*, 1982). The wives of employees with potential exposures to dioxins and PCP were compared to a control group of wives of employees with no such potential exposure. No significant association was found between PCP exposure and adverse reproductive outcomes (Townsend *et al.*, 1982).

Genetic Toxicity

Wyllie *et al.* (1975) observed no change in frequency of chromosomal aberrations such as breaks or gaps when they examined peripheral lymphocytes (25 per person) of six workers occupationally exposed to 263 to 1,888 mg/m^3 for 20 to 54 years. Schmid *et al.* (1982) and Bauchinger *et al.* (1982) conducted more detailed investigations of the potential cytogenetic effect of PCP. Three hundred lymphocytes per individual, from 22 workers who were exposed to 0.1 to 0.5 mg/m^3 PCP in factory air for 1 to 30 years, were examined for SCE and structural chromosome changes. There was a significant increase ($p < 0.05$, Mann-Whitney U-test) in the number of cells with structural chromosomal changes. The damage was mainly of the chromosomal type, with significantly increased numbers of dicentric and acentric chromosomes. No increase in the numbers of chromatid type aberrations, such as breaks and exchanges, or in the frequency of gaps, was found. Schmid *et al.* (1982) termed this a "weak clastogenic effect."

Carcinogenicity

U.S. EPA categorizes PCP as a probable human carcinogen (B2) based on its analysis of the available evidence (U.S. EPA, 2007b, file last updated 7/01/1993). U.S. EPA regards the human data to be inadequate, but the animal data to be sufficient to indicate that PCP is a probable human carcinogen. The human data were obtained from a study of 182 men who worked in the wood treatment industry in Hawaii. These men had elevated levels of PCP in their urine, but there was no increase in morbidity or mortality from cancer in this group (Gilbert *et al.*, 1990). U.S. EPA judged this study to be "uninformative."

A number of epidemiological studies and case reports have identified an association between PCP or exposures to chemicals used in wood preservative industries and manufacture and certain kinds of cancer, including soft-tissue sarcoma, malignant lymphoma, nasal and nasopharyngeal cancer, as well as liver and colon cancer.

Soft-tissue Sarcoma

A case-control study of soft-tissue sarcoma and exposure to chlorophenols (not restricted to PCP), used in Sweden as a fungicide for slime control in the production of paper pulp, and to chlorophenoxy herbicides was conducted by Hardell and Sandstrom (1979). These investigators calculated a soft tissue sarcoma relative risk ratio of 6.6 ($p < 0.001$) for workers exposed to chlorophenols. Many of these pesticides contained chlorinated dibenzodioxins and dibenzofurans as impurities. The investigators concluded that the increased risk of soft-tissue sarcoma among those using these pesticides may be attributable to these impurities rather than to the chlorophenols and chlorophenoxy compounds (Hardell and Sandstrom, 1979).

A later case-control study in Sweden, which excluded individuals with exposure to chlorophenoxy herbicides, found a soft-tissue sarcoma relative risk ratio of 3.3 for individuals exposed to chlorophenols (Eriksson *et al.*, 1981). A soft-tissue sarcoma relative risk ratio of 1.6 was calculated for individuals exposed to chlorophenols for five days or longer, 10 years prior to diagnosis (Smith *et al.*, 1984).

Malignant Lymphoma

A Swedish case-control study of 169 cases of malignant lymphoma and 338 controls was reported by Hardell *et al.* (1981). This study was conducted in a manner similar to the Swedish soft-tissue sarcoma studies cited above. Relative risk ratios were 2.2 for "low" exposure to chlorophenols, and 7.6 for "high" exposure. "Low" exposure was defined as continuous exposure to chlorophenols for not more than one week, or repeated brief exposures for not more than one month; longer exposures were classified as "high." There appeared to be no difference between Hodgkin's and non-Hodgkin's lymphoma in terms of the excess risk generated by exposure to chlorophenols.

A New Zealand case-control study of non-Hodgkin's lymphoma was reported by Pearce *et al.* (1986). This study involved 83 cases, 168 controls with other types of cancer and 228 general population controls. The relative risk ratio was calculated to be 1.2 when comparing cases to other cancer patients, and 1.4 when comparing cases with general population controls.

Two case reports of non-Hodgkin's lymphoma in the scalp among 158 male workers exposed to chemicals for five years at a PCP manufacturing plant were reported by Bishop and Jones (1981). Both individuals had also been exposed to aromatic hydrocarbons such as benzene, as well as to hexachloro- and octachloro-dibenzodioxins which occurred as contaminants, at concentrations up to 300 ppm, in the manufacturing intermediates. Cases of chloracne were also reported from this plant. The expected number of neoplasms of this type for a group of 158 men would be 0.28.

Workers in the wood and lumber industries had an increased relative risk of developing Hodgkin's disease (Green *et al.*, 1978). These investigators examined the occupational statements on death certificates in several North Carolina counties, where a significant part of the population was involved in lumbering and furniture manufacturing. A total of 167 deaths from Hodgkin's disease occurred among white males in the study population.

Two controls with other causes of death were matched to each case by sex, race, county of death, age and year of death. The relative risk for Hodgkin's disease for workers in the wood and paper industries was 1.4 (95 percent confidence interval: 0.8 to 2.3). Carpentry and lumbering had the highest relative risk ratio, 4.2 (95 percent C.I.: 1.4 to 12.5).

In a recently published study of Canadian sawmill workers (Demers *et al.,* 2006), dermal exposure to PCP was associated with increased risks of three cancers: non-Hodgkin's lymphoma, multiple myeloma and kidney cancer. There was no association between PCP exposure and the incidences of soft tissue sarcoma, lung cancer, sinonasal cancer or nasopharyngeal cancer.

Nasal and Nasopharyngeal Cancer

Workers in sawmills can be exposed to chlorophenols during wood impregnation or through inhalation of dust, especially in those plants where the lumber is handled after treatment with chlorophenols (Levin *et al.,* 1976).

Forty-four cases of nasal cancer and 27 cases of nasopharyngeal cancer were studied in Sweden by Hardell *et al.* (1982), who compared the reported frequency of exposure to chlorophenols and other chemicals with that of the combined 541 referents from earlier studies (Hardell and Sandstrom, 1979; Eriksson *et al.,* 1981). Sawmill workers and carpenters exposed to chlorophenols for more than one month were found to have a relative risk ratio for these types of cancer of 6.7 (95 percent C.I.: 2.8 to 16.2).

Hernberg *et al.* (1983) studied 167 cases of sinonasal cancer and 167 colorectal cancer cases in Denmark, Finland and Sweden. They found an association between sinonasal cancer and employment in the wood products industry. Two of the sinonasal cancer cases and none of the colorectal cancer controls had probably been exposed to chlorophenols in addition to wood dust.

Another study, based on the Danish Cancer Registry, classified 839 sinonasal cancer cases and 2,465 controls according to wood dust and chlorophenol exposure. A relative risk ratio of 0.6 (95 percent C.I.: 0.3 to 1.2) was reported after adjustment for exposure to wood dust (Olsen and Jensen, 1984).

Considering all of these studies it appears that exposure to wood dust is associated with nasal and nasopharyngeal cancer. It is not clear whether there is any association between chlorophenol exposure and these cancers. There may be other chemicals involved such as glues, shellacs, etc.

Liver and Colon Cancer

A study of colon cancer by Hardell (1981) found a relative risk ratio of 1.8 (95 percent C.I.: 0.6 to 5.3) for high exposure to chlorophenol, based on six exposed cases and 13 exposed referents (out of a total worker population of 541). Hardell *et al.* (1984) found a relative risk ratio for primary liver cancer of 2.2 (95 percent C.I.: 0.7 to 7.3) among individuals with high exposure to chlorophenols.

Summary of Carcinogenic Effects in Humans

IARC reviewed and considered all of the evidence on the carcinogenicity of PCP (IARC, 1979, 1991). IARC concluded that there is inadequate evidence for the carcinogenicity of PCP in humans, but sufficient evidence in experimental animals. IARC's overall conclusion is that PCP is "possibly carcinogenic to humans" (Group 2B).

U.S. EPA similarly reviewed all of the evidence and concluded that there is inadequate evidence for carcinogenicity of PCP in humans, but sufficient evidence in experimental animals. U.S. EPA classifies PCP as a "probable human carcinogen," Class B2 (U.S. EPA, 2007b).

We agree with these other agencies that the epidemiological evidence is not adequate to identify PCP as a carcinogen in humans. Virtually all of the studies failed to distinguish between the effects of PCP and other confounding exposures such as wood dust and other chemicals used in the wood industry.

DOSE-RESPONSE ASSESSMENT

The purpose of this section is to identify those studies which may be acceptable for use in calculating a PHG. The objective is to identify studies with adequate data for a reliable evaluation of dose-response.

Drinking water limits can be based on either carcinogenic or noncarcinogenic effects. In this section, those studies are reviewed which have sufficient data on which to base a dose-response assessment, that is, those studies on which an NOAEL or LOAEL can be based for noncarcinogenic effects or those for which a cancer potency can be estimated.

Noncarcinogenic Effects

Table 2, which is modified from Hsieh (1990), gives the NOAELs and LOAELs for PCP based on experiments on noncarcinogenic effects in animals. Experimental animals included the rat, mouse, rabbit, pig, dog, sheep and mink.

Acute Studies

The acute toxicity of PCP in rats was studied by Nishimura *et al.* (1982). They found dose-related increases in liver weights at doses of 30 mg/kg-day or greater. They also found increased liver glycogen and lactate at doses of 120 to 150 mg/kg-day. The NOAEL from this study was 10 mg/kg, based on a liver weight increase of 20 percent at the highest dose.

Subchronic Studies

Johnson *et al.* (1973) studied the effects of purified PCP in Sprague-Dawley rats at doses of 0, 3, 10 or 30 mg/kg-day for 90 days. They found that liver weights increased at the

10 and 30 mg/kg-day doses. Kidney weights increased only at the 30 mg/kg-day dose. The NOAEL for this study was 3 mg/kg-day. U.S. EPA stated that the NOAEL from this study was 10 mg/kg-day, apparently not considering increased liver weight alone an adverse effect.

Knudsen *et al.* (1974) studied the effect of PCP in Wistar rats. Ten weanling rats per sex were fed 0, 25, 50 or 200 ppm PCP for 12 weeks. This PCP contained no TCDD, but it did contain 200 ppm OCDD and other impurities. PCP has direct effects on erythrogenesis in bone marrow and spleen. PCP uncouples oxidative phosphorylation in red blood cells. This leads to accelerated formation of red blood cells. Decreased hemoglobin may have been due to shortened red blood cell lifespans, leading to reduced ATP content in the cells (Knudsen *et al.*, 1974). The NOAEL from this study was attained at the 25 ppm dose group, which (according to the authors) translates to a dose of 1.21 mg/kg-day for the male and 1.64 mg/kg-day for the female rats.

Schwetz *et al.* (1974) investigated teratogenicity of purified PCP (98 percent purity) in Sprague-Dawley rats at doses of 5, 15, 30 or 50 mg/kg-day, administered on days 6 to 15 of gestation. There were no signs of maternal toxicity. Delayed ossification of the skull was observed at doses of 5 to 15 mg/kg-day. Other soft tissue and skeletal anomalies were also observed at 15 mg/kg-day. At 30 mg/kg-day, 97.5 percent of the fetuses were resorbed. Resorptions rose to 100 percent at 50 mg/kg-day. The LOAEL from this study was 5 mg/kg-day.

Greichus *et al.* (1979) studied the effect of purified PCP in pigs at doses of 0, 5, 10 or 15 mg/kg-day for 30 days. Increased liver weights and decreased white blood cell counts were observed at 10 to 15 mg/kg-day. The NOAEL from this study was 5 mg/kg-day.

Fleischer *et al.* (1980) examined hepatotoxicity of PCP in male rats. Rats were given PCP intraperitoneally at 30 mg/kg-day. Relative liver weights increased by 24.4 percent in young rats and by 9.2 percent in old rats at this dose. Morphological changes were seen in hepatocytes, such as widening sinusoids, and increased heterochromatin to euchromatin ratio. Fat content of the cells was decreased. The LOAEL for this study was 3.52 mg/kg-day.

Kerkvliet *et al.* (1982) studied the effects of PCP pretreatment on chemical and viral tumor induction in mice. Chemical tumor induction was by 3-methylcholanthrene (MCA); viral by Moloney Sarcoma Virus (MSV). In both cases it was found that pretreatment with PCP had no effect on the frequency of tumor induction; however, liver lesions were found in the PCP-treated mice. The LOAEL for this study, based on the 50 ppm dose group, was 5 mg/kg-day, assuming a daily food consumption of 10 percent of body weight.

Jekat *et al.* (1994) treated female rats with 3.0 or 30 mg/kg-day PCP for 28 days. There were dose-responsive decreases ($p<0.0025$) in the serum levels of both T_4 (64 percent decrease) and T_3 (43 percent decrease) after 28 days. PCP also lowered thyroid hormone levels in female yearling cattle fed PCP for 42 days at 20 mg/kg-day followed by 118 days at 15 mg/kg-day (McConnell *et al.*, 1980). Significant ($p<0.01$) decreases in serum T_4 (29 percent) and serum T_3 (35 percent) were observed.

Two dietary range-finding studies were performed in B6C3F$_1$ mice in advance of the standard two year carcinogenicity study (NTP, 1989). One study was for 30 days, with a NOAEL of 2.8-4.3 mg/kg-day based on toxicity to the liver, including macroscopic and microscopic lesions and increased serum liver enzymes. A second study was for 6 months, with a LOAEL at the lowest doses tested of 43-54 mg/kg-day based on liver lesions, changes to the urinary bladder and immune suppression.

A 28-day range-finding study was also performed in rats in advance of the NTP two year carcinogenicity study (Chhabra *et al.*, 1999). Animals were fed PCP at 20 mg/kg-day or higher. This lowest dose was the LOAEL, based on increased absolute liver weights.

In a developmental toxicity study performed in Crl:CD rats, pregnant females were dosed by gavage on days 6-15 of gestation (Bernard and Hoberman, 2001). The maternal NOAEL was 30 mg/kg-day based on reduced body weight gain. The developmental NOAEL was also 30 mg/kg-day based on increased resorptions, skeletal malformations and variations, and reduced fetal weight.

A developmental toxicity study of PCP has also been performed in New Zealand White rabbits (Bernard *et al.*, 2001). Pregnant females were dosed by gavage on days 6-18 of gestation. The maternal NOAEL was 15 mg/kg-day based on reduced body weight gain and food consumption. No developmental effects were observed, yielding a developmental NOAEL of 30 mg/kg-day.

A subchronic study has also been performed in the rat via dermal exposure (U.S. EPA, 2004a), yielding a higher NOAEL than the dietary and gavage studies discussed above. Sprague-Dawley rats were exposed to PCP for 6 hours/day, 5 days/week via dermal occlusion. After 90 days, a NOAEL was established at 100 mg/kg-day based on enzyme induction, mild hepatocellular degeneration and chronic inflammation.

Chronic Studies

Chronic studies in rodents are those with exposure periods of 90 days or greater. This section discusses noncarcinogenic effects of chronic exposure. Goldstein *et al.* (1977) investigated hepatotoxicity of technical and pure grade PCP in female Sherman rats administered PCP at doses of 0, 20, 100 and 500 ppm for eight months in the diet. Tech-PCP produced hepatic porphyria and increased hepatic aryl hydrocarbon hydroxylase activity, glucuronyl transferase activity, liver weight and cytochrome P_{450} activity. Porphyria occurred at 100 and 500 ppm. In contrast pure PCP exhibited none of these effects at the doses tested, except that it did increase glucuronyl transferase activity at 500 ppm. The investigators concluded that tech-PCP produces a number of liver changes that cannot be attributed to PCP itself, but are consistent with the effects of chlorinated dioxins and furans.

Schwetz (1978) found some minor reproductive effects in rats treated with Dowicide EC-7 (90.4 percent pure). The impurities in this material are hexachlorobenzene, dioxins and furans. The NOAEL from this study was 3 mg/kg-day for reproductive effects and for chronic toxicity effects in female rats. The NOAEL for chronic toxicity in male rats was 10 mg/kg-day.

A two year carcinogenicity study has been performed in B6C3F$_1$ mice (NTP, 1989). The study included a variety of endpoints in addition to tumor formation. The lowest dose tested was 17 mg/kg-day, which was also the study LOAEL for noncarcinogenic effects, based on liver lesions and spleenic extramedullary hematopoiesis.

A multigenerational study with PCP has been performed in mink (Beard and Rawlings, 1998). A single dose level of 1.0 mg/kg-day was used in addition to control. Animals were dosed via feed from three weeks prior to mating, during gestation and lactation (F_2), and repeating the above schedule for the F_3 generation. Exposed males of both the F_2 and F_3 generations and exposed females of the F_3 generation exhibited significant decreases (approximately 17-19 percent, $p<0.05$) in serum thyroxine (T_4). Decreased relative thyroid mass ($p<0.05$) was also observed in the last group. The same authors performed a one generational study with PCP in female sheep (Beard and Rawlings, 1999). Pregnant sheep were exposed to a single dose level of PCP at 1.0 mg/kg-day via the feed throughout gestation and lactation. The weaned female offspring were then exposed to the same concentration of PCP in their feed until the age of 67 weeks. The offspring had significantly reduced serum T_4 levels (approximately 30 percent) throughout, measured from age four weeks to study termination. In addition, the increase in serum T_4 induced by thyroid stimulating hormone (TSH) was significantly reduced in the PCP-exposed animals tested at 33 and 66 weeks of age. Thyroids of treated animals also had follicles of increased size compared to controls ($p<0.01$). These studies in mink and sheep suggest that chronic exposure to 1.0 mg/kg-day of PCP disrupts thyroid function. Considering these studies along with the subchronic studies by McConnell *et al.* (1980) in cattle and Jekat *et al.* (1994) in the rat, lower circulating levels of thyroid hormones occurred in four different mammalian species treated with PCP. Due to the important roles for thyroid hormones in directing mammalian development, the lower serum levels of circulating thyroid hormones induced by PCP have recently been used to set the Child-Specific Reference Dose (chRD) for school site risk assessment (OEHHA, 2006a).

The two year carcinogenicity study in F344/N rats also included data on noncarcinogenic endpoints (NTP, 1999), for which there was a NOAEL of 10 mg/kg-day based on decreased body weights and hepatocyte cystic degeneration at 20 mg/kg-day.

A multigenerational study in the Sprague-Dawley rat was performed by Bernard *et al.* (2002). Animals were dosed with PCP by oral gavage starting 70 days before mating, during gestation and lactation (F_1 generation) and repeating above for the F_2 generation. Systemic effects observed at the lowest dose tested (10 mg/kg-day) included hepatocellular hypertrophy and vacuolation in all adults and F_2 weanlings, increased kidney weight in males, and epididymal mononuclear cell infiltration in F_1 males. Reproductive effects had a NOAEL of 10 mg/kg-day and included decreased mean litter weights and bodyweights in F_1 pups.

The most recent chronic study of PCP in animals was performed in beagle dogs (U.S. EPA, 2004a). The dogs were dosed via capsule for 52 weeks. The lowest dose tested was the LOAEL: 1.5 mg/kg-day based on histopathological changes to hepatocytes including pigment accumulation, cytoplasmic vacuolation and centrilobular hypertrophy.

Carcinogenic Effects

This section evaluates the carcinogenicity data from animals and humans to determine which dataset would be most acceptable for calculation of upper-bound, individual excess lifetime cancer risks.

Animal Studies

The most useful animal study for determining a dose-response relationship and calculating a cancer potency factor is the NTP mouse study which is summarized in Tables 4 and 5, because of its high quality and good tumor dose-response. This study has been used by U.S. EPA (2004a) and by the California Department of Toxic Substances Control (DTSC) to derive cancer potency values for human risk evaluation (CDHS, 1989). The difference between the two estimates was based on the use of different subsets of the data. U.S. EPA combined data from all cancer types from both the tech-PCP and Dowicide EC-7 experiments, but only for female mice, for reasons explained previously. DTSC based its risk estimation on hepatocellular adenomas and carcinomas combined in male mice from the EC-7 experiment. Unlike U.S. EPA, DTSC used a body weight scaling factor without a power function to develop a human equivalent dose based on animal data.

U.S. EPA reviewed the NTP study and decided that it constitutes sufficient evidence for the carcinogenicity of PCP in animals, and that the data are suitable for human risk assessment. U.S. EPA calculated a cancer potency based on the geometric mean of the slope values for all tumor types produced in female mice by both tech-PCP and EC-7. The analysis was limited to female mice to place emphasis on the hemangiosarcomas which U.S. EPA determined were particularly relevant to potential human carcinogenicity, and because the male mice experienced significant early mortality in the bioassay. U.S. EPA used a scaling factor ($[70\ kg/0.03\ kg]^{1/3} = 13.2$) based on surface area to adjust from animal to human cancer potency.

DTSC estimated the carcinogenic potency of PCP based on combined hepatocellular adenoma and carcinoma data from male mice exposed to EC-7 grade PCP. DTSC adjusted the data for early mortality by eliminating from the analysis animals that died too early to be at risk for developing tumors. This adjustment did not significantly affect the final result. In another difference from U.S. EPA, DTSC used a body weight scaling factor without a power function to derive the cancer potency estimate. DTSC used the q1* to directly calculate a Maximum Exposure Level (MEL).

OEHHA recommends that a scaling factor of 6.95 ($[70\ kg/0.03\ kg]^{0.25}$) be used to calculate a human equivalent cancer potency. This updated methodology is based on U.S. EPA's current cancer risk assessment guidelines (U.S. EPA, 2005).

OEHHA proposes to base its risk assessment on hepatocellular adenoma and carcinoma data from male mice exposed to EC-7 because this data set represents the most significant positive trend. The identical approach was used in 1997 to develop the current PHG (OEHHA, 1997). Data from tech-PCP are not considered applicable because a significant portion of its carcinogenicity may be due to impurities, particularly dioxins

and furans. Data from female mice yield estimate safe levels for cancer risk that would be higher than those calculated from data for male mice (Table 4, final column). The data from the various tumor types in male mice (combined pheochromocytomas or hepatocellular adenoma and carcinoma) produce cancer potency estimates which are substantially similar. Hepatocellular adenomas and carcinomas are fairly common in male $B6C3F_1$ mice, whereas hemangiosarcomas and pheochromocytomas are not. The calculation of a proposed PHG based on these data is explained below.

Other oral cancer risk estimates have been made based on these same NTP mouse bioassay data. CDPR (1998) considered the hemangiosarcomas in females dosed with Dowicide EC-7 to be the most relevant tumors for human risk assessment. The U.S. EPA RED for PCP (2004a) utilized hepatocellular neoplasms, adrenal medullary neoplasms and hemangiosarcomas in female mice dosed with technical grade PCP or Dowicide EC-7 to calculate a human cancer potency estimate (q1*) of 7.0×10^{-2} $(mg/kg\text{-}day)^{-1}$.

Human Studies

Human data, when available, are preferable for estimating carcinogenic potency in humans, compared to extrapolating from animal data. However, when human data are lacking or inadequate, it is prudent and generally accepted practice in risk assessment to use animal data to estimate potential human cancer risk levels.

As described previously, there is suggestive but inadequate epidemiological evidence that exposure to PCP is related to some human cancers. These studies are not conclusive that PCP is a human carcinogen nor are they adequate to be used as the basis for a dose-response assessment. Therefore, it is appropriate to use animal data for estimating the carcinogenic potency of PCP to humans.

CALCULATION OF PHG

Noncarcinogenic Effects

A public health-protective drinking water concentration based on noncarcinogenic health effects can be calculated by choosing the most appropriate animal study or group of studies, and selecting a NOAEL or LOAEL to calculate a safe exposure level for humans. For PCP, the most sensitive effect was that of decreased serum thyroid hormones (OEHHA, 2006a) at 1.0 mg/kg-day in chronically treated sheep (Beard and Rawlings, 1999) and mink (Beard and Rawlings, 1998). Although we do not know the precise quantitative relationship between lower thyroid hormone levels and the resultant developmental effects in either these test animals or in humans, preventing the decreases should prevent the downstream developmental effects. Our risk assessment methodology is to divide the critical effect level (NOAEL or LOAEL) by uncertainty factors (UFs) representing the various extrapolations or sources of uncertainty to estimate a dose that would be unlikely to cause adverse effects in the human population or sensitive subpopulations with a lifetime of exposure, as follows:

$$ADD = \frac{NOAEL/LOAEL \text{ in mg/kg-day}}{UF}$$

where,

ADD = Acceptable Daily Dose, an estimate of the maximum daily dose which can be consumed by humans for an entire lifetime without toxic effects;

NOAEL/LOAEL = no-observed-adverse-effect level or lowest-observed-adverse-effect level in the critical study;

UF = uncertainty factors (defaults of 10 for uncertainty in extrapolating from a LOAEL to a NOAEL, from animals to humans, and for variability of the human population).

Calculation of a public health-protective concentration (C, in mg/L) for a chemical in drinking water uses the following equation for noncarcinogenic endpoints:

$$C = \frac{ADD \text{ mg/kg-day} \times RSC}{DWC}$$

where,

RSC = relative source contribution for exposure to the chemical from drinking water, compared to other sources;

DWC = daily water consumption in L/kg-day, upper 95 percent confidence limits (U.S. EPA, 2004b) of the most exposed or most susceptible subpopulations.

Lower levels of circulating thyroid hormones in response to PCP have the potential to disrupt important steps in human development. These thyroid hormone-sensitive steps occur primarily during gestation and early childhood. As recently concluded by OEHHA (2006a), the UFs of 10 each for LOAEL to NOAEL extrapolation, interspecies extrapolation, and variability among humans all apply in this case, yielding the following calculation:

$$ADD = \frac{1 \text{ mg/kg-day}}{1{,}000} = 0.001 \text{ mg/kg-day}$$

Because there are no remaining legal uses for PCP in California, exposures via drinking water are expected to be low. Nonetheless, the subpopulations predicted to be most sensitive to the effect of PCP on thyroid hormones are fetuses and infants. Pregnant women could also be at extra risk because of higher water consumption levels during pregnancy. Due to their highest rate of tap water consumption (through reconstituted

baby formula), formula-fed infants less than 6 months old will be the highest exposed group, and have an RSC of 1.0. For all other groups an RSC of 0.8 will be used.

Thus, for infants <6 months old, the calculation of a health-protective concentration (C, in mg/L) is as follows:

C = 0.001 mg/kg-day x 1.0 / 0.221 L/kg-day = 0.00452 mg/L = 5 ppb (rounded)

Similar calculations for other populations, including the potentially most susceptible subpopulations, are summarized in Table 7.

Table 7. Calculated Health-Protective Drinking Water Concentrations of PCP for Representative Exposed Groups, Including Potentially Sensitive Subpopulations:

Subpopulation	Daily tap water consumption (L/kg-day)[1]	RSC	UF	Health Protective Concentration (ppb)
Infants < 6 months old	0.221	1.0	1,000	5
Toddlers < 2 years old	0.137	0.80	1,000	6
Pregnant women and fetuses	0.043	0.80	1,000	19
Lactating women	0.055	0.80	1,000	15
General population (all ages)	0.044	0.80	1,000	18

[1] U.S. EPA (2004b), upper 95th percentile values for daily consumption of community water supplies

Therefore, as shown in Table 7, the lowest health-protective concentration is derived from the calculations for exposure of infants < 6 months old, or 5 ppb.

Carcinogenic Effects

Linearized Multi-Stage Model

As discussed previously, the data set chosen for calculation of the cancer potency is the hepatocellular adenoma and carcinoma endpoint in male mice administered Dowicide EC-7 in the NTP bioassay (NTP, 1989). This data set represents the most significant

positive trend, and results in a health-conservative estimate of cancer potency. The dose-response data from this experiment were entered in the GLOBAL 86 computer program (Howe *et al.*, 1986). The program calculated a 95 percent upper confidence limit on the slope of the linearized multistage dose-response curve, or q1*, (animal) of 1.2×10^{-2} $(mg/kg\text{-}day)^{-1}$. This is the same cancer potency calculated in the current PHG for PCP (OEHHA, 1997). The q1* (human) was calculated from the q1* (animal) based on the formula:

$$q1^*(\text{human}) = q1^*(\text{animal})\times[BW(\text{human})/BW(\text{animal})]^{1/4}$$

where,

BW (human) = an adult human body weight, assumed to be 70 kg;

BW (animal) = the body weight of mice, assumed to be 30 g for this study.

Therefore,

$$q1^*(\text{human}) = 1.2\times10^{-2}\ (mg/kg\text{-}day)^{-1} \times (70\ kg \div 0.03\ kg)^{1/4}$$
$$= 1.2\times10^{-2}\ (mg/kg\text{-}day)^{-1} \times 6.95$$
$$= 8.34\times10^{-2}\ (mg/kg\text{-}day)^{-1}$$

Using this q1* (human), a public health-protective concentration (C) for the carcinogenic endpoint can be calculated using the general equation:

$$C = \frac{R}{DWC\ \text{in L/kg-day} \times q1^*\ (mg/kg\text{-}day)^{-1}} = mg/L$$

where,

R = the *de minimis* lifetime excess individual cancer risk level of 10^{-6};

DWC = daily water consumption, upper 95 percent confidence limits (U.S. EPA, 2004b) for the general population (all ages), of 0.044 L/kg-day;

Therefore,

$$C = \frac{1 \times 10^{-6}}{0.044 \times 0.0834} = 2.73\times10^{-4}\ mg/L = 0.27\ ppb$$

A public health-protective concentration for PCP based on carcinogenicity using the human q1* is therefore calculated to be 0.27 ppb.

LED_{10} Model

Alternatively, a public health-protective concentration for PCP can be calculated as recommended by the U.S. EPA guidelines for carcinogen risk assessment (U.S. EPA, 2005) from the lower-bound on dose corresponding to the 95 percent confidence limit of the 10 percent cancer risk level (LED_{10}) calculated by Global86, Tox_Risk or similar programs, using a linear extrapolation through zero risk. This can be expressed as:

$$C = \frac{R}{DWC \times CSF}$$

where,

CSF = cancer slope factor $(mg/kg\text{-}day)^{-1}$, calculated as $0.1/LED_{10}$.

Therefore,

$$C = \frac{1\times10^{-6}}{0.044 \times 0.0811} = 2.80\times10^{-4}\ mg/L = 0.28\ ppb$$

A public health-protective concentration for PCP based on carcinogenicity using the LED_{10} is 0.28 ppb.

The upper-bound individual excess lifetime cancer risk estimates for public health-protective concentrations are comparable using the linearized multistage model or the LED_{10} model. Because of the uncertainty in these calculations, guidance values based on such calculations are usually rounded to one significant figure. The estimated public health-protective concentration of 5 ppb based on noncarcinogenic health effects is significantly greater than the values based on carcinogenicity. OEHHA therefore proposes a PHG for PCP in drinking water based on protection against carcinogenicity of 0.3 ppb (0.3 μg/L). The corresponding values at 10^{-5} and 10^{-4} risk are 3.0 and 30 ppb (μg/L), respectively.

RISK CHARACTERIZATION

The proposed PHG of 0.3 ppb is higher than the current U.S. EPA maximum contaminant level goal (MCLG) of zero, and lower than the California and U.S. EPA MCLs of 1 ppb (U.S. EPA, 1991; 2007b). The U.S. EPA MCL is based on a different subset (female instead of male mice) of the same carcinogenicity data on which the PHG is based, and a different scaling factor for the body weights. The MCLG was set at zero based on the assumption of a non-threshold mechanism for carcinogenicity in rodents (U.S. EPA, 1991).

The proposed PHG is slightly lower than the current PHG of 0.4 ppb, set in 1997 (OEHHA, 1997), because of a different method of calculating exposure to PCP. The new calculation uses an upper 95th percentile value for consumption of domestic water

supplies for the entire population, based on a U.S. EPA (2004b) assessment of data from the National Health and Nutrition Examination Survey (NHANES) and the Nationwide Food Consumption Survey (NFCS). This estimate and the resulting proposed PHG are judged to be protective for a lifetime of exposure for the entire population, including sensitive subpopulations.

There are several significant sources of uncertainty in determining potential human health risks for PCP in drinking water. The best available data come from animal studies. Extrapolating from animals to humans is always an uncertain process. For example, OEHHA is currently using a scaling factor of body weight ratio to the 1/4 power to extrapolate carcinogenic potency from animal to human, for consistency with other risk assessment agencies (U.S. EPA, U.S. FDA, CDPR). In the past OEHHA used body weight ratio to the 1/3 power to make this extrapolation. This results in an almost two-fold decrease in potency estimates when mice are used.

There is uncertainty owing to the impurities in the test materials. It is not certain whether the carcinogenicity is due to PCP, to the impurities, or to the combined action of both.

Another source of uncertainty is the choice of tumor data sets on which to base the PHG. Concentrations corresponding to upper bound cancer risk levels based on various tumor data sets are shown in Table 3. Of these, OEHHA used the data set of hepatocellular adenomas and carcinomas in male mice dosed with Dowicide EC-7. This data set yielded the most significant positive trend in statistical analysis. Other risk assessors, including U.S. EPA, have chosen to use other data sets.

For PHGs, our use of the relative source contribution (RSC) has, with a few exceptions, followed U.S. EPA drinking water risk assessment methodology. U.S. EPA has treated carcinogens differently from noncarcinogens with respect to the use of RSCs. For noncarcinogens, reference doses (RfDs, in mg/kg-day), drinking water equivalent levels (DWELs, in mg/L) and MCLGs (in mg/L) have been calculated using UFs, body weights and water consumption rates (L/day) and the RSC, respectively. The default RSC range is 20 percent to 80 percent (0.2 to 0.8) depending on the relative sources. OEHHA uses a value of 1.0 where it is clear from context that no other exposure sources are available, or where the risk assessment is specifically derived from human exposure through drinking water (e.g., fluoride, barium), as does U.S. EPA.

For approaches that use low-dose extrapolation based on quantitative risk assessment, U.S. EPA and OEHHA do not factor in an RSC. This is primarily because carcinogenic risks are calculated based on extra risk, i.e., the specific risk of exposure to the chemical in drinking water. The use of low-dose extrapolation is also considered by U.S. EPA to be adequately health-protective without the additional source contributions. This is an area of uncertainty and scientific debate, and it is not clear how this assumption impacts the overall health risk assessment.

There are other sources of uncertainty such as the potential for extra carcinogenic risk from early-in-life exposures to carcinogens. Both U.S. EPA and OEHHA are developing guidelines for incorporating this factor into cancer risk assessments. In lieu of such guidelines, the standard approach has been used for this risk assessment. The sources of uncertainty discussed here are common to all risk assessments for drinking water contaminants.

OTHER STANDARDS

U.S. EPA has set an MCLG of zero and an MCL of 1 ppb based on carcinogenicity in animals (U.S. EPA, 1991, 2007b). The California MCL for PCP is 1 ppb. U.S. EPA has also established drinking water health advisories for short-term exposures of 1.0 mg/L for one day and 0.3 mg/L for 10 days, based on noncarcinogenic liver effects in animals. An RfD of 0.03 mg/kg-day for PCP was developed by U.S. EPA based on a rat oral chronic study (Schwetz *et al.*, 1978) with kidney and liver pathology being the critical effects (U.S. EPA, 2007b).

On January 1, 1990, PCP was added to the California Proposition 65 list as a chemical known to cause cancer. The current No Significant Risk Level (NSRL) for PCP for purposes of compliance with Proposition 65 is 40 µg/day (OEHHA, 2006b). The child-specific reference dose (chRD) for PCP developed by OEHHA for school site risk assessment is 0.001 mg/kg-day (the same as our non-cancer value above), based on decreased circulating levels of thyroid hormones (OEHHA, 2006a).

Both the threshold limit value (TLV) and the permissible exposure limit (PEL), established by the American Conference of Governmental Industrial Hygienists (ACGIH) and the Occupational Safety and Health Administration (OSHA) respectively, are set at 0.5 mg/m^3. Both of these assume inhalation as the route of exposure.

Another thirty states have established MCLs for PCP in drinking water. All are at 1 ppb (ATSDR, 2001).

REFERENCES

ATSDR (1994). Toxicological Profile for Pentachlorophenol (Update). Agency for Toxic Substances and Disease Registry, U.S. Public Health Service.

ATSDR (2001). Toxicological Profile for Pentachlorophenol. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service. Accessed 5/07 at http://www.atsdr.cdc.gov/toxprofiles/tp51.html.

ATSDR (2004). Airborne Chemicals from Wood Treatment Chemical. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service. Accessed 5/07 at http://www.atsdr.cdc.gov/HAC/pha/MeredithCWilliam092904-GA/MeredithCWilliams092904HC-GA.pdf.

Ahlborg U, Lindgren J, Mercier M (1974). Metabolism of pentachlorophenol. Arch Toxicol 32:271-278.

Ahlborg U, Thunberg T (1980). Chlorinated phenols: occurrences, toxicity, metabolism and environmental impact. CRC Crit Rev Toxicol 7:1-35.

American Wood Preservers Institute (1977). Pentachlorophenol -- A Wood Preservative. Prepared by the Environmental Programs Task Group, Subcommittee No. 6, McLean, Virginia.

Armstrong R, Eichner E, Klein D, Barthel W, Bennett J, Jonsson V, Bruce H, Loveless L (1969). Pentachlorophenol poisoning in a nursery for newborn infants. II. Epidemiologic and toxicologic studies. J Pediat 75:317-325.

Baader E, Bauer H (1951). Industrial intoxication due to pentachlorophenol. Ind Med Surg 20:286-290.

Barnes J (1953). Toxic Hazards of Certain Pesticides to Man. In: Monograph Series No. 16, World Health Organization, Geneva, Switzerland.

Barstad A, Peyton D, Smejtek P (1993). AHA-heterodimer of a class-2 uncoupler: pentachlorophenol. Biochim Biophys Acta 1140:262-270.

Bauchinger M, Dresp J, Schmid E, Hauf R (1982). Chromosome changes in lymphocytes after occupational exposure to pentachlorophenol. Mutat Res 102:83-88.

Baxter R (1984). Biochemical study of pentachlorophenol workers. Ann Occup Hyg 28:429-438.

Beard A, Rawlings N (1998). Reproductive effects in mink (*mustela vison*) exposed to the pesticides lindane, carbofuran and pentachlorophenol in a multigeneration study. J Reprod Fertil 113:95-104.

Beard A, Rawlings N (1999). Thyroid function and effects on reproduction in ewes exposed to the organochlorine pesticides lindane or pentachlorophenol (PCP) from conception. J Toxicol Environ Health, Part A 58:509-530.

Begley J, Teichert E, Rashad M, Klemmer H, Siemsen A (1977). Association between renal function tests and pentachlorophenol exposure. Clin Toxicol 11:97-106.

Bergner H, Constantinidis P, Martin J (1965). Industrial pentachlorophenol poisoning in Winnipeg. Can Med Assoc J 92:448-451.

Bernard B, Hoberman A (2001). A study of the developmental toxicity potential of pentachlorophenol in the rat. Int J Toxicol 20:353-362.

Bernard B, Ranpuria A, Hoberman A (2001). Developmental toxicity study of pentachlorophenol in the rabbit. Int J Toxicol 20:345-352.

Bernard B, Hoberman A, Brown W, Ranpuria A, Christian M (2002). Oral (gavage) two-generation (one litter per generation) reproduction study of pentachlorophenol (penta) in rats. Int J Toxicol 21:301-318.

Bevenue A, Haley J, Klemmer H (1967). A note on the effects of a temporary exposure of an individual to pentachlorophenol. Bull Environ Contam Toxicol 2:293-296.

Bishop C, Jones A (1981). Non-Hodgkin's lymphoma of the scalp in workers exposed to dioxins. Lancet 2:369.

Blakley B, Yole M, Brousseau P, Boermans H, Fournier M (1998). Effect of pentachlorophenol on immune function. Toxicology 125:141-148.

Blevins D (1965). Pentachlorophenol poisoning in swine. Vet Med Small Anim Clin 60:455.

Borzelleca J, Condie L, Hayes J (1984). Toxicological evaluation of selected chlorinated phenols. U.S. Environmental Protection Agency, Washington, D.C, pp. 1-19.

Boyle T, Robinson-Wilson E, Petty B, Weber W (1980). Degradation of PCP in simulated lentic environments. Bull Environ Contam Toxicol 24:177-184.

Brandt M, Schmidt E, Schmidt F (1977). Chronische lebererkrarkurg durch langjahrige intoxikation in haushalt mit PCP. Verh Dtsch Ges Inn Med 83:1609.

Braun W, Sauerhoff M (1976). The pharmacokinetic profile of pentachlorophenol in monkeys. Toxicol Appl Pharmacol 38:525-533.

Braun W, Young J, Blau G, Gehring P (1977). The pharmacokinetics and metabolism of pentachlorophenol in rats. Toxicol Appl Pharmacol 41:395-406.

Braun W, Blau G, Chenoweth M (1979). The metabolism/pharmacokinetics of pentachlorophenol in man, and a comparison with the rat and monkey. Proc Tenth Inter-American Conference on Toxicology and Occupational Medicine, Oct. 22-25, 1978. Elsevier, pp. 289-296.

Campbell A (1952). Neurological complications associated with insecticides and fungicides. Br Med J 23:415.

CDHS (1989). Carcinogenic risk assessment of pentachlorophenol. Toxic Substances Control Division (now the Department of Toxic Substances Control of the California Environmental Protection Agency). Sacramento, CA.

CDPR (1998). Pentachlorophenol Risk Characterization Document, California Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. Accessed 5/07 at http://www.cdpr.ca.gov/docs/risk/rcd.htm.

Chapman J, Robson P (1965). Pentachlorophenol poisoning from bathwater. Lancet 1:1266-1267.

Chemical Marketing Reporter (1987). "Biocide ranks thin as costs multiply."

Chhabra R, Maronpot R, Bucher J, Haseman J, Toft J, Hejtmancik M (1999). Toxicology and carcinogenesis studies of pentachlorophenol in rats. Toxicol Sci 48:14-20.

Chou K, Cook R (1979). The effects of pentachlorophenol on fetal and postpartum development in the rat. Fed Proc 38:868, abstract # 3371.

Cirelli D (1978). Pentachlorophenol. Special Pesticide Review Division, U.S. Environmental Protection Agency, Washington, D.C. PB81-109464.

Cole G, Stone D, Gattes D, Culver D (1986). Pentachlorophenol-preserved wood. Contact Derm 15:164-168.

Collins J, Budinsky R, Burns C, Lamparski L, Carson M, Martin G, Wilken M (2006). Serum dioxin levels in former chlorophenol workers. J Exp Sci Environ Epidemiol 16:76-84.

Colosio C, Maroni M, Barcellini W, Meroni P, Alcini D, Foa A (1993). Toxicological and immune findings in workers exposed to pentachlorophenol (PCP). Arch Environ Health 48:81-88.

Cooper R, Macaulay M (1982). Pentachlorophenol pancreatitis. Lancet 1:517.

Courtney K, Copeland M, Robbins A (1976). The effects of pentachloronitrobenzene, hexachlorobenzene, and related compounds on fetal development. Toxicol Appl Pharmacol 35:239-256.

Dahlhaus M, Almstadt E, Appel K (1994). The pentachlorophenol metabolite tetrachloro-p-hydroquinone induces the formation of 8-hydroxy-2-deoxyguanosine in liver DNA of male $B6C3F_1$ mice. Tox Letters 74:265-274.

Daniel V, Huber W, Bauer K, Suesal C, Mytilineos J, Melk A, Conradt C, Opelz G (2001). Association of elevated blood levels of pentachlorophenol (PCP) with cellular and humoral immunodeficiencies. Arch Environ Health 56:77-83.

Danzo B, Shappell H, Banerjee A, Hachey D (2002). Effects of nonylphenol, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE), and pentachlorophenol on the adult female guinea pig reproductive tract. Reprod Toxicol 16:29-43.

Deichmann W, Machle W, Kitzmiller K, Thomas G (1942). Acute and chronic effects of pentachlorophenol and sodium pentachlorophenate upon experimental animals. J Pharmacol Exp Ther 76:104-117.

Demers P, Davies H, Friesen M, Hertzman C, Ostry A, Hershler R, Teschke K (2006). Cancer and occupational exposure to pentachlorophenol and tetrachlorophenol (Canada). Cancer Causes Control 17:749-758.

Demidenko NM (1969). Materials for substantiation of maximally permissible concentration of pentachlorophenol in the atmosphere. Gig Trud Prof Zabol 13:58-60.

Dimich-Ward H, Hertzman C, Teschke K, Hershler R, Marion S, Ostry A, Kelly S (1996). Reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry. Scand J Work Environ Health 22:267-73.

Dow Chemical Company (1969). Toxicity summary for Dowicide 7. Report of the ad hoc study group on pentachlorophenol contaminants.

Ehrlich W (1990). The effect of pentachlorophenol and its metabolite tetrachlorohydroquinone on cell growth and the induction of DNA damage in Chinese Hamster Ovary cells. Mutat Res 244:299-302.

Eriksson M, Hardell L, Berg N, Moller T, Axelson O (1981). Soft-tissue sarcomas and exposure to chemical substances: a case referent study. Br J Indust Med 38:27-33.

Exon J, Koller L (1982). Effects of transplacental exposure of chlorinated phenols. Environ Health Perspect 46:137-140.

Fahrig R, Nilsson C, Rappe C (1978). Genetic activity of chlorophenols and chlorophenol impurities, in pentachlorophenol: Chemistry, pharmacology and environmental toxicology. Edited by KR Rao, Plenum Press, New York and London, pp. 325-338.

Fleischer M, Meib R, Robenek H, Themann H, Eckard R (1980). Ultrastructural morphometric investigations on rat liver of young and adult rats after treatment with technical pentachlorophenol (PCP). Arch Toxicol 44:243-257.

Freiter E (1979). Chlorophenols. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed, Vol 5, Edited by M Grayson, John Wiley and Sons, N.Y. pp. 864-872.

Gerhard I, Daniel V, Link S, Monga B, Runnebaum B (1998). Chlorinated hydrocarbons in women with repeated miscarriages. Environ Health Perspect 106:675-681.

Gerhard I, Frick A, Monga B, Runnebaum B (1999). Pentachlorophenol exposure in women with gynecological and endocrine dysfunction. Environ Res Sec A 80:383-388.

Gilbert F, Minn C, Duncan R, Wilkinson J (1990). Effects of pentachlorophenol and other chemical preservatives on the health of wood-treating workers in Hawaii. Arch Environ Contam Toxicol 19(4):603-609.

Goldstein J, Friesen M, Linder R, Hickman P, Hass J, Bergman H (1977). Effects of pentachlorophenol on hepatic drug-metabolizing enzymes and porphyrin related to contamination with chlorinated dibenzo-p-dioxins and dibenzofurans. Biochem Pharmacol 26:1549-1557.

Gordon D (1956). How dangerous is pentachlorophenol? Med J Aust 2:485-488.

Gorski T, Konopka L, Brodzki M (1984). Persistence of some polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans of pentachlorophenol in human adipose tissues. Roczn Pzh 35:298-301.

Gray R, Gilliland R, Smith E, Lockard V, Hume A (1985). Pentachlorophenol intoxication: report of a fatal case. Arch Environ Health 40:161-164.

Greene M, Brinton L, Fraumeni J, D'Amico R (1978). Familial and sporadic Hodgkin's disease associated with occupational wood exposure. Lancet 2:626-627.

Greichus Y, Libal G, Johnson D (1979). Diagnosis and physiologic effects of pentachlorophenols on young pigs. Bull Environ Contam Toxicol 23:418-422.

Hardell L, Sandstrom A (1979). Case-control study: soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Br J Cancer 39:711-717.

Hardell L (1981). Relation to soft-tissue sarcoma, malignant lymphoma and colon cancer to phenoxy acids, chlorophenols and other agents. Scand J Work Environ Health 7:119-130.

Hardell L, Eriksson M, Lenner P, Lundgren E (1981). Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. Br J Cancer 43:169-176.

Hardell L, Johansson B, Axelson O (1982). Epidemiological study of nasal and nasalpharyngeal cancer and their relation to phenoxy acid or chlorophenol exposure. Am J Ind Med 3:247-257.

Hardell L, Bengtsson NO, Jonsson U, Eriksson S, Larsson LG (1984). Aetiological aspects of primary liver cancer with special regard to alcohol, organic solvents and acute intermittent porphyria - an epidemiological investigation. Br J Cancer 50:389-397.

Hassan A, Seligmann H, Bassan H (1985). Intravascular haemolysis induced by pentachlorophenol. Br Med J 291:21-22.

Hattula M, Knuutinen J (1985). Mutagenesis of mammalian cells in culture by chlorophenols, chlorocatechols and chloroguiacols. Chemosphere 14:1617-1625.

Hernberg S, Westerholm P, Schultz-Larsen K, Degerth R, Kuosma E, Englund A, Engzell U, Hansen H, Mutanen P (1983). Nasal and sinonasal cancer, connection with occupational exposures in Denmark, Finland and Sweden. Scand J Work Environ Health 9:315-326.

Hillam R, Greichus Y (1983). Effects of purified pentachlorophenol on the serum proteins of young pigs. Bull Environ Contam Toxicol 31:599-604.

Hinkle D (1973). Fetotoxic effects of pentachlorophenol in the golden Syrian hamster. Toxicol Appl Pharmacol 25:Abstract # 42.

Holsapple M, McNerney P, McCay J (1987). Effects of pentachlorophenol on the in vitro and in vivo antibody response. Toxicol Environ Health 20:229-239.

Howe R, Crump K, Van Landingham C (1986). GLOBAL 86 - A computer program to extrapolate quantal animal toxicity data to low doses. Clement Assoc, Inc, Ruston, LA.

Hryhorczuk DO, Wallace WH, Persky V, Furner S, Webster JR, Oleske D, Haselhorst B, Ellefson R, Zugerman C (1998). A morbidity study of former pentachlorophenol-production workers. Environ Health Perspect 106:401-408.

Hsieh D (1990). Health risk assessment of pentachlorophenol (PCP) in California drinking water. Prepared according to Interagency Master Agreement 87-87088 between the Regents of the University of California, Davis and the State of California, Department of Health Services, Berkeley.

Hughes B, Forsell J, Sleight S, Kuo C, Shull L (1985). Assessment of pentachlorophenol toxicity in newborn calves. J Anim Sci 61:1587-1603.

IARC (1979). Pentachlorophenol. In: Monographs on the evaluation of the carcinogenic risk of chemicals to humans. International Agency for Research on Cancer 20:303-325.

IARC (1991). Pentachlorophenol. In: Monographs on the evaluation of the carcinogenic risk of chemicals to humans. International Agency for Research on Cancer 53:371-394.

Igarashi A, Ohtsu S, Muroi M, Tanamoto K (2006). Effects of possible endocrine disrupting chemicals on bacterial component-induced activation of NF-kB. Biol Pharm Bull 29:2120-2122.

Jakobson I, Yllner S (1971). Metabolism of 14C-pentachlorophenol in the mouse. Acta Pharmacol Toxicol 29:513-524.

Jansson K, Jansson V (1991). Induction of mutation in V79 Chinese hamster cells by tetrachlorohydroquinone, a metabolite of pentachlorophenol. Mutat Res 260:83-87.

Jansson K, Jansson V (1992). Induction of micronuclei in V79 Chinese hamster cells by tetrachlorohydroquinone, a metabolite of pentachlorophenol. Mutat Res 279:205-208.

Jekat F, Meisel M, Eckard R, Winterhoff H (1994). Effects of pentachlorophenol (PCP) on the pituitary and thyroidal hormone regulation in the rat. Toxicol Lett 71:9-25.

Johnson R, Gehring P, Kociba R, Schwetz B (1973). Chlorinated dibenzodioxins and pentachlorophenol. Environ Health Perspect 5:171-175.

Jung J, Ishida K, Nishihara T (2004). Anti-estrogenic activity of fifty chemicals evaluated by in vitro assays. Life Sci 74:3065-3074.

Kentor P (1986). Urticaria from contact with pentachlorophenate. J Am Med Assoc 256:3350.

Kerkvliet N, Baecher-Steppan L, Schmitz J (1982). Immunotoxicity of pentachlorophenol. Toxicol Appl Pharmacol 62:55-64.

Kimbrough R, Linder R (1978). The effect of technical and purified pentachlorophenol on the rat liver. Toxicol Appl Pharmacol 46:151-162.

Kinzell J, Ames N, Sleight S, Krehbiel J, Kuo C, Zabik M, Shull L (1981). Subchronic administration of technical pentachlorophenol to lactating dairy cattle. J Dairy Sci 64:42-51.

Kleinman G, Horstman S, Kalman D, McKenzie J, Stansel D (1986). Industrial hygiene, chemical and biological assessments of exposures to a chlorinated phenolic sapstain control agent. Am Ind Hyg Assoc J 47:731-741.

Klemmer H, Wong L, Sato M, Reichert E, Korsak R, Rashad M (1980). Clinical findings in workers exposed to pentachlorophenol. Arch Environ Contam Toxicol 9:715-725.

Knudsen I, Verschueren H, Den Tonkelaar E, Kroes R, Helleman P (1974). Short-term toxicology of pentachlorophenol in rats. Toxicology 2:141-152.

Lambert J, Schepens P, Janssens J, Docky P (1986). Skin lesions as a sign of subacute pentachlorophenol intoxication. Acta Derm Venereol 66:170-172.

Larsen R, Born G, Kessler W, Shaw S, Van Sickle D (1975). Placental transfer and teratology of pentachlorophenol in rats. Environ Lett 10:121-128.

Larsen R, Kirsch L, Shaw S, Christian J, Born G (1972). Excretion and tissue distribution of uniformly labelled ^{14}C-pentachlorophenol in rats. J Pharm Sci 61:2004-2006.

Lawlor T, Haworth S. (1979). Evaluation of genetic activity of nine chlorinated phenols, seven chlorinated benzenes and three chlorinated hexanes. Environ Mutagen 1:143.

Legator M, Bueding E, Batzinger R, Connor T, Eisenstadt E, Farrow M, Ficsor G, Hsie A, Seed J, Stafford R (1982). An evaluation of the host-mediated assay and body fluid analysis. Mut Res 98:319-374.

Lemaire G, Mnif W, Mauvais P, Balaguer P, Rahmani R (2006). Activation of α- and β-estrogen receptors by persistent pesticides in reporter cell lines. Life Sci 79:1160-1169.

Levin J, Rappe C, Nilsson C (1976). Use of chlorophenols as fungicides in sawmills. Scand J Work Environ Health 2:71-81.

Liu D, Thomson K, Strachan W (1981). Biodegradation of pentachlorophenol in a simulated aquatic environment. Bull Environ Contam Toxicol 26:85-90.

Louwagie A, Cosyn L, Callewaert J (1978). Coexistence of morbus Hodgkin and aplastic anaemia. Acta Clin Belg 33:66-68.

Mason M, Wallace S, Foerster E, Drummond W (1965). Pentachlorophenol poisoning: report of two cases. J Foren Sci 10:136-147.

Mattern I (1975). Mutagenicity testing of some nitrofuran derivatives and some chlorinated hydrocarbons. Bescherming tegen straling en chemische mutagentia 22:1-10.

McConnell E, Moore J, Gupta B, Rakes A, Luster M, Goldstein J, Haseman J, Parker C (1980). The chronic toxicity of technical and analytical pentachlorophenol in cattle. I. Clinicopathology. Toxicol Appl Pharmacol 52:468-490.

McGavack T, Boyd L, Piccione F, Terranova R (1941). Acute and chronic intoxications with sodium pentachlorophenate in rabbits. J Ind Hyg Toxicol 23:239-251.

Mehmood Z, Williamson M, Kelly D, Kelly S (1996). Metabolism of organochlorine pesticides: the role of human cytochrome P450 3A4. Chemosphere 33:759-769.

Menon JA (1958). Tropical hazards associated with the use of pentachlorophenol. Br Med J 1(5080):1156-1158.

Morville S, Scheyer A, Mirabel P, Millet M (2006). Spatial and geographical variations of urban, suburban and rural atmospheric concentrations of phenols and nitrophenols. Environ Sci Pollut Res 13:83-89.

Nishimura H, Nishimura N, Oshima H (1982). Effects of pentachlorophenol on the levels of hepatic glycogen. Japan J Indust Health 24:398-399.

NTP (1989). Toxicology and carcinogenesis studies of two pentachlorophenol technical-grade mixtures in B6C3F$_1$ mice. National Toxicology Program, U.S. Department of Health and Human Services, Research Triangle Park, N.C. NTP TR 349, NIH No. 88-2804.

NTP (1999). Toxicology and carcinogenesis studies of pentachlorophenol in F344/N rats. National Toxicology Program, U.S. Department of Health and Human Services, Research Triangle Park, N.C. NTP TR 483, NIH No. 99-3973.

OEHHA (1997). Public Health Goal for Pentachlorophenol in Drinking Water. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Berkeley and Sacramento, CA.

OEHHA (2006a). Child-specific reference doses (chRDs) for school site risk assessment, manganese and pentachlorophenol. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA, June 2006.

OEHHA (2006b). Proposition 65 Safe Harbor Levels: No significant risk levels for carcinogens and maximum allowable dose levels for chemicals causing reproductive toxicity. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland and Sacramento, August 2006.

Olsen J, Jensen O (1984). Nasal cancer and chlorophenols. Lancet 2:47-48.

Pearce N, Smith A, Howard J, Sheppard R, Giles H, Teague C (1986). Case control study of multiple myeloma and farming. Br J Cancer 54:493-500.

Proudfoot A (2003). Pentachlorophenol poisoning. Toxicol Rev 22:3-11.

Renner G, Hopfer C (1990). Metabolic studies on pentachlorophenol (PCP) in rats. Xenobiotica 20:573-582.

Roberts H (1963). Aplastic anemia due to pentachlorophenol and tetrachlorophenol. South Med J 56:632-635.

Roberts H (1981). Aplastic anemia due to pentachlorophenol. New Engl J Med 305:1650-1651.

Roberts H (1983). Aplastic anemia and red cell aplasia due to pentachlorophenol. South Med J 76:45-47.

Robson A, Kissane J, Elvick N, Pundavela L (1969). Pentachlorophenol poisoning in a nursery for newborn infants. I. Clinical features and treatment. J Pediat 75:309-316.

Sangster B, Wegman R, Hofstee A (1982). Non-occupational exposures to pentachlorophenol: Clinical findings and plasma PCP concentrations in three families. Hum Toxicol 1:123-133.

Schipper I. (1961). Toxicity of wood preservatives for swine. Am J Vet Res 22:401-405.

Schmid E, Bauchinger M, Dresp J (1982). Chromosome analyses of workers from a pentachlorophenol plant. In: Mutagens in our Environment. Proc 12th Ann Meeting, European Environmental Mutagen Society. Edited by M Sorsa and H Vaino. Alan R. Liss, Inc, New York, pp. 471-477.

Schmid J, Kiely J, Pease G, Hargraves M (1963). Acquired pure red cell agenesis. Acta Haemat 30:225-270.

Schwetz B, Keeler P, Gehring P (1974). The effect of purified and commercial grades of pentachlorophenol on rat embryonal and fetal development. Toxicol Appl Pharmacol 28:151-161.

Schwetz B, Quest J, Keeler P, Humiston C, Kociba R (1978). Results of two-year toxicity and reproduction studies on pentachlorophenol in rats. In: Pentachlorophenol Chemistry, Pharmacology and Environmental Toxicology. Edited by KR Rao, Plenum Press, New York and London, pp. 301-309.

Scow K, Goyer M, Payne E, Perwak J, Thomas R, Wallace D, Walker P, Wood M, *et al.* (1980). An exposure and risk assessment for pentachlorophenol. Office of Water Regulations and Standards, Monitoring and Data Support Division, U.S. Environmental Protection Agency, Washington, D.C. EPA/440/4-81-021, PB#85-211944.

Simmon V, Kauhanen K, Tardiff R (1977). Mutagenic activity of chemicals identified in drinking water. In: Progress in Genetic Toxicology: Proc 2nd Internat Conf on Environ Sci. Elsevier, Amsterdam, pp. 249-258.

Smith A, Pearce N, Fisher D, Giles H, *et al.* (1984). Soft-tissue sarcoma and exposure to phenoxyherbicides and chlorophenols in New Zealand. J Natl Can Inst 73:1111-1117.

Spencer G (1957). Poisoning of cattle by pentachlorophenol in kerosene. J Am Vet Med Assoc 130:299-300.

St. Omer V, Gadusek F (1987). The acute oral LD_{50} of technical pentachlorophenol in developing rats. Environ Toxicol Chem 6:147-149.

Stedman T, Booth N, Bush P, Page R, Goetsch D (1980). Toxicity and bioaccumulation of pentachlorophenol in broiler chickens. Poult Sci 59:1018-1026.

Stevens H, Richardson A (1979). The rapid screening of body tissues for pentachlorophenol with special reference to a poisoning fatality. J Foren Sci Soc 19:125-129.

Sun H, Xu L, Chen J, Song L, Wang X (2006). Effect of bisphenol A, tetrachlorobisphenol A and pentachlorophenol on the transcriptional activities of androgen receptor-mediated reporter gene. Food Chem Toxicol 44:1916-1921.

Taylor T, Tucker T, Whalen M (2005). Persistent inhibition of human natural killer cell function by Ziram and pentachlorophenol. Environ Toxicol 20:418-424.

Terasaka S, Inoue A, Tanji M, Kiyama R (2006). Expression profiling of estrogen-responsive genes in breast cancer cells treated with alkylphenols, chlorinated phenols, parabens, or bis- and benzoylphenols for evaluation of estrogenic activity. Toxicol Lett 163:130-141.

Townsend J, Bodner K, Van Peenen P, Olson R, Cook R (1982). Survey of reproductive events of wives of employees exposed to chlorinated dioxins. Am J Epidemiol 115:695-713.

Triebig G, Krekeler H, Gossler K, Valentin H (1981). Investigations of neurotoxicity of chemical substances at the workplace, II. Int Arch Occup Environ Health 41:357-367.

Truhaut R, Epee P, Boussemart E (1952). Recherches sur la toxicologie du pentachlorophenol, II. Arch de Maladies Prof 13:567.

Uede K, Nagai M, Osafune M (1962). Contamination of drinking water with pentachlorophenol. Osaka Sheritsu Eisei Kenkyo-Sho Kenleyu Hokoku 7:19.

Uhl S, Schmid P, Schlatter C (1986). Pharmacokinetics of pentachlorophenol in man. Arch Toxicol 58:182-186.

Umezaki K, Ikegami S, Ichikawa T (1993). Effects of restricted feeding on the absorption, metabolism and accumulation of pentachlorobenzene in rats. J Nutr Sci Vitaminol 39:11-22.

U.S. EPA (1985). Drinking water criteria document for pentachlorophenol. Environmental Criteria and Assessment Office for the Office of Drinking Water, U.S. Environmental Protection Agency, Washington, D.C, EPA 600/X-84-177-1, PB86-118015.

U.S. EPA (1991). Maximum contaminant level for pentachlorophenol. U.S. Environmental Protection Agency, Washington, D.C. Fed Reg 3600 (01/30/91), 56 FR 3526 (01/30/91), 56 FR 30266 (07/01/91).

U.S. EPA (2004a). Reregistration Eligibility Decision for Pentachlorophenol. U.S. Environmental Protection Agency, Washington, D.C. Docket ID No. EPA-HQ-OPP-2004-0402.

U.S. EPA (2004b). Estimated per capita water ingestion and body weight in the United States-an update. U.S. Environmental Protection Agency, Washington, D.C. EPA-822-R-00-001.

U.S. EPA (2005). Guidelines for carcinogen risk assessment. U.S. Environmental Protection Agency, Washington, D.C. EPA/630/P-03/001F. Accessed at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283.

U.S. EPA (2007a). Pentachlorophenol and its use as a wood preservative. U.S. Environmental Protection Agency, Washington, D.C. Accessed at: http://www.epa.gov/pesticides/factsheets/chemicals/pentachlorophenol_main.htm.

U.S. EPA (2007b). Pentachlorophenol (last updated 7/01/1993). Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Washington, D.C. Accessed 6/07 at http://www.epa.gov/iris/subst/0086.htm.

Vogel E, Chandler J (1974). Mutagenicity testing of cyclamate and some pesticides in Drosophila melanogaster. Experientia 30:621-623.

Wainstok de Calmanovici R, San Martin de Viale L (1980). Effect of chlorophenols on porphyrin metabolism in rats and chick embryo. Int J Biochem 12:1039-1044.

Walls C, Glass W, Pearce N (1998). Health effects of occupational pentachlorophenol exposure in timber sawmill employees: a preliminary study. N Z Med J 111:362-364.

Waters M, Sandhu S, Simmon V, *et al.* (1982). Study of pesticide genotoxicity. In: Genetic Toxicology, edited by RA Fleck and A Hollaender, Plenum Press, New York and London, pp. 275-326.

Welsh J, Collins T, Black J, Graham S, O'Donnell M (1987). Teratogenic potential of purified pentachlorophenol and pentachloroanisole in subchronically exposed Sprague-Dawley rats. Food Chem Toxicol 25:163-172.

Williams P (1982). Pentachlorophenol, an assessment of the occupational hazard. Am Ind Hyg Assoc J 43:799-810.

Wong A, Crosby D (1978). Photolysis of pentachlorophenol in water. In: Pentachlorophenol Chemistry, Pharmacology, and Environmental Toxicology, edited by KR Rao. Plenum Press, New York, pp. 19-25.

Wood S, Rom W, White G, Logan D (1983). Pentachlorophenol poisoning. J Occup Med 25:527-530.

Wyllie J, Gabica J, Benson W, Yoder J (1975). Exposure and contamination of the air and employees of a pentachlorophenol plant, Idaho, 1972. Pest Monit J 9:150-153.

Zhao B, Yang J, Liu Z, Xu Z, Qiu Y, Sheng G (2006). Joint anti-estrogenic effects of PCP and TCDD in primary cultures of juvenile goldfish hepatocytes using vitellogenin as a biomarker. Chemosphere 65:359-364.

Zober A, Schaller K, Gossler K, Krekeler H (1981). Pentachlorophenol and liver function. Int Arch Occup Environ Health 48:347-356.