US EPA TOXICOLOGICAL REVIEW

OF

PENTACHLOROPHENOL
(CAS No. 87-86-5)

In Support of Summary Information on the
Integrated Risk Information System (IRIS)

October 16, 2000

Notice

This document is a **preliminary draft.** It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency position on this chemical. It is being circulated for peer review on its technical accuracy and science policy implications.

U.S. Environmental Protection Agency
Washington, D.C.

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These documents are provided for public viewing during an external scientific peer review period. While EPA is not soliciting public comments by this action, any scientific views received on the content of the Toxicological Review or IRIS Summary prior to June 30, 2001 will be considered in subsequent drafts. Please direct any correspondence to: Dr. Timothy F. McMahon, USEPA, Ariel Rios Building, 1200 Pennsylvania Avenue, Mail Code 7510C, Washington D.C. 20460-0001. Please also send a record keeping copy to:

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FOREWORD

The purpose of this toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to chronic exposure to pentachlorophenol . It is not intended to be a comprehensive treatise on the chemical or toxicological nature of pentachlorophenol.

In Section 6, EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose response. Matters considered in this characterization include knowledge gaps, uncertainties, quality of data, and scientific controversies. This characterization is presented in an effort to make apparent the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment of other questions relating to IRIS, the reader is referred to EPA's Risk Information Hotline at 513-569-7254.

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Reviewers

This document and summary information on IRIS have received peer review both by EPA scientist and by independent scientists external to EPA. Subsequent to external review and incorporation of comments, this assessment has undergone an Agency-wide review process whereby the IRIS Program Manager has achieved a consensus approval among the Office of Research and Development; Office of Air and Radiation; Office of Prevention, Pesticides, and Toxic Substances; Office of Solid Waste and Emergency Response; Office of Water; Office of Policy, Planning, and Evaluation, and the Regional Offices.

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Summaries of the external peer reviewer's comments and the disposition of their recommendations are in Appendix A.

1. INTRODUCTION

This document presents background and justification for the hazard and dose-response assessment summaries in EPA's Integrated Risk Information System (IRIS). IRIS summaries may include an oral reference dose (RfD), inhalation reference concentration (RfC) and a carcinogenicity assessment.

The RfD and RfC provide quantitative information for noncancer dose-response assessments. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis but may not exist for other toxic effects such as some carcinogenic responses. It is expressed in units of mg/kg/day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. The inhalation RfC is analogous to the oral RfD, but provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or system effects). It is generally expressed in units of mg/m^3.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral exposure and inhalation exposure. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates are presented in three ways. The *slope factor* is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The *unit risk* is the quantitative estimate in terms of either risk per µg/L drinking water or risk per $µg/m^3$ air breathed. Another form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

Development of these hazard identification and dose-response assessments for pentachlorophenol has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA guidelines that were used in the development of this assessment may include the following: the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA,1986a), *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986c), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), *Proposed Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1995a), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998b), *Proposed Guidelines for Carcinogen Risk Assessment* (1996a), and *Reproductive Toxicity Risk Assessment Guidelines* (U.S. EPA, 1996b); *Recommendations for and Documentation of Biological Values or Use in Risk Assessment* (U.S. EPA, 1988); (proposed) *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a); *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA,1994b); *Peer Review and Peer Involvement at the U.S. Environmental Protection Agency* (U.S. EPA, 1994c); *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA,1995c); *Science Policy Council Handbook: Peer Review* (U.S. EPA, 1998b); and memorandum from EPA Administrator, Carol Browner, dated March 21, 1995, Subject: Guidance on Risk Characterization (U.S. EPA, 1995a).

2. CHEMICAL AND PHYSICAL INFORMATION RELEVANT TO ASSESSMENTS

The physical/chemical properties of Pentachlorophenol (PCP) are summarized in Table 1. PCP exists in a solid crystalline state, colorless, white, brown or tan in color. It has very limited solubility in water, but is readily soluble in alcohol (Budavari et al., 1996). PCP has a phenolic odor that is very pungent when heated. Purity of technical grade PCP generally ranges from 86-90%, and impurities found in technical grade PCP consist of several congeners of the chlorinated dibenzodioxins , chlorinated dibenzofurans, and chlorophenols. Of the chlorinated dibenzodioxin and dibenzofuran contaminants, it is predominantly the higher chlorinated congeners that are found as impurities within technical grade PCP. The physicochemical properties of these contaminants are listed in Tables 2a and 2b. In addition to the dibenzodioxin and dibenzofuran contaminants, hexachlorobenzene and chlorophenoxy constituents are also be present in technical grade PCP. The composition of different grades of PCP as found in the general literature and as reported by IARC and NTP are listed in Table 3. Grades described as analytical or pure are generally ≥98% PCP; the levels of dioxins and furans are low to non-detectable. Hughes et al. (1985) reported that commercial technical grade PCP contain 85–90% PCP, 10–15% trichlorophenol and tetrachlorophenol, and <1% chlorinated dibenzodioxin, chlorinated dibenzofurans, and chlorinated diphenyl ethers.

Table 1. Physicochemical Data For Pentachlorophenol

Parameter	Value	Reference
Synonyms	Dowicide 7, Dowicide EC-7, PCP, Penta, Penchlorol	HSDB, 1999; RTECS, 1999; Budavari et al., 1996
CAS registry no.	87-86-51	RTECS, 1999
Chemical formula	C_6HCl_5O	Budavari et al., 1996
Molecular weight	266.34	Budavari et al., 1996
Physical state	White monoclinic crystalline solid, crystals, colorless crystals, needle-like crystals; dark gray to brown (technical grade)	Allan, 1994; Roy. Soc. Chem., 1992; Budavari et al., 1996
Odor	Phenolic, very pungent only when hot	Roy. Soc. Chem., 1992; Budavari et al., 1996
Density	1.978 @ 22°C/4°C	Budavari et al., 1996
Vapor pressure at 20°C	0.00011 @ 20°C	Allan, 1994
Vapor density	9.20 (air = 1)	HSDB, 1999
Melting point	190-191°C	Budavari et al., 1996
Boiling point	~309-310°C	Budavari et al., 1996
Solubility in water	80 mg/L @ 20°C 14 mg/L @ 26.7°C	Roy. Soc. Chem., 1992 HSDB, 1999
Partition Coefficients Log K_{OW} Log K_{OC}	 5.01 4.5	 HSDB, 1999, ATSDR, 1999 ATSDR, 1999
Henry's Law Constant	2.45×10^{-8} atm•m^3/mole	HSDB, 1999
Conversion factors in air	1 mg/L = 99.1 ppm 1 ppm = 0.01088 mg/L	HSDB, 1999

Source: U.S. EPA, 1999

Table 2a. Chemical Physicochemical Data For Dioxin Contaminants of Pentachlorophenol

General Chemical Formula	Common Name	Vapor Pressure (mm Hg)	Water Solubility @ 25°C (mg/L)	Henry's Law Constant ($atm \bullet m^3/mol$)	Log K_{OW}
C_6HCl_5O	Pentachlorophenol	0.00415	14	0.079	–
1,2,3,7,8-PeCDD	Pentachlorodibenzo-*p*-dioxin	4.4×10^{-10}	0.000118	2.6×10^{-6}	6.64
1,2,3,4,7,8,-H_xCDD	Hexachlorodibenzo-*p*-dioxin	3.8×10^{-11}	4.42×10^{-6}	1.7×10^{-5}	7.8
1,2,3,6,7,8-H_xCDD	Hexachlorodibenzo-*p*-dioxin	3.6×10^{-11}	4.42×10^{-6}	1.7×10^{-5}	7.8
1,2,3,7,8,9 H_xCDD	Hexachlorodibenzo-p-dioxin	4.9×10^{-11}	4.42×10^{-6}	1.7×10^{-5}	7.8
1,2,3,4,6,7,8 H_pCDD	Heptachlorodibenzo-p-dioxin	5.6×10^{-12}	2.4×10^{-6}	1.26×10^{-5}	8.0
1,2,3,4,6,7,8,9 OCDD	Octochlorodibenzo-*p*-dioxin	8.25×10^{-13}	7.4×10^{-8}	6.75×10^{-6}	8.2

Table 2b. Chemical Physicochemical Data For Furan Contaminants of Pentachlorophenol

General Chemical Formula	Common Name	Vapor Pressure (mm Hg)	Water Solubility @ 25°C (mg/L)	Henry's Law Constant ($atm \bullet m^3/mol$)	Log K_{OW}
1,2,3,7,8 PeCDF	Pentachlorodibenzofuran	1.7×10^{-9}			6.79
2,3,4,7,8 PeCDF	Pentachlorodibenzofuran	2.6×10^{-9}	2.36×10^{-4}	4.98×10^{-6}	6.5
1,2,3,4,7,8 HxCDF	Hexachlorodibenzofuran	2.4×10^{-10}	8.25×10^{-6}	1.43×10^{-5}	7.0
1,2,3,6,7,8 HxCDF	Hexachlorodibenzofuran	2.2×10^{-10}	1.77×10^{-5}	7.31×10^{-6}	7.0
2,3,4,6,7,8 HxCDF	Hexachlorodibenzofuran	2.0×10^{-10}	ND	ND	7.0
1,2,3,4,6,7,8 HpCDF	Heptachlorodibenzofuran	3.5×10^{-11}	1.35×10^{-6}	1.41×10^{-5}	7.4
1,2,3,4,7,8,9 HpCDF	Heptachlorodibenzodioxin	1.07×10^{-10}	ND	ND	ND
2,3,4,7,8-PCDF	Pentachlorodibenzofuran	ND	ND	ND	ND
1,2,3,4,6,7,8,9 OCDF	Octachlorodibenzofuran	3.75×10^{-12}	1.16×10^{-6}	1.88×10^{-6}	8.0

ND, no data available.

Table 3. Impurities and Contaminants in Different Grades of Pentachlorophenol					
Contaminant/impurity	Pure/Analytical[a]	Technical Grade[b]	Technical Grade[c]	DP-2[a]	Dowicide EC-7[a]
Pentachlorophenol	98.6%	86-90%	not reported	91.6%	91%
CHLOROPHENOLS					
Dichlorophenol	–	–		0.013%	–
Trichlorophenol	<0.01%	0.01%	<1%	0.044%	0.007%
Tetrachlorophenol	1.4%	3.8%	4.4–10.2%	7.0%	9.4%
Hexachlorobenzene	10 ppm	50 ppm		15 ppm	65 ppm
DIOXINS					
Tetrachlorodibenzodioxin	<0.08 ppm	<0.1		–	<0.04 ppm
Pentachlorodibenzodioxin	–	<0.1	<0.03–100 ppm	–	–
Hexachlorodibenzodioxin	<1 ppm	5–29 ppm		0.59 ppm	0.19 ppm
Heptachlorodibenzodioxin	–	88–524 ppm	0.6–520 ppm	28 ppm	0.53 ppm
Octachlorodibenzodioxin	<1 ppm	690–1500 ppm	5.5–3600	173 ppm	0.69 ppm
FURANS					
Tetrachlorodibenzofuran		<<4 ppm	0.02–0.45 ppm		
Pentachlorodibenzofuran	–	1.4 –10 ppm	<0.03–40 ppm	–	–
Hexachlorodibenzofuran	–	4–10 ppm	<0.03–90 ppm	12.95 ppm	0.13 ppm
Heptachlorodibenzofuran	–	88–400 ppm	<0.1–400 ppm	172 ppm	0.15 ppm
Octachlorodibenzofuran	–	18–260 ppm	<0.1–260 ppm	320 ppm	–
Chlorohydroxy-diphenyl ethers dibenzofuran	0.64%	6.21%	5–6.2%	4.05%	–

[a]Reported by NTP, 1989. The DP-2 and EC-7 formulations are no longer manufactured and are listed for informational purposes only.
[b]Reported in the general literature
[c]Summarized by IARC, 1991

3. TOXICOKINETICS RELEVANT TO ASSESSMENTS

The toxicokinetics of pentachlorophenol (PCP) has been studied in both humans and animals. These studies showed that PCP is rapidly and efficiently absorbed from the gastrointestinal tract and excreted primarily in urine. The biotransformation of PCP has been reviewed by Renner and Mücke (1986). Conjugation products (especially PCP glucuronide) and parent compound have been confirmed in several species, including humans.

Several reports have provided data on urinary PCP levels in humans. Although most of these data come from studies of occupational and non-occupational exposures, some data were generated under controlled experiment conditions. Renner and Mücke (1986), however, in reviewing the metabolism of PCP, noted that establishing a direct relationship between PCP in body fluids and exposure level may be difficult because PCP is a metabolite of other environmental contaminants (e.g., hexachlorobenzene, pentachlorobenzene, pentachloronitrobenzene) and is itself metabolized.

Uhl et al. (1986) studied the uptake and elimination of PCP in three healthy male subjects given the following doses of PCP: 3.9 mg (Subject B), 4.5 mg (Subject A), 9 mg (Subject C) or 18.8 mg (Subject C). In two additional experiments, Subjects C and B received 0.98 or 2.37 mg ([^{13}C]PCP). As noted, one subject received three different doses and another subject received two doses. The PCP was dissolved in 40% ethanol and taken without dietary restrictions. Daily urine levels of PCP, conjugates, and metabolites were monitored for various times up to 70 days after dosing with PCP, and blood and urine levels were monitored up to 53 days after dosing with [^{13}C]PCP. Although the results of this study suggest a seasonal variation in urinary PCP levels, the influence of uncontrolled variables such as diet preclude a definitive assessment. The data do, however, provided insight into urinary PCP levels resulting from non-occupational, ambient exposure.

Elimination half-life was 20 days in urine after an 18.8-mg dose and 18 days in urine and 16 days for blood after a 0.98-mg dose based on first-order elimination kinetics. Clearance was shown to be very slow, only 0.07 mL/min for total PCP and 1.25 mL/min for free PCP. At least 96% of the PCP was bound to plasma protein, which contributed to the long elimination half-life and slow clearance. PCP-glucuronide conjugate accounted for about 28% of the PCP in urine on day 1 and about 60% from day 15 to 38 after dosing with 18.8 mg PCP. The data showed no traces of any other metabolites of PCP. Neither tetrachlorohydroquinone (TCHQ), 2,3,4,5-tetrachlorophenol nor 2,3,4,6-tetrachlorophenol were detected in urine after dosing a subject with 0.98 mg [^{13}C]PCP. However, Ahlborg et al. (1974) detected PCP as well as the metabolites tetrachlorohydroquinone and tetrachloropyrocatechol in the urine of workers occupationally exposed to PCP. They did not quantify the levels of metabolites in urine. These data show that PCP is eliminated slowly from plasma in humans, and is eliminated primarily as a glucuronide conjugate. More recent studies by Mehmood et al. (1996), which indicate the formation of the tetrahydroquinone metabolite of PCP in vitro using human liver tissue, are supportive of this earlier finding.

Bevenue et al. (1967) reported on a case in which a man immersed his hands for 10 minutes in a solution containing PCP. The initial urinary concentration measured 2 days after the incident was 236 ppb. The level declined to 34% of the initial concentration by day 4, 20% after day 13, 10% after 1 month, and 7% after 2 months. This report shows that PCP is rapidly absorbed through the skin, eliminated rapidly during the first 4 days, and then more slowly thereafter. Because elimination is rapid initially, the concentration of PCP in urine was likely much higher during the first 24 hours after

exposure than after 2 days. These data, when compared to the findings of Uhl et al. (1986), suggest that significant differences may exist in elimination kinetics of PCP relative to exposure route.

PCP levels have been detected in the blood and urine of individuals who work with PCP, in individuals who had no known contact with PCP in an occupational environment, and in individuals living in homes made of wood treated with PCP. Uhl et al. (1986) reported that the median PCP concentrations in plasma of 12 nonspecifically-exposed persons was 25 µg/L and daily urinary elimination for 30 subjects was 19 µg/day. Jorens et al. (1991) reported that PCP in the cerebrospinal fluid (CSF) of patients with neurologic symptoms ranged from 0.24 to 2.03 µg/L fluid with a mean of 0.75 µg/L. Plasma PCP levels ranged from 4 to 60 µg/L (0.4 to 6 µg/dL) with a mean of 22 µg/L. No correlation existed between PCP levels in plasma and CSF. The plasma level reported by Jorens et al. (1991) was similar to that reported by Uhl et al. (1986).

Jones et al. (1986) reported on mid-week plasma and urinary PCP concentrations in 209 wood preservative workers and 101 workers not occupationally exposed to PCP. Sprayers had the highest mean plasma PCP concentration of 6 µg/dL (range = 0.2–29.0 µg/dL) and urinary concentration of 274 mmol/mmol creatinine (range = 11–1260 mmol/mmol creatinine). Timber-yard workers had a mean plasma concentration of 4.8 µg/dL (range 0.3–45.0 µg/dL) and mean urinary concentration of 74 mmol/mmol creatinine. Formulators had plasma concentrations of 1.3 µg/dL and urinary concentrations of 39.6 mmol/mmol creatinine. The mean plasma concentration for unexposed worker was 0.26 µg/dL for the group and 0.7 µg/dL for nine non-PCP timber-treatment operators with mean urinary level of 35.5 mmol/mmol creatinine. Blood and urine levels were monitored daily for four consecutive days. Workplace PCP air concentrations were not monitored, however, so a correlation with blood and urine levels could not be established. The correlation between blood and urinary levels was 0.76.

Casarett et al. (1969) reported mean 10-day urine concentrations of 5.6 ppm and 3.2 ppm in two groups of workers handling PCP under different conditions. The decrease in urine concentration in workers following different periods of absence showed a mean decrease of 39% within the first 24 hours and 60 to 82% over the next 17 days. Continued excretion of PCP was noted after 18 days absence from the job. A semilog plot shows a linear relationship between plasma and urine concentrations at plasma concentrations $\leq$0.1 ppm and plateau for plasma concentrations >10 ppm.

In another study, air concentrations, blood levels, and urinary excretion of PCP was studied 2 days before exposure to a 45-minute exposure and 5 days after exposure (Casarett et al., 1969). Mean air concentrations of 230 and 432 ng/L (90.6 and 146.9 µg, respectively, calculated doses) were associated with 88% and 76% excretion of PCP in the urine. Excretion was slow during the first 24 hours ($t_{½}$ = 40-50 hours) and more rapid after the first day ($t_{½}$ = 10 hours). In one subject, urine concentrations returned to baseline after 48 hours, but remained elevated in the other subject.

Begley et al. (1977) reported on blood and urine PCP levels in 18 PCP-exposed workers before, during, and after a 20-day absence from their jobs. Except for a brief rise on postexposure day 6, blood PCP levels showed a steady decline to 50% of the level on the last day of work during a 20-day absence. There was a 6-day lag in the decrease in urine level; after day 20 urine levels had decreased about 50%. Begley et al. (1977) also noted that the high PCP levels were accompanied by impaired renal function measured by creatinine and phosphorus clearance and phosphorus reabsorption.

Cline et al. (1989) reported serum PCP levels ranging from 69–1340 ppb with a mean of 420 ppb for 123 residents of PCP-treated log homes. Sex differences were not noted for the PCP concentration in log home residents, but age differences were observed. Children ages 2–15 had serum PCP levels 1.7 to 2.0 times higher than that of their parents. Cline et al. (1989) attributed the higher PCP levels in children to difference in the ventilation rate to body weight ratio, which is 0.48 for adults and 0.21 for children (cited from Ratcliffe, 1981). A pregnant woman in this group had a high serum PCP level (1240 ppb) and also had a high serum cord level (1180 ppb). Urine PCP levels for the log home residents ranged from 1–340 ppb with a mean of 69 ppb. Serum levels plotted against urine levels showed a high degree of correlation (r=0.92) when urine levels were corrected for creatinine concentration.

Cline et al. (1989) also reported the blood levels in workers occupationally exposed to very high but unknown concentrations of PCP. Six workers at one plant had whole blood levels of 6000 to 23,000 ppb of PCP; the one with the highest level died. Four workers at another plant had blood levels ranging from 8600 to 45,200 ppb of PCP and urine levels ranging from 2400 to 13,800 ppb. Cline et al. (1989) further reported serum PCP levels of 15-75 ppb with a mean of 40 ppb in 34 subjects with no known occupational exposure to PCP. The concentration of PCP in urine ranged from 1-17 ppb with a mean of 3.4 ppb.

Because of the prevalence of PCP in the environment, urine levels in the general population were studied by Treble and Thompson (1996) and Thompson and Treble (1996). These studies were conducted under the premise that PCP exposure via the food chain is a prevalent route for non-occupational exposure. An interesting note is the fact that all of the samples tested in the work of Treble and Thompson contained quantifiable levels of PCP. There were significant gender or age-dependent differences in urinary PCP levels in these studies.

In the study by Treble and Thompson (1996), urine samples were collected over a 24-hour period from individuals living in rural and urban regions of Saskatchewan, Canada, and analyzed for PCP by gas chromatography-mass spectrometry. The subjects (26 males and 43 females) ranged in age from 6 to 87 years. Normal PCP concentrations ranged from 0.05 to 3.5 ng/mL and average PCP elimination was 4.3 nmol/day. There was no evidence of an age-related influence on PCP elimination nor did a high urinary PCP concentration necessarily correspond to a high 24-hour excretion of PCP (i.e., urinary volume must also be considered in addition to urinary PCP concentration).

Thompson and Treble (1996) also reported on seasonal variations in urinary PCP among the general population. This study examined urine samples collected from 87 individuals (males and females; ages 4 to 86 years) in September, 1992 and from 38 individuals (males and females; 6 to 87 years) in January, 1995. The September collection group exhibited greater urinary PCP concentrations than did the January collection group for minimum (0.5 vs 0.1 ng/mL), maximum (9.1 vs 3.6 ng/mL), median (1.3 vs 0.5 ng/mL), and average (1.6 vs 0.9 ng/mL) urinary concentrations.

One set of studies compared the toxicokinetics of orally administered PCP in human, nonhuman primates, and rodents. Braun et al. (1979) reported on studies in four healthy male subjects; Braun and Sauerhoff (1976) reported on the studies utilizing male and female Rhesus monkeys; and Braun et al. (1977) reported on the metabolism and pharmacokinetics of PCP in male and female Sprague Dawley

rats. The rats were dosed with 10 or 100 mg/kg [^{14}C]PCP, monkeys with 10 mg/kg [^{14}C]PCP, and humans with 0.1 mg/kg unlabeled PCP.

The absorption half-life ($t_{½}$) for the human volunteers was 1.3 hours with a maximum plasma concentration (C_{max}) of 0.2 µg/mL and a time to peak plasma concentration (T_{max}) of 4 hours. The $t_{½}$ for plasma elimination was 30 hours and 33 hours for urinary excretion. Elimination was consistent with a first-order one-compartment pharmacokinetic model. The maximum excretion rate occurred 40 hours after dosing; the delay between C_{max} and T_{max} was attributed to enterohepatic recirculation of PCP. Humans dosed with 0.1 mg/kg PCP excreted 86% of the administered dose in urine and 4% in feces. Unmetabolized PCP accounted for 74% of the administered dose in urine and 2% in feces; PCP conjugated with glucuronide accounted for 12% of the administered dose in urine and 2% in feces (Braun et al., 1979)

The absorption rate constant for PCP administered to rats was 1.95 and 1.56 h^{-1} for males and females, respectively. The plasma T_{max} was 4-6 hours. Sex differences were noted for some of the toxicokinetics parameters. After administration of a 10-mg/kg dose, 78-80% of the dose was excreted in urine and about 19% in feces. After administration of 100 mg/kg, males excreted 72% of the administered dose in urine and 24% in feces, whereas females excreted 54% in urine and 43% in feces. Expired air accounted for a small amount of the dose. A two-compartment open system model described the data with elimination $t_{½}$ or 13-17 hours for the rapid phase (both doses) and 33-40 hours for the slower phase at 10 mg/kg and 121 hours for 100 mg/kg (males). Females did not show biphasic elimination at the 100 mg/kg dose. Unmetabolized PCP accounted for 48% of the administered dose in urine, tetrachlorohydroquinone accounted for 10%, and PCP glucuronide conjugate accounted for 6% (Braun et al., 1977).

In Rhesus monkeys administered a single 10-mg/kg dose, absorption and elimination was first order with absorption $t_{½}$ ranging from 1.8 to 3.7 hours, plasma elimination $t_{½}$ ranging from 72 to 84 hours, urinary excretion $t_{½}$ of 41 hours for males and 92 hours for females. The plasma T_{max} was 12-24 hours at a C_{max} of 10-30 µg/mL. Similar to rats, the Rhesus monkeys exhibited gender-related differences in the excretion of PCP. Urinary excretion accounted for 69-78% of the administered dose and feces for 12-24%. Unlike humans and rats, all of the PCP eliminated in the urine of monkeys was unchanged parent compound (Braun and Sauerhoff, 1976).

The pharmacokinetic parameters obtained from a simulation dose of 0.1-mg/kg administered dose are summarized in Table 3. Although a two-compartment elimination describes the data for rats and a one-compartment model for humans and monkeys, the rat appears to be a better model for humans based upon the remaining parameters. A simulated model for seven daily doses on 0.1 mg/kg followed by 7 days of recovery showed that rats and humans attain 90% of steady state in 1.5 and 3.5 days, respectively, with similar steady state plasma concentrations. The monkeys attained only 78% of steady state by the end of the 7-day ingestion period. The estimated plasma concentration at the end of the ingestion period was 0.5 µg/mL for rats and humans and 0.9 µg/L for monkeys.

As noted above, studies by Braun and coworkers suggested that pharmacokinetic parameters are more similar for humans and rats than for humans and monkeys. Studies in humans showed that PCP is readily absorbed via oral, inhalation, and skin exposure. Plasma and urine levels show a high degree of correlation. Elimination from the body is a slow process although PCP does not appear to accumulate in

the body. The slow elimination may be due to protein binding. PCP in humans undergoes both phase I and phase II biotransformation.

Table 3. Comparison of Toxicokinetic Parameters in Rats, Monkeys, and Humans for a Simulated 0.1-mg/kg Dose of Pentachlorophenol

Parameter	Rat		Monkey		Human
	Male	Female	Male	Female	
Absorption, $t_{½}$ (h)	0.4		3.649	1.81	1.3
Absorption rate constant, h^{-1}	1.95	1.52	0.215	0.383	1.16
Peak plasma conc. (c_{max}), µg/mL	0.35		0.1-0.3		0.2
Time to peak plasma conc. (T_{max}), h	4-6		12-24		4
Elimination, $t_{½}$ (h)	17(rapid) 40 (slow)	13 (rapid) 33 (slow)	72	83.5	33
Elimination rate constant, h^{-1}	0.0398 (rapid) 0.0173 (slow)	0.0518 (rapid) 0.0213 (slow)	0.0103	0.0083	0.0210
Volume of distribution, mL/kg	278		116		348

Sources: Braun and Sauerhoff, 1976; Braun et al., 1977; Braun et al., 1979

Rozman et al. (1982) showed that a large portion of urinary excretion of PCP in monkeys is due to intestinal reabsorption of PCP excreted into bile. Three male Rhesus monkeys equipped with a bile duct by-pass were administered 50 mg /kg of [^{14}C]PCP by stomach intubation. During the first 24 hours, 21% of the administered dose was excreted into urine, 0.3% into feces, and 19% into bile. From day 2 to 7 after dosing, 35% of the administered dose was excreted into urine, 70% into bile, 3% into feces. The monkeys received a second dose of 50 mg/kg [^{14}C]PCP followed 24 hours later by 4% cholestyramine (binds phenols) in the diet for 6 days. Cumulative excretion of PCP into urine and bile was reduced to 5% and 52%, respectively, of the administered dose, whereas cumulative excretion into feces was increased to 54% of the dose. These data suggest that enterohepatic recirculation of PCP plays a major role in urinary excretion of the compound. These data are not directly comparable to those obtained by Braun and Sauerhoff (1976) because of the bile duct by-pass; however, these data show a relative correlation with the excretion pattern.

Wester et al. (1993) reported on the dermal absorption of PCP through the skin of female Rhesus monkeys. PCP contaminated soil (17 ppm [^{14}C]-PCP) was applied at a concentration of 0.7 µg/cm^2 of skin. PCP in acetone was applied at a concentration of 0.8 µg/cm^2 of skin. The samples remained in contact with the skin for 24 hours. Absorption of PCP from soil was 24% and from acetone 29% of the applied dose; 11.1% of the applied dose was excreted in urine over a 14-day period. The half-life for excretion was 4.5 days after topical application in soil or acetone, which was comparable to that obtained after i.v. administration. The efficient absorption of PCP from skin and long half-life are indicative of high bioavailability, a situation similar to that observed in humans (Bevenue et al., 1967).

PCP inhaled by rats showed rapid uptake from the respiratory tract and excretion from the body. Hoben et al. (1976b) exposed Sprague-Dawley rats to PCP aerosols for 20 minutes and sacrificed the

animals at 0, 6, 12, 24, 48, and 72 hours after exposure. Between 70 and 75% of the PCP could be accounted for as unmetabolized PCP during the first 24 hours; the highest level was in urine > liver = plasma > lungs. PCP in lung and liver showed a steady decrease throughout the study; plasma levels showed a steady decrease after a peak at 6 hours; and urine showed a steady decrease after 24 hours. The estimated half-life was 24 hours, and there was no evidence of accumulation or tissue binding.

Rats exposed to PCP aerosols repeatedly for 20 minutes/day for 5 days showed only a slight net increase in lung and plasma levels immediately after the second exposure, no net increase in liver level (Hoben et al., 1976b). Twenty-four hours after each exposure, lung, liver, and plasma levels were lower, but urine levels increased suggesting that increased urinary excretion may explain the lack of accumulation of body burden upon repeated exposures. However, the study authors noted that increased urinary excretion did not account entirely for the lack of accumulation; they also concluded that metabolism was likely involved.

Reigner et al. (1991) studied toxicokinetic parameters in male Sprague-Dawley rats dosed with PCP (99% purity) at 2.5 mg/kg by i.v. or gavage administration. Absorption was rapid and complete (bioavailability was 91%) after oral administration with plasma levels peaking after 1.5 to 2 hours at 7.3 µg/mL and declining with a half-life of 7.5 hours; the data were fitted with a first order one-compartment model. Plasma elimination was biphasic for i.v. administration with half-lives of 0.7 and 7.1 hours; the data were fitted with an open two-compartment model. The AUCs were similar for i.v. and oral administration (96 and 94 µg•h/mL, respectively). Total excretion was 68 and 62% of the dose, total urinary excretion was 58 and 52%, total urinary TCHQ excretion was 31 and 27% for i.v. and gavage administration, respectively. These data are in contrast to those of Braun et al. (1977) who showed that plasma elimination after oral administration follows a biphasic pattern with much longer half-lives than that obtained by Reigner et al. (1991).

Yuan et al. (1994) studied the toxicokinetics of PCP administered to F344 rats by gavage or dosed feed. For the gavage study, groups of 18 male rats were given PCP (>99% pure) in aqueous methylcellulose at doses of 9.5 or 38 mg/kg; blood was collected from the orbital sinus at 5 minutes to 20 hours. For dosed feed studies, groups of 42 male rats were placed on diets containing 302 or 1010 ppm PCP for 1 week; blood was collected at different times during treatment. In addition, groups of 18 male and 18 female rats were administered PCP at a dose of 5 mg/kg by intravenous injection. Blood was collected as described for the gavage study.

The data from the intravenous study were fitted to a two-compartment model. Sex differences were noted for elimination t½ (5.6 hours for males, 9.5 hours for females) and volume of distribution (0.13 L/kg for males and 0.19 L/kg for females). For the gavage study, the t½ for absorption of 1.3 hours and plasma concentrations peaked in about 2–4 hour indicating very rapid absorption from the gut. One-compartment first order absorption and elimination models were fit to the gavage data because the rapid absorption masked the fast distribution phase. Bioavailability estimated from the area under the curve for intravenous injection and gavage administration was 100% at 9.5 mg/kg and 86% at 38 mg/kg. For the dosed feed study, absorption was also rapid and followed first-order kinetics. Mean daily intake of PCP was 21 and 64 mg/kg based on body weight and food consumption data. Plasma concentrations showed repeated cycles of peaks and troughs coinciding with feeding cycles, i.e. highest concentrations at night and lowest during the day; however, plasma concentration did not reach pretreatment levels during the day. The investigators noted that absorption and elimination $t_{½}$ were not affected by the change from gavage to dosed feed administration. Bioavailability was estimated as 52 and 30%, for the

302- and 1010-ppm dietary concentrations, respectively, which is much lower than the values obtained from the gavage study. The investigators further noted that the lower bioavailability for the dosed feed study suggests that PCP interacts with components in feed (Yuan et al., 1994).

Ahlborg et al. (1974) reported that NMRI mice and Sprague-Dawley excreted less than 50% of radioactivity in urine during the first 96 hours after oral administration of 25 mg/kg [14C]PCP with about twice as much appearing in the urine of rats than mice. About 70% of the radioactivity appeared in the urine after intraperitoneal injection of 25 mg/kg; mice and rats excreted approximately the same amount. PCP made up 41–43% of the radioactivity in urine of mice and rats and TCHQ made up 5% of the radioactivity in rats and 24% in mice. Another metabolite tetrachlorocatechol made up 35% of the radioactivity in urine in the mouse and 52% in the rat. Because TCHQ inhibited β-glucuronidase activity, the degree of glucuronide conjugation could not be determined. However, boiling the urine with hydrochloric acid converted all the radioactivity to PCP (54–57%) and TCHQ (43–46%) in rats and mice.

Within 96 hours after injecting mice i.p. with 1 or 0.5 mg [14C]PCP, 72–83% of the dose was excreted in urine and 3.8–7.8% in feces; the remainder of the dose was found in specific organs and the carcass (Jakobson and Yllner, 1971). Rapid absorption and excretion of PCP was exhibited by the appearance of 45–60% of the dose in urine within the first 24 hours. The greatest amount of PCP distributed in the body was found in the liver, intestines and stomach. Lesser amounts of the dose were found in the heart, kidney, brain. Approximately 30% of the PCP in urine was unmetabolized, 7-9% was bound but released by acid treatment, and 15–26% was the metabolite TCHQ.

Larsen et al, (1972) reported that less than 0.04% of a 59-mg/kg oral dose of [^{14}C]PCP (99.5% pure) administered to male and female rats (strain not reported) was eliminated in expired air as $^{14}CO_2$ within 24 hours. After administration of 37–41 mg/kg, females excreted 41% of the radioactivity in urine within 16 hours, 50% within 24 hours, 65% within 72 hours and 68% within 10 days. Fecal excretion accounted for 9.2 to 13.2% of the administered dose. Excretion showed a biphasic pattern; a rapid excretion phase during the first 24 hours and a slower phase thereafter.

Juhl et al. (1985) studied the metabolism of PCP in human S9 fraction of liver preparations and compared the results with those obtained from S9 liver preparation from non-induced and Aroclor1254-induced male Wistar rats. Human S9 fraction preparations converted PCP to TCHQ. Maximum conversion occurred after incubation for 3 hours, after which the level of TCHQ steadily declined to non-detectable levels at 24 hours. The authors attributed the decline to the oxidation capacity of the liver preparation or the further oxidation of TCHQ via semiquinone radicals. The patterns of conversion of PCP to TCHQ in human and rat liver S9 preparations showed very little difference.

PCP metabolites were measured in urine and feces from male Wistar rats administered 8 mg/kg/day PCP by gavage for 19 days (Engst et al., 1976). Under these conditions, most of the PCP in urine was unmetabolized; small amounts of 2,3,4,5-tetrachlorophenol, 2,3,4,6- and/or 2,3,5,6-tetrachlorohenol, and 2,3,4-trichlorophenol were found. Only a small amount of unmetabolized PCP and no metabolites were identified in feces. The PCP in feces was considered to be unabsorbed.

Van Ommen et al. (1986) studied the in vitro metabolism of PCP utilizing rat liver microsomal preparations from untreated male and female Wistar rats and from rats treated with hexachlorobenzene, phenobarbital, 3-methlycholanthrene, or isosafrole. Rat liver microsomes converted PCP only to

tetrachloro-1,4-hydroquinone (1,4-TCHQ) and tetrachloro-1,2-hydroquinone (1,2-TCHQ) via cytochrome P-450 enzymes. The ratio of 1,4-TCHQ/1,2-TCHQ production was 5:1 for male rats and 1.6:1 for female rats receiving no inducer. The ratio decreased in rats treated with the enzyme inducers in the following order: hexachlorobenzene > pentachlorophenol >3-methylcholanthrene ≃ isosafrole. The sex difference observed in untreated rats was not observed in rats treated with the inducers except phenobarbital. PCP was bound to microsomal proteins. Protein binding was dependent on metabolism, and the amount bound did not vary considerably with the microsomal preparations (63–75 $pmol \bullet min^{-1} \bullet mg^{-1}$) except for that obtained from phenobarbital-induced female rat (104 $pmol \bullet min^{-1} \bullet mg^{-1}$). The apparent K_m-value for covalent binding to protein was 13 µM.

Reigner and colleagues studied the pharmacokinetics of PCP in rats and mice in an effort to develop a model to predict exposure based upon steady-state plasma concentration. In a report by Reigner et al. (1992a), plasma concentrations of PCP in rats was estimated following exposure to the chemical via drinking water. A three-day exposure of five male Sprague-Dawley rats to 30 µg PCP/mL water was used as the basis of the experiments. It was found that a one-compartment model with zero order kinetics for clearance, volume of distribution, and bioavailability adequately predicted steady-state plasma PCP concentrations (C_{ss}) which reflected overall exposure. Based upon comparisons with data from intravenous studies, the C_{ss} for oral (i.e., drinking water) exposures could be accurately predicted by the relationship of bioavailability, rate of intake and clearance. Reigner et al. (1992b) also examined the pharmacokinetics of orally administered PCP (15 mg/kg) in male $B6C3F_1$ mice. The data were consistent with an open one-compartment model. Absorption followed first-order kinetics. Peak plasma concentration (28 µg/mL) was achieved at 1.5 hours. Absorption was complete and a bioavailability of 1.06 was determined. Elimination half-life was 5.8 hours. An analysis of metabolites revealed that only 8% of the administered PCP was excreted as parent compound.

Deichmann et al. (1942) reported that absorption of PCP was immediate and rapid in rabbits given single 18-mg/kg oral dose of PCP. Peak blood levels were reached in 7 hours after dosing rabbits with 37 mg/kg PCP, about 92% of the dose was recovered in urine, feces, and tissues combined (~71% in urine and feces) within the first 24 hours, and elimination from the blood was almost complete within 4 days after dosing. The largest fractional tissue dose was recovered from muscle, bone, and skin; however, 0.7 to 2% of the dose was recovered in the liver. Deichmann et al. (1942) also showed that rabbits administered 25 mg/kg PCP sodium salt orally excreted 64 to 70% of the dose in urine and feces within 7 and 12 days, and 49 to 56% was excreted after administration of 50 mg/kg.

In a repeat dosing study, Deichmann et al. (1942) showed that peak blood concentrations of 0.6 mg% (mg/100 mL blood) occurred within 4 days and did not change beyond 1.0 mg% for the remaining duration of the study after administration of 0.1% PCP sodium salt (equivalent to 3 mg/kg) repeatedly for 90 successive doses (except Sundays). The investigators noted that the blood concentrations were similar to those attained after 100 daily skin applications of 100 mg each.

Parker et al. (1980) examined groups of yearling (10–14 months) Holstein cattle (3/group) administered analytical PCP (aPCP), technical grade PCP (tPCP), 10% tPCP/aPCP mix, and 35% tPCP/aPCP mix to determine the levels of PCP and contaminants in blood, liver, and adipose tissue. Each treatment group was given 20 mg/kg body weight for 42 days then decreased to 15 mg/kg body weight for the remainder of the study (total treatment time = 160 days). A group of 3 yearlings served as controls. Treatment groups included animals given 10, 35, and 100% tPCP. Total PCP consumed was 0, 733 (all aPCP), 768, 687, and 613 g (all tPCP), respectively, and total tPCP consumed by the 10 and

35% tPCP groups was 77 and 241 g, respectively. The concentrations of PCP in blood serum were 0.13, 77, 87, 69, and 33 ppm, respectively. The predominant dioxin contaminants found in the liver were tenatively identified as 1,2,3,4,6,7,9 heptachlorodibenzodioxin, 1,2,3,4,6,7,8 heptachlorodibenzodioxin, and octachlorodibenzodioxin. Of the furan contaminants, 1,2,3,4,6,8 hexachlorodibenzofuran, 1,2,4,6,7,8 hexachlorodibenzofuran, 1,2,3,4,6,7,8 heptachlorodibenzofuran, 1,2,3,4,6,8,9 heptachlorodibenzofuran, and octachlorodibenzofuran were tentatively identified. These contaminants showed dose-related increases in the liver. The same components plus octachlorodibenzofuran (OCDF) levels showed dose-related increases in adipose tissue. The levels, however, were much lower than those detected in liver.

Investigations have been conducted which examined the possible mechanism(s) and metabolite(s) by which PCP induces liver toxicity. Lin et al. (1997, 1999) demonstrated that protein adducts of quinone and semiquinone are formed in the livers of Sprague-Dawley rats and B6C3F$_1$ mice administered PCP by gavage. Tetrachloro-1,4-benzoquinone was the major protein adduct in the livers of rats and tetrachloro-1,4-benzoquinone mice and tetrachloro-1,2-benzoquinone adducts were the major adducts in mice administered 20 mg/kg PCP by gavage. Protein adducts were used as a measure of tissue (liver) dose. Tetrachloro-1,2-benzoquinone adducts were not detected in rat liver homogenates in vitro. The estimated tissue dose of tetrachloro-1,4-benzoquinone was 3.6 times higher in rat liver cytosol than in the mouse cytosol and 2.7 times greater in the mouse nucleus than in the rat nucleus. The estimated total dose of all quinones was fourfold higher in mouse nuclei than in rat nuclei. The cytosol also contained much higher levels of adducts than did the nucleus. The semiquinone and quinone metabolites of PCP appeared to bind covalently to cellular proteins.

Lin et al. (1999) also showed that the reactive metabolites, tetrachlorobenzoquinone as well as tetrachlorosemiquinone, form adducts in the livers of Sprague-Dawley rats and B6C3F$_1$ mice in proportion to oral doses of 5-40 mg/kg PCP. Tetrachloro-1,4-benzosemiquinone adducts were proportionally greater at the lower doses and was 40-fold greater in rats than in mice. However, at the higher doses, tetrachloro-1,4-benzoquinone adduct production was proportionally greater and was 2- to 11-fold greater in mice than in rats. The investigators concluded that the quinone reactive metabolites (tetrachloro-1,2- and tetrachloro-1,4-quinones) and not the semiquinones form the major adducts in the liver of mice administered PCP. Only small amounts of the semiquinone adducts were formed in the mouse liver. Formation of quinone metabolites in the mouse occur via direct oxidation of PCP rather than the indirect oxidation via the semiquinone intermediate.

Lin et al. (1999) also showed that after subchronic treatment of Fischer 344 rats with 1000 ppm PCP (60 mg/kg/day) in the diet for 27 weeks, tetrachloro-1,4-benzoquinone adducts were detected in liver cytosol and nuclei. No 1,2-benzoquinone adducts were detected . The steady state cytosol and nuclear adduct levels were similar to the level predicted from Sprague-Dawley rats given a single dose of PCP. Lin et al. (1999) speculated that the species differences in metabolism of PCP to semiquinone and quinone metabolites are responsible for carcinogenicity observed in the liver of mice administered PCP in contrast to the lack of liver carcinogenesis in rats administered PCP in long-term experiments.

Larsen et al. (1975) observed that PCP levels peaked in maternal blood 8 hours after dosing Charles River CD dams [^{14}C]PCP on gestation day (GD) 15. The level steadily dropped during the remaining part of the 32-hour monitoring period. The level in the placenta peaked at a much lower levels 12 hours after dosing, and the level reaching the fetus remained extremely low compared with that of maternal blood throughout monitoring period.

In conclusion, the available data indicate that PCP is readily absorbed regardless of exposure route and exhibits a small volume of distribution. In rodents, PCP is primarily eliminated as conjugation products in the urine. Studies in monkeys and human data, however, have shown that PCP may be eliminated unchanged in the urine. The absorption and elimination half-lives and the maximum plasma concentrations for orally administered PCP in rats, mice, monkeys are summarized in Table 4. Human data from Braun et al. (1979) are also included for comparison. The kinetics of orally administered PCP for all of the species studied are consistent with a one- or two-compartment open model exhibiting first order kinetics. Based upon the available data, the toxicokinetics of PCP in humans may be more similar to that of rats and mice than Rhesus monkeys.

Table 4. Summary of Some Toxicokinetic Parameters in Rats, Monkeys, and Humans for Orally Administered Pentachlorophenol

Species	Absorption $t_{1/2}$ (hrs)	Plasma T_{max} (hrs)	Elimination $t_{1/2}$ (hrs)	Process Description	Reference
Human	1.3	4	30-33	1st order, one compartment	Braun et al., 1979
Rhesus monkey	1.8-3.7	12-24	72-84	one compartment,open	Braun and Sauerhoff, 1976
Rat	-	4-6	13-17 (fast) 33-40 (slow)	two compartment, open	Braun et al., 1977
Rat	1.3	2-4	5.6-9.5	1st order, one compartment	Yuan et al., 1994
Mouse	0.6	1.5	5.8	1st order, one compartment, open	Reigner et al., 1992b

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS — EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS

This section will review the available evidence of health effects in humans resulting from exposure to pentachlorophenol (PCP). In particular, the acute and chronic toxicity, teratogenic/ reproductive effects, and carcinogenicity are discussed. In assembling these data, several sources were consulted, including the U.S. EPA's Office of Pesticide Programs' Incident Data Base, Poison Control Center data received by the Office of Pesticide Programs , the California Department of Pesticide Regulation, the National Pesticide Telecommunications Network, and open scientific literature reports.

From OPP's Incident Data Base, only two cases were reported. In the first case, a pesticide incident was reported in 1992, when a woman called the Office of Pesticide Programs to report that workers at a plant using pentachlorophenol were experiencing health effects. She reported chemical burns and dermatitis. No further information on the disposition of the case was reported. In the second case, a female neighbor complained of ill health after exposure to fumes from timber treatments of PCP in a nearby building. No further information on the disposition of the case was reported.

From Poison Control Center data, a total of 122 unintentional exposures were reported to the Toxic Exposure Surveillance System from 1993 through 1996. Children under six years of age were involved in 32 of the exposures and half of these were followed to determine outcome. Only five of the children were reported to have developed symptoms, all of which were minor. Six of the children were reported seen in a health care facility and one was hospitalized. The number of cases reported in children under age six is too small for meaningful comparisons with other pesticides.

There were 90 exposures in adults and older children, 30 of which had a minor outcome, nine with moderate outcome, and one case that was considered life-threatening. Thirty-four cases were seen in a health care facility, two were hospitalized, and one was admitted for critical care. Compared to other pesticides, pentachlorophenol had somewhat higher percents of cases that had a moderate (based on 9 cases) or life-threatening (based on a single case) outcome. However, this finding was due to a relatively small number of cases. A smaller proportion of cases was hospitalized or admitted for critical care (ICU) for PCP than for all pesticides combined.

From the California Department of Pesticide Regulation, detailed descriptions of 71 cases submitted to the California Pesticide Illness Surveillance Program (1982-1996) were reviewed. In 48 of these cases, pentachlorophenol was judged to be responsible for the health effects. Only cases with a definite, probable or possible relationship were reviewed. Of the reports of illness in California, 58% of the total were irritative effects to the eye and skin. The remaining 42% were systemic in nature, including symptoms of headache, nausea, and difficulty breathing. However, only half of the systemic cases were classified as having a probable or definite relationship between the exposure and the health effects. For the time period 1982 through 1994, pentachlorophenol ranked 51st out of 253 active ingredients responsible for systemic poisonings in California. One individual was hospitalized in 1982 for skin grafts due to second and third degree burns after carrying treated lumber for four weeks. The burns were reported to the shoulder, neck, chin, back, and thigh, and characterized as an allergic reaction by one investigator.

4.1.1 Incident Reports Associated with Acute Toxic Effects of PCP Published in Scientific Literature.

Several reports are available from the open scientific literature regarding human health effects as a result of exposure to pentachlorophenol. One of the earliest reports recognizing the serious toxic effects of PCP in humans was published by Truhaut et al. in France (1952). The authors described the then current procedures for treatment of lumber to prevent rotting. Workers known as "treaters" soaked freshly sawn lumber in tubs containing a 3% solution of a mixture of 80% pentachlorophenate of sodium and 20% tetrachlorophenate of sodium. After soaking, the lumber was then carried to other workers called "stackers" to be put in stacks. Based on examinations of more than 100 lumber "treaters", symptoms of PCP exposure included skin irritation with blisters, congestion of mucous membranes of eyes and nose, loss of appetite, loss of weight, constriction of throat, respiratory stress, and fainting. Urine levels of PCP in 16 workers who had worked for two months as "treaters" were between 3 and 10 mg/l.

Truhaut et al. (1952) also reported on the deaths of two workers following exposure to PCP. The first worker had worked as a stacker for one month, then for four days as a treater. Prior to his death, he experienced headache, achiness, sweating, and rapid breathing. Autopsy findings included liver poisoning, degenerative lesions in kidney, considerable edema in the lungs, and PCP in liver, kidney, blood, stomach, intestine, heart, lung, and urine. The second fatal case involved a man who worked as a treater for six days. His symptoms included marked lack of appetite, extreme tiredness, profuse sweating, extreme thirst, and an elevated rectal temperature of 43 degrees C. Pathology findings included considerable congestion and edema of the lungs, and albumin in the urine. At the time of the Truhaut et al. report, acute and short-term toxic effects of exposure to PCP were known and had resulted in implementation of simple protective measures such as wearing gloves and aprons when handling material wetted with PCP. However, the possibility of death from PCP exposure, other than by acute poisoning, was not known. This brief case series provides only limited data upon which to base conclusions, but does suggest death can occur from heavy exposures occurring over a relatively short period of days or weeks.

In one study of over 600 factory workers (O'Malley et al., 1990), a cumulative incidence of 7% of the workers reporting chloracne and an annual average incidence of 2% reporting chloracne was described. The PCP produced at this plant was contaminated with chlorinated dioxins and dibenzofurans which have been reported to cause chloracne in other human and animal studies. Those workers with records of direct skin exposure to PCP had a four fold increase in the risk of developing chloracne compared to other workers. The interval between the last report of direct skin contact and the diagnosis of chloracne ranged from 7 weeks to about 14 years among 13 cases. Four of the 13 cases occurred withing 6 months of contact, four occurred between 1 and 2 years after contact, and three occurred more than 10 years after exposure.

Lambert et al. (1986) reported on 3 cases related to non-occupational PCP exposure. Two cases developed pemphigus vulagaris, an autoimmune disease where the patient develops successive blisters (bullae) which can be potentially fatal if the disease becomes widespread. Both cases had extensive exposure to the sun and only incidental exposure to PCP. In one case the 41 year old male purchased a PCP treated bookcase and in the other case, the 28 year old female had several rafters in the living room treated with PCP. A third case of urticaria occurred in a 35 year old male who worked with PCP-treated wooden framework. The authors noted a "striking parallelism" in all three cases between their disease

course and PCP serum levels and stated that these cases suggest "possible new hazardous effects of PCP".

Klemmer et al.(1980) compared clinical findings in a group of 47 workers exposed to PCP and 42 controls. Age standardized prevalence rates for conjunctivitis, chronic sinusitis, and chronic upper respiratory conditions were significantly higher for PCP-exposed workers. It was noted that the conjunctivitis cases only occurred among workers involved in pressure treatment and therefore had mixed exposure to PCP and other chemicals. The authors report that the sinusitis cases typically involved low grade infections that did not require medical intervention. They concluded that workers exposed to PCP during wood treatment under the conditions of their study did not experience serious health effects.

Cole et al. (1986) reported a case involving a 32 year old carpenter who developed chloracne of six months duration. The patient was part owner of a firm that constructed piers for small boat marinas. The lumber used was pre-treated with PCP. Though he was aware of the requirements for protection when working with treated wood, he chose to disregard them and was often lying atop the lumber to measure it accurately. His skin condition developed about 9 months after beginning work. After four and a half months of treatment his skin condition improved considerably and he has remained symptom free for the ensuing two years of observation.

Cooper and Macaulay (1982) reported a case of a 51 year old joiner who applied PCP and zinc naphthanate to new floorboards with a brush and no protective equipment as required on the label. He developed abdominal pain, vomiting and dark urine that were diagnosed as pancreatitis. The authors felt that the evidence of symptoms of PCP poisoning implicated PCP as the cause of the pancreatitis rather than the zinc naphthanate.

Gray et al. (1985) reported the case of a 33 year old man who used a jackhammer to break up large blocks of PCP which were ground into powder. He developed lethargy, rapid respiration, and sweating, which led to his hospitalization. At the hospital he became comatose with high fever and pulmonary edema and died. An OSHA investigation found the employee had not been adequately trained and improper protective equipment had been used.

Wood et al. (1983) reported on five cases of PCP poisoning, two of which were fatal. Typical symptoms included high fever, sweating, rapid heartbeat and breathing, and abdominal pain. These cases occurred at two small wood preservative manufacturing plants. In one of the fatalities the worker had been involved in crushing 2,000 pound blocks of PCP with a jackhammer in a small, poorly ventilated room. The second fatality had been involved in a dry mixing process in an area with poor ventilation. A general air sample taken from this area found PCP levels (4.6 mg/m^3) nine times the OSHA standard.

The U.S. Environmental Protection Agency conducted a survey of PCP-treated log homes and their occupants at the request of the Kentucky Department of Health Services (use of PCP in log home construction has been prohibited since 1986). Environmental and medical data were collected on 21 homes. Serum and urinary levels of PCP were highest in children 4-7 years old and lowest in the over 12 years old age group. For children 4-7 years old, geometric mean levels of PCP were 52 ng/mL in serum (25% greater than levels in those older than 12 years) and 0.036 mg/g creatinine in urine (just over twice as high as those older than 12 years). No significant differences were reported on a health questionnaire between health complaints and serum or urinary levels of PCP. A clinical laboratory examination did not

find differences on tests of liver function, microsomal enzyme induction, or renal function with levels of PCP. No significant difference was reported for the neurologic examination or for lymphadenopathy. However, there was a relationship between a finding of skin abnormalities and levels of PCP in the urine or serum. The types of skin abnormalities were not described. The author noted that skin abnormalities might lead to increased absorption of PCP resulting in higher biologic PCP concentrations in blood and urine, rather than PCP being a cause of skin abnormalities.

An earlier review of PCP found that immersion of hands for 10 minutes in a 0.4% solution caused pain and inflammation (Bevenue et al. 1967). Dust and mist concentrations greater than 1.0 mg per cubic meter can result in painful irritation of upper respiratory tract resulting in violent sneezing and coughing in persons not previously exposed to PCP (US EPA 1980). Some nose irritation has been reported at levels as low as 0.3 mg per cubic meter.

An incident occurred in a nursery for newborn infants in St. Louis in 1967 (Armstrong et al. 1969, Smith et al. 1996). Sodium pentachlorophenate had been used as an antimildew agent by the hospital laundry (such use is no longer allowed). Nine cases of illness were seen with fever and profuse sweating. As the disease progressed, respiratory rates increased and breathing became labored. Other common findings included rapid heart rate, enlarged liver, and irritability followed by lethargy. Laboratory tests showed progressive metabolic acidosis, proteinuria, increased levels of blood urea nitrogen, and x-rays suggestive of pneumonia or bronchiolitis. Two of the cases were fatal. The only source of exposure for the infants was skin absorption of the residues of sodium pentachlorophenate on the diapers, undershirts, and bedding. The product label warned against use in laundering diapers and the amount used was 3-4 times the amount recommended for regular laundry. Analysis of freshly laundered diapers showed a quantity of PCP ranging from 1.4 to 5.7 mg per diaper. One infant had 11.8 mg of PCP per 100 ml of serum before a transfusion was performed. A fatal case was found to have 2.1-3.4 mg per 100 grams in various body tissues. The average duration of the hospital stay in the nursery (when contaminated diapers were used) till the appearance of the first symptoms was 9 days.

A study in Germany examined data on 320 subjects with neurologic disorders categorized as probably or possibly due to environmental agents (Lohmann et al. 1996). Of these 320 cases, 136 (79 females and 57 males) showed signs of multiple chemical sensitivity (MCS). Indoor wood preservatives including PCP and/or lindane were implicated as causative agents in 63% of the MCS cases. The authors note that this was a purely descriptive study rather than a controlled epidemiologic study, so that proof of a causal relationship is not intended. Given the relatively large percentage of MCS cases associated with PCP, further study of PCP as a potential cause of MCS is warranted.

An extensive review of human PCP poisoning by Jorens and Schepens (1993) concluded that “use of PCP-based products as indoor wood preservatives poses an unacceptable risk to human health.” They recommend that workers in plants and sawmills be required to wear protective clothing that would prevent any skin contact with PCP. They report that four European countries, Sweden, the Federal Republic of Germany, Switzerland, and Denmark, have banned all use of PCP.

4.1.2 Case Series Involving Chronic Effects Associated with Health Effects of PCP in Humans

4.1.2.1 Cross-Sectional Studies

Bishop and Jones (1981) reported the occurrence of two cases of non-Hodgkin's lymphoma (NHL) among 158 workers at a plant that, until 1978, had manufactured PCP and its sodium salt. Several homologues of tetrachlorodibenzodioxin (TCDD), particularly the hexachloro and octachloro dibenzodioxins, were known to exist as contaminants of chemical intermediates (300 ppm) and the plant's final product (5 ppm). During the period of PCP production, a number of cases of chloracne were diagnosed; most were mild, some moderate, and a very few, severe. After cessation of PCP production in 1978, the two cases of NHL were discovered.

The first case was in a 69 year-old male involved in PCP manufacture from 1959 to 1972. In 1976, a tumor in the scalp developed with histology showing infiltration of the dermis and subcutaneous tissue with lymphoid cells suggesting NHL. This patient also had mild chloracne of the face and trunk. The second case occurred in a 53 year-old male who worked as an operator in PCP manufacturing from 1957 to 1978. During his employment, he had severe chloracne of the face, neck, trunk, and genitals. In 1978, this patient developed a tumor in the right occipital region of the scalp with histology showing malignant lymphoma described as NHL. Both NHL patients had worked in processes involving exposure to other chemicals including aromatic hydrocarbons, among them benzene.

No Standard Mortality Ratio (SMR) analysis was reported by the authors, but the expected number of cancers of this type (International Classification of Disease [ICD] 200 and 202) in this population of 158 workers was reported as 0.28. Considering ICD 200 alone, the expected number of cases would be 0.2.

Gilbert et al. (1990) conducted a cross-sectional study of 88 wood treaters in Hawaii and 58 controls to assess differences in morbidity and mortality. The exposed group was selected from a total of 182 workers who had worked for long periods and had chronic low-level exposure to wood treating chemicals including PCP. Exposed workers had to be currently employed in a Hawaiian wood treatment company for at least three months at the time of recruitment for the study or have been previously employed at least 12 months in a Hawaiian wood treatment company since 1960, including at least one 3-month period of continuous employment as a wood treater. Unexposed workers were matched on age, gender, race, level of physical activity, and weight. Of the total of 182 exposed workers recruited for the study, only 88 agreed to participate. Comparisons were made of detailed medical histories, laboratory and physiological tests, physical examinations, actual versus anticipated cancers, and causes of death for the exposed and unexposed.

While the occupationally exposed workers had significantly higher levels of PCP in urine compared to the controls (mean of 174 ppb vs. 35 ppb), no significant differences were seen in medical histories or results of physical exams between the cases and controls. With the exception of elevated hepatic enzymes in both groups, the laboratory data and review of organ systems revealed no clinically significant differences between exposed and unexposed groups. The three incident cases of cancer and the six deaths among the exposed workers were fewer than expected.

In a cross-sectional study of 398 women employed in day-care centers in Germany, the effect on the women's offspring resulting from exposure of the women to wood preservatives was studied by Karmaus and Wolf (1995). A number of health effects were measured by medical checkups with blood and urine sampling and face-to-face interviews for occupational, lifestyle, and reproductive histories. Official medical documents were used to obtain data on pregnancy outcome, birthweight, and length. Measurements of PCP, HCH, PCDD, and PCDF concentrations had been performed independently by the government as a screening program to control indoor air exposures. For each of the 556 pregnancies from the total study population, exposure to wood preservatives was estimated based on whether the woman had worked in any of 24 facilities known to have PCP concentrations >100 ppm. This assessment resulted in an exposed group of 214 and a control group of 184.

Of the 556 pregnancies, only 49 occurred during periods when the mothers were subject to exposure to wood preservatives. Of these 49 exposed pregnancies, only 32 were associated with first exposures. The number of induced pregnancies, spontaneous abortions, and births by cesarean section were increased in the exposed pregnancy group. Birthweights were reduced by 150 g and birth lengths reduced by 2 cm in the exposed group. Other observations included a higher prevalence of twins and more frequent complications during pregnancy in the exposed group compared to the unexposed group. Limitations of the study included some inequities between the exposed and unexposed groups and the possibility of bias. The women in the exposed group were older, had a higher average parity, were more often exposed in private homes, and more often had a desire for a child. The proportion of participation was lower in the control group. Birthweight and length data were verified with some knowledge of exposure status, and therefore could be somewhat biased. The study provides reasonable evidence that exposure of mothers during pregnancy to wood preservatives may decrease birthweights and lengths of offspring. However, considerable differences between the exposed and unexposed groups, and the possibility of some data collection bias, somewhat diminishes the importance of findings. Because exposures were to multiple substances, any negative detrimental effect cannot be attributed to a specific substance.

A cross-sectional study was performed by Walls et al. (1998) on a group of 127 timber sawmill workers who were self-identified as having health concerns related to PCP exposure. A questionnaire-based survey was used to collect data on occupational and lifestyle histories, exposure to PCP, past health status, and current symptoms. An exposure metric incorporating length of PCP exposure and a cumulative score for types of PCP work, type of vehicle, use of personal protection, and intensity of exposure, was calculated for each participant. Based on this exposure metric, participants were categorized into three exposure groups.

Within the limits imposed by the data used in this study, a dose-response relationship was identified between PCP exposure and reported symptoms associated in the literature with PCP exposure (sweating, weight loss, fatigue), and with a screening measure for neuropsychological dysfunction. The study was not designed to show association between PCP exposure and chronic or fatal diseases, such as cancer. While the results of the study agree with those in a number of other similar studies, major limitations lie in the fact that the study participants self-identified and many also had exposures to other chemicals typically used in the timber industry and to organopesticides.

4.1.2.2 Case Control Studies

Pearce et al. (1985) conducted a case-control study of 734 male malignant lymphoma and multiple myeloma patients to investigate possible associations of these diseases with particular occupations, especially farming. The cases consisted of all male patients registered with the New Zealand Cancer Registry between 1977 and 1981 who were classified under ICD codes 200-203 and who were at least age 20 at the time of registration. Four controls for each case (n=2936) also were selected from the registry and matched on age (within two years), year of registration, and who were not registered as cases of NHL, Hodgkins's disease, multiple myeloma, or Soft Tissue Sarcoma (STS).

The risk factor investigated in this study, occupation, was determined from cancer and death registrations, both of which included a brief description of each individual's current or most recent occupation at time of registration. This occupational information, codified through the New Zealand Standard Classification of Occupations was used to compare occupational distributions of cases and controls. Social class distributions also were compared for the cases and controls. A significant excess of professional and technical workers and workers in agriculture, forestry, and fishing were observed in the case group. A significant excess also was seen in occupations of the upper social classes. The authors suggested that the excess of professional and technical persons in the case group may have resulted from social class confounding.

The precision of the exposure variable (occupation) used in this study was very crude, and the excesses observed for agricultural occupations were not large. With regards to evaluating possible associations of PCP exposure with NHL, malignant lymphoma, or multiple myeloma, the significance of the findings in this study are limited.

Eriksson et al. (1990) assessed the influence of previous jobs and exposures to a number of agents, including pesticides, in a study of 237 males with STS and 237 controls matched on age, gender, and county of residence in Sweden. Cases were identified as all male patients, aged 25 to 80 years, who were reported to a cancer registry in Sweden with a diagnosis of STS. Exposure was assessed from responses to a questionnaire mailed to living participants or to next-of-kin of deceased participants. Included were questions about participants' complete work history, details on 16 specific occupations including farming, forestry, carpentry, painting, and mining, questions about various exposures, and questions about smoking. Incomplete information on exposures of particular interest was completed through telephone interviews. Completed questionnaires were collected for 218 cases and 212 controls. Exposure to chlorophenols and organic solvents for one week or more continuously or at least one month totally was classified as high grade; less exposure was classified as low grade.

Exposure to phenoxyacetic acids and high grade exposure to chlorophenols yielded a Relative Risk (RR) of 1.83 (95% Confidence Interval [CI] = 1.10-3.04) in the matched analysis, while exposure to phenoxyacetic acids only yielded a nonsignificantly increased RR of 1.34 (CI = 0.70-2.56). More interesting for the purpose of this review, high grade exposure to chlorophenols, excluding phenoxyacetic acid produced a RR of 5.25 (CI = 1.69-16.34). The same type exposure to PCP yielded a RR of 3.85 (CI = 1.15-12.88). The median latency for development of STS in persons with high grade exposure was 31 years, and exposure to PCP was a factor in almost all cases. No significant differences in relative risk of disease for cases and controls were observed for exposure to any other chemicals.

A case-control study of 30 males with STS and 52 males with malignant lymphoma was conducted to determine if there was an association between these diseases and past exposure to chlorinated phenoxy acid herbicides or chlorophenols (Smith and Christophers, 1992). The study was conducted in Australia, and cases were selected from all male cancer patients 30 years or older at the time of registration in the Victorian Cancer Registry over the period of 1982-1988. One population control and one cancer control for each case were matched on age, place of residence, and gender.

Exposure to pesticides and wood preservatives was assessed through interviews administered by an occupational hygienist with experience in pesticide exposures. The interview included questions about occupational history, education, leisure activities, and alcohol and tobacco use. If the interviewee reported exposure to the substances of interest for the study, details of the nature and duration of the exposure(s) were sought. Interview results showed that 16 cases, 18 population controls, and nine cancer controls were definitely or probably exposed to chlorinated phenoxy compounds or chlorophenols for at least one day prior to five years before the year of disease diagnosis. An additional seven cases, six population controls, and four cancer controls were possibly exposed.

Very little evidence was produced in this study to show an association between development of STS or malignant lymphoma and exposure to chlorinated phenoxy herbicides or chlorophenols. None of the relative risks for cases versus cancer controls or for cases versus population controls were significantly elevated. This is particularly notable since PCP is the main chlorophenol wood preservative used in Victoria, Australia.

Hardell et al. (1994) investigated possible associations between NHL and selected occupations or exposures to chlorophenoxyacetic acid, chlorophenols, or organic solvents. The 105 cases consisted of all men, 25-85 years old, who were admitted to an oncology center in Umea, Sweden between 1974 and 1978 with verified NHL. The 335 controls were matched to cases on gender, age, place of residence, vital status, and deceased controls also were matched on year of death.

Exposure assessment was based on responses to mailed questionnaires, supplemented with information collected via telephone. Occupations were classified by an established system and exposure to the substances of interest was classified as low-grade (less than one week continuously or less than one month in total) or high-grade if more than that. The questionnaire also provided for designation of the specific type of pesticide or preservative exposure. PCP was the chlorophenol most prominently used in Sweden.

No increased risk for NHL was found for any occupations identified from the exposure assessment questionnaire. The odds ratio for exposure to phenoxyacetic acids or chlorophenols was 4.6 (CI = 2.7-7.8) and for exposure to all types of phenoxyacetic acids was 5.5 (CI = 2.7-11). Exposure to organic solvents yielded odds ratio of 2.9 (CI = 1.6-5.6) for high-grade and 1.8 (CI = 0.8-3.8) for low-grade. Exposure to DDT also was positively associated with NHL (odds ratio = 2.4, CI = 1.2-4.9); smoking, use of snuff, or exposure to asbestos was not associated with NHL.

Of greater interest for this review, odds ratio for high-grade exposure to chlorophenols was 9.4 (CI = 3.6-25) and for low-grade exposure to chlorophenols was 3.3 (CI = 1.6-6.8). The odds ratio for high-grade exposure to PCP specifically was 8.8 (CI = 3.4-24). The risk for NHL was shown to be increased with increasing exposure to chlorophenols as measured in number of days.

Hardell et al. (1995) aggregated data from four previous case-control studies for a meta-analysis of association between exposure to pesticides and development of STS. With few exceptions, methods for the four supporting studies were similar. Cases were selected from cancer registries and controls from population registries. Deceased controls from a national registry on causes of death were used for deceased cases. A total of 434 male cases and 948 male controls were selected.

Exposure was assessed via an extensive self-administered questionnaire that queried for work history including specific job categories and exposures, smoking habits, and leisure time exposures. When necessary, telephone interviews were used to clarify or supplement the written questionnaire. For classification as exposed to phenoxyacetic acids or chlorophenols, a minimum of one day was required. Chlorophenol exposure was classified as high-grade (one week or more continuously or at least one month total) or low-grade if exposure was less. Occupations were classified according to the Nordic Working Classification.

No significant odds ratios were observed for any occupations with potential exposure to phenoxyacetic acids, chlorophenols, or dioxins. Risk of STS was significantly increased for workers exposed to chlorophenols. Most interesting for the purpose of this review was the odds ratio of 2.8 (CI = 1.5-5.4) for exposure to PCP. Contrary to other reports, tobacco use did not increase the risk for STS.

Dimich-Ward et al. (1996) conducted a case-control study on the 19,675 offspring of 9,512 sawmill production and maintenance workers to determine any association between paternal exposure to dioxin-contaminated chlorophenols and adverse reproductive outcomes in offspring. Cases were selected as children born to fathers who worked for at least one year between 1950 and 1985 in sawmills with potential for exposure to chlorophenates. For each case, five controls were chosen from the total set of offspring at risk when the case event occurred. For cases and controls, only offspring born after their father began employment at the study sawmills were used in the analyses.

Since chlorophenate measurements were not available, exposure assessments for each job title were made by experienced workers for each time period characterized as having relatively constant exposure. Each worker's exposure estimate was calculated by multiplying this exposure constant by duration of employment in each job for each time period.

Relative risk estimates for five major reproductive health indicators, including prematurity, size for gestational age, birthweight, stillbirth, and neonatal death, were calculated for each 100 hours of fathers' exposures to chlorophenates, estimated by four different methods based on hours of exposure relative to time of conception. None of the five major reproductive health indicators were positively associated with any of the exposure variables. When further analyses were performed to look for associations between fathers' exposures and a broad range of birth defects in offspring (3-digit ICD categories), statistically significant increases in risk for anomalies of the eye and genital organs, and for anencephaly or spina bifida, were associated with at least one of the exposure variables. Because of the large number of comparisons made in the analyses, the strength of the associations observed between fathers' exposures and anomalies of the genital organs and for anencephaly or spina bifida in offspring were weak. However, the association between fathers' exposures and anomalies of the eye in offspring were highly statistically significant ($p < 0.005$). When congenital anomalies, positively associated with fathers' exposures and with at least ten cases, were analyzed using four-digit ICD codes, fathers with higher cumulative exposure to chlorophenates during the three-month period before conception showed a 5.7-fold increased risk of having children with congenital cataracts (CI = 1.4-22.6). None of the other

associations between congenital anomalies and fathers' exposures, observed in the previous analyses, were very different when analyzed using the more specific ICD sub-categories.

This study has increased credibility because of the large size of the sawmill cohort and the specificity of the measured outcomes. The study is limited by the imprecise exposure estimates common to the majority of studies of health effects of exposure to chlorophenols and common contaminants. Also, because of the large number of comparisons made to identify associations between parental exposures and birth defects in offspring, the probability of observing chance positive associations was increased.

Gerhard et al. (1999) conducted a study of 171 women who were referred to a gynecological clinic in Germany because of infertility or other gynecological and/or endocrinological conditions to investigate possible effects of PCP exposure on the endocrine system. PCP serum levels greater than 20 μg/liter were measured in 65 of the women. The other 106 women who served as controls had PCP levels less than 20 μg/liter and were matched on age, underlying condition, and geographical region.

The median PCP level in the PCP group was 35.9 μg/liter compared to 9.5 μg/liter for the controls. Concentrations of FSH and triiodothyronine (T3) were significantly lower in the PCP group while stimulated cortisol concentrations were significantly higher. Euthyroid goiters were found more frequently in the PCP group than the controls (50% versus 30%).

This study showed that relatively high serum PCP levels in women are associated with a number of gynecological hormonal effects. While significant differences were observed between the PCP exposed and the controls, most measured parameters were within normal ranges. Interpretation and significance of the findings for the purpose of this review are limited, because of the quite unique characteristics of the study population. Adequate matching of controls increased the significance of the results.

4.1.2.3 Cohort Studies

A group comparison study was conducted to determine if differences in biochemical or hematological parameters, or in illness conditions existed between workers with or without exposure to PCP (Klemmer et al. 1980). Within a total cohort of 422 workers in Hawaii, 42 had no history of occupational exposure, 333 had histories of mixed exposures to various pesticides while working as farmers or pest control operators, and 47 worked at firms involved with treatment of wood products with PCP. Twenty-six workers in the PCP-exposed group were also exposed to other wood preservatives.

Results of clinical laboratory analyses showed that PCP exposure was highly associated with increased numbers of immature leucocytes (band cells), increased blood plasma cholinesterase levels, and increased alkaline phosphatase levels. Other analyses showed PCP exposure associated with increased gamma globulin, basophils, uric acid, and reduced serum calcium.

Analysis of illness prevalence rates showed that rates for conjunctivitis, chronic sinusitis, and chronic upper respiratory conditions were significantly higher among workers exposed to PCP than among the controls. Prevalence rates of infections of the skin and subcutaneous tissue, and gout were also higher in the PCP-exposed individuals, but not significantly.

The significant differences in clinical laboratory measurements between PCP-exposed and unexposed workers in this study do not appear to be associated with serious illness, with the possible exception of the increased uric acid levels and gout. Otherwise, the only detrimental health effects seen were increased prevalence of low-grade infections and inflammatory tissue reactions.

Triebig et al. (1987) conducted a longitudinal study of nerve conduction velocity (NCV) on 10 individuals who had worked with PCP or PCP-containing substances including tetrachlorophenol (TCP), γ hexachlorocyclohexane (lindane), and aldrin for an average of 16 years (range = 4-24 years). NCV measurements were available for comparison for years 1980 and 1984 for the 10 subjects. In addition, serum and urine concentrations of PCP and were measured.

Limited industrial hygiene data showed PCP concentrations in the air during the subjects' employment of less than the allowable limit (500 $\mu g/m^3$). Results of biological monitoring showed serum concentrations between 38-1270 $\mu g/m^3$ (upper normal limit = 150 $\mu g/m^3$) and urine concentrations between 8-1224 $\mu g/m^3$ (upper normal limit = 60 $\mu g/m^3$) showing definite internal exposure. No significant changes in NCV during the period 1980-1984 were demonstrated in any of the subjects, leading to the conclusion that occupational exposure to PCP over several years at the levels reported likely does not result in adverse effects on the peripheral nervous system.

Robinson et al. (1987) conducted a cohort mortality study of 2,283 plywood mill workers who were potentially exposed to PCP as well as wood dust, wood volatiles, formaldehyde, and carbon disulfide. The workers were employed at four softwood plywood mills in Washington and Oregon between 1945 and 1955 and followed through 1977. Protein glues were used to join the veneer plies, and PCP was often added to the glues as a mold preventative. PCP was also added to oils used as mold release agents during finishing of the plywood panels. Based on plant employment records, a subcohort of workers who were known to have exposure to PCP and formaldehyde were identified.

No statistically significant excess mortality was found in this study, although nonsignificant excesses were seen for lymphatic and hematopoietic cancer excluding leukemia (SMR=156, CI = 90-252). The excess risk increased with duration of employment which is consistent with other studies of wood processing industry workers. Based on two cases an SMR of 333 was observed for Hodgkin's disease within the subcohort identified specifically as having exposure to PCP and formaldehyde.

A number of cohort analyses have been conducted using the International Registry of Workers Exposed to Phenoxy Herbicides and Contaminants. The registry is maintained by IARC in association with US National Institute of Environmental Health Sciences and includes workers with potential for exposure during production or use (typically spraying) of chlorophenoxy herbicides or chlorophenols such as PCP. Polychlorinated dioxins such as tetrachlorodibenzo-*p*-dioxin (TCDD) and furans are often found as contaminants during production of both groups of compounds and therefore also are potential exposures for production workers and users. Saracci et al. (1991) and Kogevinas et al. (1992) reported a historical mortality study of 18,910 production workers or sprayers (male and female) from ten countries whose records were found in the registry. Follow-up was based on computerized national record systems or on active follow-up procedures. Exposure assessment for the study cohort was based on questionnaires completed by industrial hygienists, workers, or other factory personnel. Production records and job histories were also used when available. Workers were categorized according to type of work

(production or spraying), type of chemical (chlorophenoxy herbicide, chlorophenol, or TCDD), year since first exposed, years of exposure, and type of department (main production, maintenance and cleaning, other, and unclassifiable). Exposure classifications were as follows: exposed (n=13,482), probably exposed (n=416), unknown (n=541), and non-exposed (n=3951). Exposed workers (13,482) were defined as those known to have sprayed chlorophenoxy herbicides and those who worked at factories that produced chlorophenoxy herbicides or chlorophenols in departments such as synthesis, formulation, maintenance, laboratory, transportation, cleaning, and others likely to provide opportunity for exposure to these substances.

For the total cohort, mortality from all causes was lower than expected, although workers in the unknown exposure group showed high all-cause mortality (SMR=319, CI = 182-518). Workers in the exposed group had SMRs greater than 200 for cancers of unspecified digestive organs, nose and nasal cavity, breast (males), testis, other endocrine glands, thyroid, and for Soft Tissue Sarcoma (STS). Four deaths from STS occurred among males who had worked as sprayers. All deaths occurred 10-19 years after first exposure which produced a six-fold excess risk for STS within the entire cohort. For this category of duration of exposure, the excess risk for exposed sprayers was even greater (SMR=882, CI = 182-2579). Mortality from Hodgkin's disease was less than expected. Mortality from NHL was slightly increased among production workers with most of the 11 deaths occurring more than 10 years after the workers were first exposed. Increased risks for cancers of the thyroid and other endocrine glands were also found, but these were based on very few deaths.

While the major emphasis of this study was exposure to chlorophenoxy herbicides, many workers in the study population also had exposure to chlorophenols, including PCP. In addition, many of the production workers had potential for exposure to dioxin and furan contaminants which is usually the case for any workers exposed to PCP or other chlorophenols. The excess risk found for death from STS following long-term exposure is consistent with a number of other studies of similar populations.

Cheng et al. (1993) investigated the prevalence of chloracne, urinary porphyins, and nerve conduction velocities in a cohort of 109 workers who had worked in the PCP department at a large production plant in China during the years 1968 to 1985. In this plant, four separate buildings are involved in the pentachlorophenol manufacturing process: the T.B. building (trichlorobenzene), the HCB building (hexachlorobenzene), the PCPNa building (pentachlorophenate sodium), and the PCP building (pentachlorophenol). The cohort included four subgroups who worked in these four separate buildings. The workers did not typically rotate among different jobs, but work clothes were laundered in the same machine. Workers from all four buildings were defined as the exposed group. A control group, matched on age and gender, was selected from workers in a NaCl plant with no known hazardous exposures. Data collection consisted of examination by a dermatologist, retrieval of work history, and analysis of a spot urine sample for delta-amino levulinic acid (δ ALA) and porphyrins. Median and peroneal motor nerve conduction was also measured for workers and controls.

The prevalence rate of chloracne in the cohort was 60-95% with the highest prevalence seen in workers in the T.B. building(20/21, 95%) and among the maintenance workers (13/15, 87%). Chloracne developed an average of one year after first exposure and progressed from disfiguring facial blemishes, through cysts, to scarring. Areas most affected were the scrotum, around the eye, and behind the ear.

Levels of urinary δ ALA and porphyrins were higher among workers in the PCP plant than in controls. There was no significant difference in levels of δ ALA or porphyrins among the four subgroups.

Workers in the T.B. and PCP buildings had slower motor nerve conduction (both median and peroneal) when compared with matched controls. However, differences were statistically different only for median nerve conduction in the workers in the T.B. building.

Therefore, this study demonstrated that workers in the pentachlorophenol plant tended to have higher incidences of chloracne, increase level of urinary porphyrins and/or δ ALA, and slower motor motor neve conduction.

A cohort of 770 workers at a large US chemical manufacturing plant with potential for exposure to PCP was evaluated for mortality from 1940 through 1989 (Ramlow et al., 1996). This cohort was a subset of a larger cohort of people who worked in departments with potential for exposure to technical-grade PCP products found to contain polychlorinated dibenzodioxins (PCDDs) and dibenzofurans as process byproducts. Potential for exposure to PCP was assessed by evaluating available industrial hygiene data, including some quantitative environmental PCP measurements, and process data. Potential exposure for each job held by cohort members were assigned an estimated exposure intensity score on a scale of 1 (low) to 3 (high). An estimated cumulative exposure index was calculated for each subject by multiplying duration for each job by the estimated exposure intensity for the job and summing.

The study cohort provided 20,107 person-years of observation, during which 229 deaths were observed. No excess in deaths for all causes, nor for all cancers were seen. There were also no excess deaths in the cancer categories of particular interest for this type of population including cancers of the liver (primary) and thyroid gland, leukemia, and other lymphohematopoietic cancers. Noncancer mortality statistics were also unremarkable. Unexpectedly, there were small excesses in deaths from cancers of the stomach, larynx, and kidney, none of which were statistically significant.

When cumulative PCP exposure was logged for 5 and 15 years, possible trends for excess deaths were observed for cancer of the kidney, other and unspecified lymphohematopoietic cancer, gastric and duodenal ulcer, cirrhosis of the liver, and for all accidents.

Hertzman et al. (1997) conducted a cohort study of more than 26,000 sawmill workers in Canada to further investigate the suspected association of exposure to chlorophenate wood preservatives with increased risk of NHL and STS. Secondary illnesses of interest included Hodgkin's disease, lung cancer, and nasal cancer. The study cohort was selected from 11 chlorophenate using mills (23,829 workers) and three control mills that did not use chlorophenates (2658 workers). Plant records were available to determine work histories for study cohort members, including duration of work within different job titles. Representative exposures were determined for three or four time periods for each mill. A cumulative exposure score was calculated for each worker by multiplying the job title specific exposure score for each job held by the worker by the length of employment and summing.

The study cohort provided 583,190 person-years of observation in the chlorophenate mills and 41,280 person-years of observation for the nonchlorophenate mills. SMRs and SIRs were calculated by counting

person-years by two methods, (1) until the year last known alive and (2) until the end of the follow-up period (1990 for SMRs, 1989 for SIRs). Within the total cohort, there were 4710 deaths between 1950 and 1990, and 1547 incident cases of cancer between 1969 and 1989.

The all-cause SMRs for workers at chlorophenate mills were 0.96 and 0.81 for these two methods. Few positive associations between chlorophenate exposure and mortality were observed. When mortality was plotted against level of exposure to chlorophenates, no statistically significant exposure response gradient was seen for any causes of death of interest, although there was hint of a trend for lymphosarcoma.

SIRs for several cancers appeared to be in excess when person-years were counted to the last known year alive, but were not in excess when person-years were counted to 1989. Nonsignificant excesses for both NHL and SRS were observed in analyses using both methods for calculating person-years. The authors opined that the increased risk for NHL, even though slight, was meaningful since (1) the case fatality rate was lower than expected and (2) a trend of increasing risk with increased exposure was observed when person-years lost to follow-up were included. SIRs greater than 1.5 were also observed for cancers of the tongue, gum, eye, and endocrine gland, and for nasal cancer, but these also were nonsignificant.

Many of the above-listed PCP studies are well structured and appear in the literature to be well executed. Populations are well defined, controls are generally selected appropriately, and analyses are appropriate and adequate. However, major weaknesses in exposure assessment methods often limit the validity of reported findings, either positive or negative. Of the original articles reviewed, a large majority used questionnaire or interview data, provided either by the study participants or by surrogates, as exposure variables. Often, even this information was necessarily for mixed exposures including known or unknown contaminants rather than for PCP alone. Very rarely was actual industrial hygiene monitoring data available for assessment of individual exposures. In some instances, industrial hygiene expertise was used to judge exposures, but this assessment is also relatively crude.

Even considering the above limitations, a reasonably strong argument can be made that exposure to PCP is associated with increased risks of a number of diseases, namely chloracne, STS, and NHL. Increased risks of developing STS were reported in six studies, although statistical significance was reached in only three. Of five studies reporting increased risk for NHL, only one was statistically significant. Increased risks were also reported for lymphatic cancer, hematopoietic cancer, and PD, but the associations were generally not significant. While it is known that nerve conduction velocity is slowed by exposure to chlorophenols, as well as many other chemicals, studies with this dysfunction as an endpoint showed ambivalent results. Two studies showed associations between exposure of parents to chlorophenols and negative effects in subsequently-born offspring, but results in these studies were not statistically significant.

Considering the number of studies, the consistency among a number of outcomes, as well as the general absence of statistical significance, there appears to be reasonable evidence that exposure to chlorophenols may often be associated with chloracne, STS, NHL, and possibly abnormal births. Whether these deleterious health effects result from exposure to PCP specifically, or to one or more other chemicals typically found as contaminants, is not clear. Based on the evidence collected to date, careful control of exposures to chlorophenols, including PCP, is certainly warranted.

4.2. PRECHRONIC AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS

4.2.1. Prechronic Studies

4.2.1.1. Oral studies

4.2.1.1.1. Laboratory animals

The oral LD_{50} for male and female rats receiving PCP (90.4% containing 0.9 ppm hexachlorodibenzo-p-dioxin) by gavage in corn oil vehicle was 155 mg/kg for males and 137 mg/kg for females (Norris, 1972). Deichmann et al. (1942) reported an oral LD_{50} value of 27.3 mg/kg for rats administered PCP in 0.5% Stanolex fuel oil, 77.9 mg/kg for PCP administered in 1% olive oil, and 210.6 mg/kg for sodium pentachlorophenate administered in 2% water. Oral LD_{50} values for mice, rats, and hamsters ranged from 27–175 mg/kg as reported by IARC (1991). Clinical signs observed in dogs, rabbits, rats, and guinea pigs consist of increased blood pressure, hyperpyrexia, hyperglycemia, glycosuria, hyperperistalsis, increased urinary output followed by decreased urinary output, and rapidly developing motor weakness. Dying animals showed signs of complete collapse, asphyxial convulsive movements, and rapid onset of rigor mortis upon death. Necropsy examinations showed vascular damage with heart failure and involvement of "parenchymous" organs (Deichmann et al., 1942).

Deichmann et al. (1942) reported no deaths or signs of toxicity in a group of 23 rabbits given 3 mg/kg of technical grade PCP (tPCP) as a 1% aqueous solution (dosing method not reported but probably gavage) for 90 successive doses except on Sundays. In another study by Deichmann et al. (1942), five rabbits were administered tPCP orally at a dose 35 mg/kg/day as a 0.5% solution for 15 days followed by a 5% solution to gradually increase the dose 600 mg/kg/day (twice the lethal dose) during the next 19 days. All animals died, one after ingesting a total dose of 1.9 g, two after ingesting 2.9 g, and two after ingesting 3.9 g. Effects attributed to PCP administration included weight loss and anemia.

Deichmann et al. (1942) also administered tPCP in the diet to groups of 10 rats at a dose of 5 mg/day in 8.5 g food for 26 weeks or 3.9 mg/day in 13 g food for 28 weeks. The comparison group was not described. No growth occurred in rats administered 5 mg/day, and the rats receiving 3.9 mg/day had body weights below normal. No gross findings were noted for either group and microscopic findings were considered insignificant.

In a study conducted by Knudsen et al. (1974) groups of ten male and ten female Wistar weanlings were fed diets containing 0, 25, 50, or 200 ppm tPCP (contained 200 ppm OCDD and 82 ppm pre-OCDD) for 12 weeks. The only effects that appeared to be related to administration of the test material or which the effect was considered biologically significant was the dose-related increase in aniline hydroxylase in liver microsomes and centrilobular vacuolation. Aniline hydroxylase activity was significantly elevated in male rats given the 200-ppm diet for 6 or 12 weeks and female rats given 200-ppm diet for 6 weeks; the activity also showed a consistent increase at 50 ppm at both time points. The incidence of centrilobular vacuolation was increased in male rats at 50 ppm (4/10) and 200 ppm (5/10) compared with 2/10 for the control and 0/10 for the 25-ppm group. The LOAEL for this study was 50 ppm based on liver toxicity; the NOAEL was 25 ppm.

Kimbrough and Linder (1978) compared the effect of tPCP (84.6%) and purified PCP (>99%) (sometimes referred to as analytical PCP (aPCP)) administered in the feed to male and female Sherman

rats for 8 months and observed that tPCP caused more severe effects than did pure PCP. PCP was administered at concentrations of 0, 20, 100, or 500 ppm. The weight-normalized doses ranged from ~0.85–1.7 mg/kg/day at 20 ppm, ~4.1–8 mg/kg/day at 100 ppm, and ~20–40 mg/kg/day at 500 ppm. No deaths or signs of toxicity were observed with either tPCP or aPCP, but final body weights at 500 ppm were significantly reduced by 15-16% for both sexes fed tPCP and by 10% for males fed aPCP. Dose-related effects were observed in the liver, particularly in rats fed tPCP. Liver weights were elevated in both sexes at 500 ppm tPCP. Treatment with 500 ppm tPCP caused liver toxicity manifested by periportal fibrosis, hepatocyte hypertrophy, vacuolation, pleomorphism, and necrosis, bile duct proliferation, adenofibrosis (cholangiofibrosis), cytoplasmic hyaline inclusions, and abundant brown pigment in macrophages and Kupffer cells (porphyria) in one or both sexes. At 100 ppm tPCP, similar but less severe effects were observed except adenofibrosis and bile duct proliferation did not occur at this dose. A small neoplastic nodule was seen in the liver of one rat given the 100-ppm dietary concentration. The only effect observed at 20 ppm tPCP was slight hepatocyte hypertrophy and vacuolation. In rats administered 500 ppm aPCP, liver findings included slight hepatocyte hypertrophy, eosinophilic cytoplasmic inclusions, and brown pigment in macrophages in animals of one or both sexes. This study showed that the no-observed-adverse-effect levels (NOAEL) for tPCP and aPCP are different: <20 ppm dietary concentration for tPCP and 100 ppm for aPCP.

Kimbrough and Linder (1975) reported the light microscopic and ultrastructural effects in the liver of male rats (strain not specified) administered 1000 ppm tPCP or aPCP for 90 days. Each PCP treatment group consisted of 10 male rats, and a group of 10 control rats was included for each treatment group. The liver was enlarged in all animals treated with PCP. Light microscopy revealed foamy cytoplasm or pronounced vacuolation of hepatocytes, single cell hepatocellular necrosis, cytoplasmic inclusions, slight interstitial fibrosis, and prominent brown pigment in macrophages and Kupffer cells in the liver of rats fed tPCP. Ultrastructurally, the smooth endoplasmic reticulum was increased, many lipid vacuoles were present, and the mitochrondria had an atypical appearance. In rats fed the aPCP, the hepatocytes were enlarged and many cells contained cytoplasmic inclusions; ultrastructurally, a slight increase in smooth endoplasmic reticulum, atypical mitochondria, and some lipid vacuoles were observed. This study showed that administration of tPCP and aPCP cause similar ultrastructural effects in the liver.

Renner et al. (1987) reported on the toxicity of PCP administered by gavage to rats for 4 weeks followed by 2 weeks of recovery. Groups of 24 female Sprague-Dawley rats (3-months old) were given aPCP (<99%) 0.2 mmol/kg/day (53.27 mg PCP/kg/day), 1 mL/day corn oil (vehicle), or no treatment for the entire study duration. The results showed that body weights were not significantly affected by treatment with PCP; no clinical signs were observed, but three PCP-treated animals died on day 28 or 32 of the study. Relative liver weight (% body weight) was elevated during treatment, but returned to normal after treatment. Erythrocyte parameters (RBC, hematocrit, and hemoglobin) levels were decreased throughout treatment and showed no evidence of reversal during recovery; erythrocytes appeared polychromatic and anisocytotic. Microscopic effects in the liver consisted of enlarged pleiomorphic hepatocytes with degeneration of liver cells, and acidophilic bodies in the sinusoids.

The NTP (1999) reported on a 28-day toxicity study in groups of 10 male and 10 female F344N rats administered PCP (99% purity) in the diet at concentrations of 0, 200, 400, 800, 1600, or 3200 ppm; average daily doses were 0, 20, 40, 75, 150, and 270 mg/kg, respectively. One male and two females receiving 3200 ppm died before the end of the study. A net weight loss was observed for male and female rats receiving 3200 ppm. Females had 14–60% reductions in mean final body weights at

200–1600 ppm and males had 8 and 36% reductions at 800 and 1600 ppn, respectively. Decreased food consumption likely contributed to decreased body weight gain at the two highest doses for both sexes. Microscopic effects of PCP administration were confined to the liver (hepatocyte degeneration and centrilobular hypertrophy) and testes (degeneration of the germinal epithelium). The incidence and severity of hepatocyte degeneration was significantly increased in males receiving ≥400 ppm and in females receiving ≥800 ppm. The incidence of centrilobular hypertrophy was significantly increased only at 3200 ppm in both sexes. In males, degeneration of the testicular germinal epithelium occurred in all males receiving 3200 ppm, but in none of the control or lower dose groups. The LOAEL was 400 ppm (40 mg/kg/day) for male rats based on liver toxicity and 200 ppm (20 mg/kg/day) for females based on reduced body weight. The NOAEL was 200 ppm for males and <200 ppm for females

Villena et al. (1992) examined the microscopic lesions in liver and kidneys of rats receiving PCP (grade not specified) for different treatment times. This study also included an examination of lesions in the sciatic nerve. Groups (number not reported) of male Wistar rats were given drinking water containing PCP at concentrations of 0.3 mM (80 mg/L) for 60 days, 1.0 mM (266 mg/L) for 60 days or 90 days, 3.0 mM (800 mg/L) for 120 days, or drinking water without added PCP. The investigators did not describe effects in rats given 0.03 mM or 1.0 mM PCP for 60 days. Microscopic effects in the liver at 1.0 mM for 90 days or 3.0 mM for 120 days consisted of increased granular endoplasmic reticulum, hydropic vacuolar degeneration, and total cell degeneration (necrosis), congested portal veins, enlarged and congested sinusoids, and bile duct hyperplasia. Changes in the kidneys occurred primarily in the cortex and were characterized by glomerular congestion with thickening of the capillary wall, glomerular hyalinization, and hyaline casts in the lumen of the proximal convoluted tubules. The investigators noted that the kidney was more affected than the liver, and the effect implies that destruction could progress to loss of function. It should also be noted that PCP has low solubility in water (80 mg/L; Budavari et al., 1996), while the sodium salt is freely soluble in water. The investigators did not state whether the animals were treated with tPCP, aPCP or a sodium nor were effects on body weights, food or water consumption, or clinical signs described. Thus, the results of this study should be interpreted with caution.

Johnson et al. (1973) described a study in which Sprague-Dawley rats were fed diets containing three grades of PCP (commercial, improved, and chemically pure) for 90 days. None of these grades contained TCDD; the commercial PCP was 85-90% pure and contained 19 ppm HxCDD and 1980 ppm OCDD; the improved PCP was 88–93% pure and contained only 1 ppm HxCDD and 26 ppm OCDD; the chemically pure PCP contained no detectable levels of chlorinated dioxins. Specific contaminant congeners were not identified in this study. Treated rats received PCP at doses of 3, 10, or 30 mg/kg/day and controls received an untreated diet. No grade of PCP had an effect on body weight. Treatment with commercial PCP caused depressed erythrocyte count, hemoglobin concentration, and hematocrit at 30 mg/kg/day; elevated serum alkaline phosphatase levels at all concentrations and serum albumin at 10 and 30 mg/kg/day; and elevated liver and kidney weights at all concentrations. Microscopic lesions (minimal focal hepatocellular degeneration and necrosis) were seen only in the liver at 30 mg/kg/day. The only effects seen after administering chemically pure PCP and improved PCP were elevated liver weight at 10 and 30 mg/kg/day and elevated kidney weight at 30 mg/kg/day. The LOAEL for commercial PCP was 3 mg/kg/day and 10 mg/kg/day for improved and pure PCP. The NOAELs were <3 mg/kg/day for commercial, and 3 mg/kg/day for improved and pure PCP.

In an NTP (1989) study, groups of male and female $B6C3F_1$ mice were fed tPCP (90.4% purity), Dowicide EC-7 (EC-7, 91% purity), or aPCP (98.6% purity) for 30 days. The male groups consisted of

19 mice; the female groups consisted of 11 control mice, 15 mice/group treated with tPCP, and 5 mice/group treated with EC-7 or aPCP. Dietary concentrations based on the PCP content were 0, 20, 100, 500, 2500, or 12,500 ppm. Treatment-related effects included clinical signs, increased mortality, decreased body weight gain, leukopenia, liver toxicity, and induction of hepatic microsomal enzymes (Table 6). The data show that effects occurred primarily at concentrations ≥500 ppm; however, liver lesions observed in one female mouse receiving 100 ppm aPCP is likely treatment related. Effects other than those listed in Table 6 are discussed below. Rectal temperature was decreased by at least one degree in most groups of mice receiving 2500 or 12,500 ppm all grades. Urine color ranged from yellow to dark brown in males and females fed the mid and high dietary concentrations of all PCP grades. Total liver porphyrins were increased in males receiving all three grades and in females receiving tPCP and aPCP. Special studies on mitochondrial oxidative phosphorylation showed uncoupling of oxidative phosphorylation (decreased phosphate:oxygen ratio) at the high concentrations of aPCP, at low concentrations of tPCP, and the lower concentrations of EC-7 (<2500 ppm). The phosphate:oxygen ratio was increased at 2500 ppm EC-7. The LOAELs and NOAELs for this study are presented in Table 6.

Table 6. Findings in Male and Female $B6C3F_1$ Mice Fed PCP Continuously for 30 Days

Effects	Technical Grade PCP	Dowicide EC-7	Pure PCP
PCP concentration	20, 100, 500, 2500, 12,500 ppm	20, 100, 500, 2500, 12,500 ppm	20, 100, 500, 2500, 12,500 ppm
Mortality	14/19 ♂, 7/15 ♀ at 12,500 ppm	19/19 ♂, 5/5♀ at 12,500 ppm 9/19 ♂, 1/5 ♀ at 2500 ppm	19/19 ♂, 5/5 ♀ at 12,500 ppm 2/19 ♂ at 2500 ppm
Clinical signs	Weakness, lethargy, shallow breathing, severe weight loss, convulsions, and death at 12,500 ppm		
Body weight	weight loss, 12,500 ppm both sexes; decreased weight gain, 2500 ppm ♂	decreased weight gain at 2500 ppm ♂	decreased weight gain at 2500 ppm, both sexes
Liver weights	Absolute and relative weights increased at higher concentrations, both sexes		
Serum enzymes	Alkaline phosphatase, cholesterol, SGPT increased for all animals, both sexes		
Serum γ-glutamyl transpeptidase	Greatly increased in both sexes at 2500 and 12,500 ppm	no treatment-related increase	
Hematology	Marked reduction in leukocyte count (lymphocytes primarily affected) in males and monocytosis in both sexes; platelet count increased by tPCP, both sexes		
Hepatic microsomal enzymes	AHH increased for both sexes, dose related for tPCP; P450 increased in both sexes, dose related for tPCP and aPCP		
Liver lesions[a]	≥500 ppm, both sexes, more diffuse and severe than with other grades	≥500 ppm ♂, ≥2500 ppm ♀	≥500 ppm ♂, ≥100 ppm, ♀
LOAEL	500 ppm, both sexes	500 ppm ♂, 2500 ppm ♀	500 ppm ♂, 100 ppm ♀
NOAEL	100 ppm, both sexes	100 ppm ♂, 500 ppm ♀	100 ppm ♂, 20 ppm ♀

Source: NTP, 1989
[a]Centrilobular cytomegaly, karyomegaly, nuclear atypia, degeneration, or necrosis

Kerkvliet et al. (1982a) administered tPCP (86% purity) in the diet to groups of 8-12 random-bred Swiss-Webster or C57Bl/6 (B6) female mice for 8 weeks. The Swiss-Webster mice received 0, 50,

250, or 500 ppm and the B6C3F1 mice received 0, 50, 100, or 250 ppm. Additional groups of six Swiss-Webster female mice received 0 or 250 ppm tPCP in the diet for 8 weeks followed by an 8-week recovery; the animals were sacrificed at 2-week intervals throughout treatment and recovery. Additional groups of 15–16 B6 female mice were administered 0 or 1000 ppm aPCP (>99% purity) for 8 weeks. No treatment-related effect was observed on body weight for either strain. Liver weights were significantly increased at the mid (+13 to +18%) and high doses (+34 to +57%) for both strains. Thymus weights were reduced at the high dose for both strains, significantly for B6 mice at 250 ppm. According to the investigators, liver pathology was similar to that described by Kerkvliet et al. (1982b) (see below). In the serial sacrifice study in Swiss-Webster mice, relative liver weight, serum ALT and LDH levels were elevated as early as 2 weeks after treatment with tPCP. Complete recovery occurred by 4-6 weeks after treatment was stopped. B6 mice treated with 1000 ppm aPCP had no changes in body weight compared with controls, but had relative liver and spleen weights that were significantly elevated by 76 and 26%, respectively showing that effects on the liver can be caused by PCP alone without the contaminants. The LOAELs for this study were 250 ppm for Swiss-Webster mice and 100 ppm for B6 mice, based on liver toxicity. The NOAEL was 50 ppm for both stains. This study was conducted to assess the effect of PCP on immune response in mice; these results are discussed in Section 4.4.2.

Kerkvliet et al. (1982b) reported that male B6 mice administered 0, 50, or 500 ppm tPCP (86% purity) or aPCP (>99% purity) for 12 weeks showed no effects on growth rate, overt signs of toxicity, or microscopic changes in the kidney, spleen, or adrenal gland. The liver showed dose-related mild to marked hepatocyte swelling for both grades of PCP. Mild to marked hepatocyte swelling, nuclear swelling and vacuolization with eosinophilic inclusions in nuclear vacuoles, and mild to moderate multifocal necrosis were observed at 500 ppm.

In a study conducted by NTP, groups of 25 male B6C3F1 mice and groups of 10 female mice of the same strain received either technical grade pentachlorophenol (90.4% purity) at 200, 600, or 1800 ppm; Dowicide EC-7 (91% purity) at 200, 600, or 1200 ppm; pentachlorophenol DP-2 (91.6% purity) at 200, 600, or 1200 ppm; or pure pentachlorophenol (98.6% purity) at 200, 500, or 1500 ppm for 26-27 weeks. In addition to standard parameters, behavioral studies and body temperature measurements were performed on groups of 10 animals/sex at weeks 5 and 26. Behavioral measurements included examination for neurologic effects (righting reflex, spontaneous motor activity, acoustical startle response, visual placement response, grip strength, and rotarod testing). Mice designated for measurement of liver biochemistry were also examined for induction of liver AHH. It is important to note that in this study, the various dose groups were exposed to differing levels of chlorinated dibenzodioxins and chlorinated dibenzofurans, contaminants of pentachlorophenol that are known to produce immunotoxic effects.

Effects of administration of the four grades of PCP to mice for 6 months are summarized in Table 7. All groups of female mice receiving each grade of PCP had significantly increased absolute and relative liver weights. Groups of male mice receiving ≥200 ppm tPCP or aPCP, 1200 ppm EC-7, and 600 and 1200 ppm DP-2 also had significantly increased liver weights. Spleen weights were increased for all groups of male mice except the low dose of each grade; spleen weights were significantly decreased in females at 1200 ppm EC-7 and DP-2 and 600 ppm tPCP. Thymus weights were not significantly affected. Liver lesions consisting of karyomegaly, cytomegaly, hepatocellular degeneration and necrosis occurred in all males and females at all doses and grades of PCP. Liver pigmentation (porphyrin) was observed in at least six to ten males and females administered all doses of tPCP, the mid and high dose of DP-2 or EC-7,

and the high dose of aPCP. The slight increase in porphyrin was not considered indicative of porphyria. Liver inflammation was observed in eight to ten high-dose male mice receiving tPCP, DP-2, and aPCP and the females receiving tPCP. Bile duct hyperplasia occurred in all high-dose mice receiving tPCP. In addition, degenerative changes in the spleen, bone marrow, thymus, and testes occurred in animals that died before study termination. Effects observed with tPCP were generally more severe than those observed with other grades; however, nasal lesions were seen only with aPCP and EC-7. Other effects included dark urine color and elevated urine creatinine levels in high-dose males administered each grade, and dark urine color in high-dose females administered EC-7 and aPCP. In contrast to the 30-day study, rectal temperature was not elevated and leukocyte counts were not affected.

There were no treatment-related neurobehavioral effects observed at 5 weeks except for those mice receiving technical grade pentachlorophenol, in which a dose-dependent decrease in motor activity and rotarod performance was reported. After 26 weeks exposure, an increase in both motor activity and startle response was observed in female mice. No consistent effects were observed in any of the other behavioral parameters measured for any of the four grades of pentachlorophenol. Technical grade pentachlorophenol exposure resulted in the most marked inhibtion of the plaque-forming response following immunization with sheep red blood cells at all doses tested, while the DP-2 formulation resulted in marked inhibition only at the highest dose. Dowicide EC-7 and pure pentachlorophenol did not affect this response. The degree of immunosupression was consistent with the degree of exposure to dioxin and dibenzofuran contaminants in pentachlorophenol. The LOAEL was 200 ppm for all grades of PCP because liver lesions were observed in all groups of mice tested. A NOAEL was not established for either PCP grade, because liver toxicity was observed at all doses for each grade of PCP.

Table 7. Comparison of the Effects of Four Grades of PCP Administered Continuously in Feed to Male and Female B6C3F$_1$ Mice for 6 Months

Effects	Grade[a]			
	Technical (90.4% purity)	DP-2 (91.6% purity)	Dowicide EC-7 (91% purity)	Pure (98.6% purity)
PCP concentration	200, 600, 1800 ppm	200, 600, 1200 ppm	200, 600, 1200 ppm	200, 500, 1500 ppm
Mortality	100% ♂, ♀ at 1800 ppm (highest dose); 0% at lower doses	2/10 ♂ at 1200 ppm; no other mortality observed	1/10 ♂ at 200 ppm; no other mortality observed	2/20 ♂ at 200 ppm; no other mortality observed
Clinical signs	piloerection, enophthalmos, hunched posture, thinness, weakness, and inactivity at 1800 ppm tPCP and 1200 ppm DP-2		none	none
Final Body weights	no effect on survivors	no effect	11–13% decrease	no effect
Body weight gain	no effect on survivors	⇓at 1200 ppm, ♂	⇓ at 1200 ppm, ♂, ♀	⇓ at 1500 ppm, ♂, ♀
Serum enzymes SGPT	dose-related ⇑ all grades, both sexes, DP-2 most effective;			
SGOT	⇑ at 600 ppm,♂, ♀	⇑ at 1200 ppm, ♂, ♀	no treatment-related ⇑	⇑ at 1500 ppm, ♀
γ-GTP	no effects	marked ⇑ at 1200 ppm, ♂	no effects	⇑ at 1500 ppm, ♂
Liver weight	⇑ at 200 and 600 ppm, ♂, ♀	⇑ at 600 and 1200 ppm, ♂; ≥200 ppm, ♀	⇑ at 1200 ppm, ♂; ≥200 ppm, ♀	⇑ all doses, ♂, ♀,
Hepatocellular lesions[b]	all doses, less severe in females than in males			
Liver pigment	all doses, ♂, ♀	600 and 1200 ppm, ♂, ♀	600 and 1200 ppm, ♂, ♀	1500 ppm, ♂, ♀
Bile duct hyperplasia	all ♂ and ♀ at 1800 ppm	no effect	no effect	no effect
Urinary bladder pigmentation	minimal severity at all doses, less severe in females than in males receiving EC-7 or aPCP			
Nasal lesions[c]	no effect	no effect	≥600 ppm ♂, all doses ♀	1500 ppm, ♂; all doses ♀
Hepatic microsomal AHH induction	200 and 600 ppm ♂	all doses, maximum at 600 ppm	1200 ppm	1500 ppm
Hepatic P450 induction	200 and 600 ppm	all doses	1200 ppm	1500 ppm
NOAEL	none established; effects at all concentrations			

Source: NTP, 1989

[a]. Dietary concentrations: tPCP 200, 600, 1800 ppm; DP-2 and Dowicide EC-7: 200, 600, 1200 ppm; pure PCP: 200, 500, and 1500 ppm.

[b]Cytomegaly, karyomegaly, degeneration, and necrosis

[c]Nasal mucosal metaplasia and goblet cell hyperplasia

4.2.1.1.2. Domestic animals

In a study on young, 6-week-old pigs, tPCP (purity not reported; contained 4.7% TCP and 3.2 ppm total octachlorodibenzodioxins and furans) was administered in capsules at doses of 0, 5, 10, or 15 mg/kg/day for 30 days (Greichus et al., 1979). Each group consisted of six pigs; the sex was not reported. No overt clinical signs or weight changes were noted in PCP-treated pigs compared with the controls. RBC parameters evaluated at 15 and 30 days showed no changes significantly different from those of controls; the WBC for the 15-mg/kg/day group was significantly lower than control values at 15 and 30 days and for the 10-mg/kg/day group at 30 days; however, all values were within normal range. The only serum chemistry change was significantly elevated blood urea nitrogen (BUN) at 10 and 15 mg/kg/day after treatment for 15 days; the increase at 15 mg/kg/day at study termination did not achieve statistical significance. The relative liver weights were increased by 18% and 17% at 10 and 15 mg/kg/day, respectively; histopathological findings in the liver consisted of nonspecific cloudy swelling of hepatocytes accompanied by cellular enlargement, finely vacuolated cytoplasm, and decreased sinusoids. The investigators did not state specifically, but it is assumed that the histopathologic changes occurred at 10 and 15 mg/kg/day. Blood PCP levels ranged from 63 to 71.5 ppm for all doses at 15 days and 67.6 to 78.1 ppm at 30 days; no clear dose effect was observed. The highest tissue levels were in kidney and liver followed by muscle. The LOAEL for pigs treated with PCP for 30 days was 10 mg/kg/day based on liver toxicity; the NOAEL was 5 mg/kg/day.

Hughes, et al. (1985) fed tPCP (85–90%) or aPCP (99.02%) to 15 Holstein bull calves (7 days old). aPCP and tPCP was dissolved in corn oil, added to milk, and fed twice daily to the calves at doses of 0, 2, or 20 mg/kg/day. One calf in each of the high-dose groups fed aPCP or tPCP died after acute toxicity (elevated temperature, rapid respiration, severe diarrhea, acute purulent pneumonia). The doses were lowered to 1 and 10 mg/kg/day, respectively, after 5 days and treatment was continued for a total treatment time of 42 or 43 days. Severe toxic effects occurred primarily in calves receiving tPCP. One calf treated with 10 mg/kg/day was moribund at the time of necropsy. Body weight gain measured up to day 35 of treatment was decreased by 80% in calves receiving 10 mg/kg/day tPCP and by 41% in calves receiving 10 mg/kg/day aPCP compared with the controls. The overall marked decrease in weight was due primarily to a 93% decrease in weight gain for tPCP-treated calves relative to controls between days 20-35; the decrease for aPCP-treated calves was only 17%. Calves receiving 1 mg/kg/day of aPCP and tPCP gained slightly less weight than controls. During the last 3-weeks of treatment, tPCP-treated calves consumed only 15% as much grain as controls. Thyroid hormone levels in serum were measured during the first 35 days of treatment. Serum T_3 levels were reduced by 49–55% after treatment with 10 mg/kg/day of aPCP, by 58–69% after treatment with 10 mg/kg/day tPCP, 22–27% after treatment with 1 mg/kg/day aPCP, and 44–56% after treatment with 1 mg/kg/day tPCP. Serum T_4 levels were reduced by 37–58% after treatment with 1 mg/kg/day tPCP and only about 25% after treatment with 1 mg/kg/day aPCP. T_3 and T_4 responsiveness to TRH challenge were not affected by treatment with either grade. Organ weights most notably affected by PCP treatment were thymus and spleen in calves treated with 10 mg/kg/day tPCP or aPCP. The thymus weight was reduced by 83% with tPCP and 54% with aPCP. Microscopic lesions consistent with thymus atrophy were observed in tPCP-treated calves. Spleen weight were reduced by 52% with 10 mg/kg/day tPCP and by 32% with 10 mg/kg/day aPCP. Squamous

metaplasia was observed in the Meibomian gland of the eye lid of the three calves treated with 10 mg/kg/day tPCP, but in none of the calves treated with aPCP. The investigators attributed the above effects to contaminants in PCP and not PCP. Because less severe effects were observed with aPCP, contaminant may not be entirely the cause of the effects. In vitro tests of kidney function (*p*-aminohippurate (PAH) and tetraethyl ammonium (TEA) uptake) indicated that these energy-dependent functions were impaired by 10 mg/kg/day PCP and not the contaminants. Hughes et al. (1985) measured plasma PCP levels in calves during treatment. A rapid increase was observed and a plateau was reached between 5 and 10 days. No difference was observed between the maximum plasma levels attained with tPCP and aPCP. Plasma PCP levels off at about 100 ppm in plasma in calves given 10 mg/kg/day and at about 13-14 ppm in calved given 1 mg/kg/day. The PCP level in plasma of control calves did not exceed 1 ppm.

McConnell et al. (1980) administered either 100% aPCP, 10% tPCP/aPCP mix, 35% tPCP/aPCP mix, or 100% tPCP to groups of three yearling (10–14 months) Holstein cattle to determine the effect of contaminants on PCP toxicity. Actual purity of PCP was not reported. Each treatment group was given 647 ppm as PCP in feed (20 mg/kg body weight) for 42 days decreased to 491 ppm (15 mg/kg body weight) for 118 days of the study (total treatment time = 160 days). A group of three yearlings served as controls. Discussions on the effects of these treatments on thyroid hormone and immune function are presented in Sections 4.3.1 and 4.4.2, respectively. The diet containing 100% tPCP was more toxic than that of the 100% aPCP diet. Growth and feed efficiency were depressed by all PCP treatments, but more severely by tPCP. The general appearance of tPCP-treated yearlings was "unthrifty" toward the end of the study. Yearlings receiving PCP had a number of clinical and pathological abnormalities including anemia, increased hepatic mixed function oxidase and γ-glutamyl transpeptidase activities; increased relative liver and lung weights; thymus atrophy; marked villous hyperplasia of the urinary bladder mucosa, which extended into the renal pelvis, renal papillae, and terminal portions of the collecting ducts (most striking lesion); hyperplasia of the gall bladder and bile duct mucosa; hyperkeratosis of ductal lining and dilated ducts containing keratinaceous material in the Meibomian glands in the eyelid; and hyperkeratosis of the skin. Many of these effects can be associated with exposure to dioxin and/or furan contaminants in PCP. Generally, these effects were dose-related with respect to tPCP, i.e., more severe in cattle given 100% tPCP.

Kinzell et al. (1981) reported that treatment of four lactating Holstein dairy cattle (6 weeks postpartum) with dietary tPCP (85–90% purity) delivering a dose of 0.2 mg/kg/day for 75 to 84 days followed by 2 mg/kg/day for an additional 56 to 60 days (total treatment time, 131–144 days) had no effect on body weight, food consumption, hematology, clinical chemistry or urinalysis tests. Four cattle served as controls. Relative organ weights for liver, lung, kidney, and adrenals were increased by 37–37% compared with control weights; gross and microscopic lesions were observed in the kidney (chronic diffuse interstitial nephritis) and urinary bladder (thickening of bladder wall). In vitro tests revealed impairment of kidney function (decreased PAH, TEA, and α-aminoisobutyrate (AIB) uptake). No histopathologic effects attributable to PCP were observed in the liver.

4.2.1.2. Inhalation studies

Hoben et al. (1976a) conducted an inhalation study in which groups of 12 male Sprague-Dawley rats were exposed to PCP aerosols by inhalation exposure. Durations of exposure were 28–44 minutes resulting in calculated doses of 10–14.5 mg/kg body weight received during exposure (assuming

inhalation rate of 80 mL/minute). The dose-response curve was very steep; 33% of animals receiving 10.1 mg/kg died and 83.3% receiving 14.5 mg/kg died. The LC_{50} was 11.7 mg/kg.

4.2.1.3. Other Routes of Exposure

A 13-week dermal toxicity study was conducted in male and female Sprague-Dawley rats receiving 0, 100, 500, or 1000 mg/kg doses of PCP (88.9%) applied to clipped dorsal skin for 6 hours/day for 91 days (Osheroff et al., 1994). The PCP, applied without vehicle, was held in place by a gauze patch. PCP caused some degree of skin irritation (acanthosis and chronic inflammation) in both sexes at all doses. Liver toxicity (hepatocellular degeneration and chronic inflammation) was observed at the mid and high doses in both sexes. This study shows that PCP is absorbed from the skin at levels sufficient to cause liver toxicity. The LOAEL for this study was 500 mg/kg/day based on liver toxicity and the NOAEL was 100 mg/kg/day.

4.2.2. Chronic Studies

4.2.2.1. Oral studies

In a chronic toxicity study, Schwetz et al. (1978) administered commercial PCP (DOWICIDE® EC-7) (EC-7) in the diet of male and female Sprague-Dawley rats at concentrations delivering doses of 0, 1, 3, 10, 30 mg/kg/day. Treated or control diets were fed to males for 22 months and females for 24 months. Each group consisted of 25 rats of each sex. No treatment-related effects were observed for clinical signs, food consumption, survival, hematologic parameters, or organ weights. The investigators stated that mean body weights of high-dose females were significantly less than that of controls during most of the study. Serum alanine aminotransferase (ALT) activity was slightly increased in both sexes at the highest dose at study termination; the increase did not exceed 1.7-fold for either sex. Histopathological examination showed pigment accumulation in the centrilobular hepatocytes in the liver and epithelial cells of the proximal convoluted tubules in the kidney in 26–30% of female rats receiving 10 and 59–70% of 30 mg/kg/day compared with 0% in controls and lower dose group females. Only one of 27 male rats receiving 30 mg/kg/day had brown pigment in hepatocytes. The LOAEL for this study was 10 mg/kg/day for females based on pigment accumulation in liver and kidney cells; the NOAEL was 3 mg/kg/day. The NOAEL was not established for male rats, because increased serum enzyme levels alone and pigment in the liver of only one male rat is insufficient data for establishing an effect level.

In a study reported by NTP (1999), groups of 50 male and 50 female Fischer 344 rats were administered PCP (approximately 99% pure, with no detectable levels of chlorinated dibenzodioxin, dibenzifuran, diphenyl ether, or hydroxydiphenylether) in feed at concentrations levels of 0, 200, 400, or 600 ppm (average daily dose = 0, 10, 20, and 30 mg/kg, respectively), for 105 weeks. The levels of tetrachlorophenol and hexachlorobenzene were not reported. In an additional stop-exposure study, groups of 60 male and 60 female rats were maintained on feed containing 1000 ppm PCP (average daily dose = 60 mg/kg) for 52 weeks followed by untreated feed until study termination at 2 years. Two-year survival rates of male rats receiving 600 ppm for 2 years or 1000 ppm for 52 week significantly exceeded that of controls (62 and 64%, respectively vs 24% for control); survival of other groups was similar to that of controls. Mean body weights were decreased in both male and female rats at various times during the study. Mean body weights were within 94, 91, 89, and 82% of control weight in male rats and within 94, 91, 84, and 78% of control weights in female rats receiving 200, 400, 600, or 1000 ppm PCP, respectively. In the stop-exposure study, body weights recovered to within 4% of control weight after

treatment stopped at 52 weeks. The liver was the primary target for nonneoplastic toxicity, particularly in male rats. At the 7-months interim evaluation of the stop-exposure group, serum alkaline phosphatase levels in males and sorbitol dehydrogenase levels in males and females were significantly elevated by 20–90% compared with control levels. Alanine aminotransferase (ALT) levels in males were elevated but not significantly. Microscopic examination of 1000-ppm rats sacrificed at 7 months significantly showed higher incidences of centrilobular hepatocyte hypertrophy in (6/10 rats) and females (6/10 rats) and cytoplasmic hepatocyte vacuolization in males (8/10 rats) compared with the control incidences (0/10). The incidences of these findings were not significantly increased for the 2-year study. The1000-ppm males in the stop-exposure study had significantly higher incidences of liver lesions consisting of chronic inflammation (64% vs 44% for controls), basophilic focus (62% vs 34% for controls), and cystic degeneration of hepatocytes (56% vs 32% for controls) than the controls. The incidence of cystic degeneration was significantly increased at 400 (56%) and 600 ppm (78%). In addition, the incidence of hepatodiaphragmatic nodules was significantly increased in all groups of males receiving PCP (10–16% vs 0% for controls); no clear dose response was observed. Hepatodiaphragmatic nodules were described as developmental anomalies commonly observed in F344 rats; the increased incidence observed in this study was not considered related to exposure with PCP.

The incidences of liver lesions in female rats in the 2 year study were similar to those of controls or significantly lower than that of controls (cytoplasmic hepatocyte vacuolation: 2% vs 14% for control). This study showed that male rats were more susceptible to PCP exposure than female rats with one exception, males and females were equally responsive to PCP in the stop-exposure study. The LOAEL was 400 ppm (20 mg/kg/day) for male rats based on liver toxicity; the NOAEL for male rats was 200 ppm (10 mg/kg/day). The LOAEL was 600 ppm (30 mg/kg/day) for female rats based on a biologically significant decreases in body weights and the NOAEL was 400 ppm (20 mg/kg/day) . This study was also reported by Chhabra et al., 1999.

In a second study conducted by NTP, groups of 50 male and 50 female $B6C3F_1$ mice were administered feed containing 100 or 200 ppm tPCP (90.4% purity) or 100, 200, or 600 ppm EC-7 (91% purity) continuously for 2 years (NTP, 1989). Two groups of 35 mice of each sex maintained on untreated feed served as controls. Both tPCP and EC-7 contain 90% pentachlorophenol and different levels of contaminants. The average daily PCP and contaminant doses associated with each dietary concentration are summarized in Table 8.

Mean body weights of male mice receiving tPCP and EC-7 and females receiving tPCP or 100 or 200 ppm EC-7 were similar to control weights throughout the study. Females receiving 600 ppm EC-7 weighed only 78 –91% as much as the control weights during the second year of the study. No statistically significant effects were observed on survival in either male or female mice receiving tPCP or EC-7. Survival of male controls for the tPCP study was abnormally low (34% survival) at the end of the study. This study showed that the liver was clearly the target for systemic toxicity for both grades of PCP and in both sexes. The following liver lesions occurred at statistically significant higher incidences in PCP-treated males at all doses of tPCP and EC-7 than in the control: clear cell focus, acute diffuse necrosis, diffuse cytomegaly, diffuse chronic active inflammation, multifocal accumulation of brown pigmentation (lipofuscin and cellular debris) in Kupffer cells, and proliferation of hematopoietic cells (extramedullary hematopoiesis). Males also had a significantly higher incidence of bile duct hyperplasia at both doses of tPCP but at only the 600-ppm dose of EC-7. Females receiving all doses of tPCP and

EC-7 had significantly higher incidences than the control mice of the following liver lesions: cytomegaly, necrosis, inflammation, and pigment accumulation. In addition, the incidence of clear cell focus was significantly increased in females treated with 200 ppm tPCP and 200 and 600 ppm EC-7 compared with the control incidences. The incidence of extramedullary hematopoiesis was higher in female mice receiving 200 ppm tPCP and at all doses with EC-7 than in control mice. In contrast to male mice, the incidence of bile duct hyperplasia was not significantly increased in females treated with tPCP, but was significantly higher in females treated with 600 ppm EC-7 than in the control mice. The only lesion related to impurities was bile duct hyperplasia in male mice receiving 100 and 200 ppm tPCP. However, 600 ppm EC-7 was very effective in inducing bile duct hyperplasia in in male and female mice.

Other nonneoplastic findings considered treatment related were observed in the spleen, nose, and mammary glands (NTP, 1999). The incidence of extramedullary hematopoiesis in the spleen was significantly higher in males (100 and 200 ppm) and females (200 ppm) receiving tPCP compared with that of the controls. The incidences of acute focal inflammation of the mucosal gland and focal metaplasia of the olfactory epithelium was increased in male and female mice receiving the 600-ppm dose of EC-7; these lesions did not occur in any male of female mouse receiving tPCP. In females receiving tPCP, the incidence of cystic hyperplasia of the mammary gland was significantly higher at 200 ppm (59%) than that of tPCP controls (23%), but not when compared with the EC-7 control (58%); therefore, this lesion is not considered treatment related. Under the condition of these studies, tPCP and EC-7 were equally effective in male mice except for bile duct hyperplasia. However, tPCP was generally more effective in female mice than EC-7 except for bile duct hyperplasia and nasal lesion (NTP, 1989). NOAELs could not be established for either tPCP or EC-7, because effects in the liver occurred at the lowest dose tested in male and female mice. Some findings occurred at incidences approaching 100% at 100 ppm indicating that a much lower dose could have been tested.

tPCP was observed to have significantly higher levels of chlorinated dibenzodioxins and dibenzofurans than either DP-2 or EC-7. Specifically, the concentration of heptachlorodibenzodioxin was observed to be approximately 10 times and 500 times higher for technical grade PCP than for DP-2 and EC-7 respectively. Higher concentration were also observed for octachlorodibenzodioxin and hexachlorodibenzodioxin. Thus, mice were exposed to higher levels of these contaminants from tPCP treated food than from DP-2 or EC-7 treated food (NTP, 1989). Despite this, there were no apparent differences in liver toxicity caused by tPCP and EC-7, suggesting that PCP causes liver toxicity in the mice. Only tPCP resulted in significant increases in the incidences of lesions in the spleen of male mice and mammary gland of female mice, suggesting that the lesions were caused by impurities. Lesions in the nose were prominent in mice receiving EC-7 but not in mice receiving tPCP suggesting that an impurity (tetrachlorophenol) caused these lesions.

Table 8. Average Daily Dose of Pentachlorophenol (mg/kg) and Contaminants (µg/kg) to B6C3F$_1$ in the 2-year Feeding Study										
	Males					Females				
PCP/Contaminant	100 ppm		200 ppm		600 ppm	100 ppm		200 ppm		600 ppm
	tPCP	EC-7	tPCP	EC-7	EC-7	tPCP	EC-7	tPCP	EC-7	EC-7
Pentachlorophenol[a]	18	18	35	37	118	17	17	35	34	114
Trichlorophenol	1.1	0.8	2.3	1.6	4.7	1.1	0.8	2.2	1.5	4.6
Tetrachlorophenol	430	1100	860	2100	6300	415	1000	830	2000	5800
Hexachlorobenzene	0.6	0.7	1.1	1.5	4.4	0.54	0.7	1.1	1.4	4.2
TCDD	–	–	–	–	–	–	–	–	–	–
HxCDD	0.11	0.002	0.23	0.004	0.01	0.11	0.002	0.22	0.004	0.01
HpCDD	3.3	0.006	6.7	0.01	0.04	3.2	0.006	6.5	0.01	0.03
OCDD	15.6	0.008	31	0.02	0.05	15.1	0.008	31	0.02	0.05
PCDF	0.016	–	0.03	–	–	0.014	–	0.03	–	–
HxCDF	0.11	0.001	0.24	0.003	0.009	0.11	0.001	0.22	0.003	0.008
HpCDF	1.0	0.002	2.0	0.003	0.01	1.0	0.002	1.9	0.003	0.01
OCDF	0.5	–	1.0	–	–	0.5	–	1.0	–	–
HpCHDE	10	–	20	–	–	10	–	20	–	–
OCHDE	220	–	430	–	–	210	–	420	–	–
NCHDE	400	–	800	–	–	390	–	780	–	–
HxCHDF	20	–	40	–	–	20	–	30	–	–
HpCHDF	50	–	110	–	–	50	–	100	–	–

Source: NTP, 1989, pages 106-107.
[a]Daily dose in mg/kg body weight.

In a chronic toxicity study in dogs, (Meclar, 1996) pentachlorophenol (90.9% a.i.) was fed (gelatin capsules) to four beagle dogs/sex/dose at dose levels of 0, 1.5, 3.5, or 6.5 mg/kg/day for 52 weeks. At 6.5 mg/kg/day, one male and one female dog were sacrificed in extremis on days 247 and 305, respectively, due to significant clinical toxicity (significant weight loss, lethargy, marked dehydration, vomiting, icterus). Group mean body weight in surviving male dogs at the 6.5 mg/kg/day dose was decreased by 15% at week 13, and 21% at study termination. In females, a 19% decrease in group mean body weight was observed at week 13, and bodyweight remained significantly decreased until study termination. Decreased red cell count (16%), hemoglobin (9%), and hematocrit (8%), were observed in males at the 6.5 mg/kg/day dose at week 13. These decreases were also observed at week 26 and at necropsy. In females, significant decreases of 10-17% in these hematologic parameters were observed at 6.5 mg/kg/day from week 26 until study termination. Activities of alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase were significantly elevated for both sexes throughout the study at the 6.5 mg/kg/day dose. Gamma-glutamyltranspeptidase activity was increased in male dogs at week 13 by 45%. Absolute and relative liver weights in males and females were elevated by 32% and 49% over control at 6.5 mg/kg/day. Absolute and relative thyroid weights were also increased significantly in females at the 6.5 mg/kg/day dose. Gross stomach lesions consisting of multiple, raised mucosal foci were observed in increased incidence in all treated groups of male and female dogs with only one female control dog showing a similar lesion. Dark, discolored liver was also observed in increased incidence in male and female treated dogs, but a dose-response was observed only for males. Microscopically, increased incidence of lymphocytic mucosal inflammation was observed in the stomach of treated males and females. The lesion was present in all teated and control groups, but the severity of the lesion was increased, especially at the 3.5 and 6.5 mg/kg/day doses.

4.2.2.2. Inhalation studies

No long-term inhalation studies were found in the literature searched.

4.2.3. Cancer Studies

4.2.3.1. Oral studies

In a study conducted by BRL (1968), groups of 18 male and 18 female B6C3F1 and B6AKF1 mice given Dowcide-7 (EC-7) by gavage from day 7–28 of age (46.4 mg/kg per dose) followed by continuous feeding of a diet containing 130 ppm Dowcide-7 for up to 18 months developed no neoplasms associated with treatment with the test material. In another study in which the same strains and number of animals per group were administered Dowcide-7 as a single subcutaneous dose of 46.4 mg/kg also showed a negative carcinogenic response.

Schwetz et al (1978) conducted a 2-year study in male and female Sprague-Dawley rats maintained on diets containing EC-7 (90.4% PCP) at concentrations delivering PCP doses of 0, 3, 10, or 30 mg/kg/day; males were actually fed the diets for 22 months and females for 24 months. There were no treatment-related neoplasms observed in this study.

Neoplasms were seen in the NTP (1999) study in which groups of 50 male and 50 female Fischer 344 rats were administered PCP (approximately 99% pure) in feed at concentrations of 0, 200, 400, or 600 ppm continuously for 105 weeks; additional groups of 60 male and 60 female rats were maintained on feed containing 1000 ppm PCP for 52 weeks followed by untreated feed until study termination at 2 years. The average daily doses of PCP were reported as 10, 20, 30, and 60 mg/kg for male and female rats fed the 200-, 400-, 600-, and 1000-ppm diets, respectively as reported in the study. Histopathologic examination showed a significantly higher incidence of malignant mesothelioma in 1000-ppm males compared with that of controls; the incidence exceeded the range of historical controls. The mesotheliomas originated from the tunica vaginalis. The incidence of nasal squamous cell carcinomas was also elevated in 1000-ppm males; the incidence did not achieve statistical significance compared with that of concurrent controls, but exceeded the range of historical controls. Nasal squamous cell carcinoma at 200 ppm was the only neoplastic findings in male rats treated for the entire 2 years that occurred with a higher incidence than that of historical controls. However, the finding at 200 ppm is not considered treatment related because the incidence at 400 and 600 ppm was less than or no greater than that of controls. Therefore, the only treatment-related neoplasms occurred in male rats exposed to 1000 ppm PCP in the stop-exposure study. There were no treatment-related increases in the incidences of neoplasms at any anatomical site in females receiving PCP. These data and results of the statistical analysis are presented in Table 9. Under the conditions of this study, NTP (1999) concluded that this study showed some evidence of carcinogenicity of PCP in male Fischer 344 rats, based on increased incidences of mesothelioma and nasal squamous cell carcinoma in the stop-exposure study.

Table 9. Incidences of Treatment-Related Neoplasms in Male F344 Rats Fed Purified Pentachlorophenol for up to 2 Years					
Neoplasms and Statistical Analysis	Dose (mg/kg/day)				
	0	10	20	30	60[a]
Number of Animals Per Group	50	50	50	50	50
Malignant Mesothelioma Overall rate[b] Adjusted rate[c]	 1 (2%) 2.6%	 0 (0%) 0%	 2 (4%) 5.1%	 0 (0%) (0%)	 9 (18%) 20.6%
Statistical analysis Poly -3 test[d] Fisher's exact test	 p=0.447N	 p=0.509N p=0.500N	 p=0.511 p=0.500	 p=0.472N 0.500N	 p=0.014 p=0.008
Historical control incidence (mean ±standard deviation)	40/1354 (3.0% ± 2.3%), range = 0%–8%				
Nasal Squamous Cell Carcinoma Overall rate[b] Adjusted rate[c]	 1/50 (2%) 2.7%	 3/50 (6%) 8.1%	 1/50 (2%) 2.6%	 0/50 (0%) (0%)	 5/50 (10%) 11.7%
Statistical analysis Poly -3 test[d] Fisher's exact test	 p=0.171N	 p=0.299 p=0.309	 p=0.756N	 p=0.471N p=500N	 p=0.128 p=0.102
Historical control incidence (mean ±standard deviation)	5/1314 (0.5% ±1.0%); range = 0%–4%				

Source: NTP, 1999
[a]Stop-exposure study; rats received treated feed for 52 weeks and untreated feed until study termination at 2 years.
[b]Number of animals with neoplasms/number of animals examined.
[c]Poly-3 estimated incidence after adjustment for intercurrent mortality.
[d]Trend-test under control column (60 mg/kg/day group excluded), pairwise comparison test under treatment group column. Poly-3 test accounts for intercurrent mortality; N refers to negative trend.

In a second study, groups of 50 male and 50 female B6C3F1 mice were administered feed containing 100 or 200 ppm tPCP (90.4% purity) or 100, 200, or 600 ppm EC-7 (91% purity) continuously for 2 years (NTP, 1989). Two groups of 35 mice of each sex maintained on untreated feed served as controls for each grade of PCP. Both tPCP and EC-7 contain 90% pentachlorophenol. The average daily PCP and contaminant doses associated with each dietary concentration are summarized in Table 8. Statistical analysis included the Life Table Test that considered tumors as fatal in animals dying before study termination, the Logistic Regression Test that regarded all lesions as nonfatal, and the Fisher Exact and Cochran-Armitage Trend Test that compared the overall incidence rates of treated groups with controls. Nonneoplastic findings were discussed in Section 4.2.2.1.

The incidences of treatment-related neoplasms and results of the statistical analysis are presented in Tables 10 (males) and 11 (females). In male mice, the incidences of hepatocellular adenoma and carcinoma were significantly elevated by both grades of PCP compared with control incidences. The incidence of hepatocellular adenoma was significantly elevated in males receiving 100 ppm tPCP diet (43% vs 16% for controls), but not males receiving 100 ppm EC-7 diet (27% vs 14% for controls). The

incidence of hepatocellular carcinoma was only marginally increased (p=0.06 or 0.07) by both grades at 100 ppm and significantly increased at 200 ppm when compared with individual control groups. However, the incidence of hepatocellular carcinoma in the 100-ppm group was significantly (p=0.006) elevated when compared with the combined control groups. The incidence of hepatocellular adenoma/carcinoma combined was significantly increased with all doses of tPCP and EC-7. The incidences were greater in male mice receiving tPCP than in males receiving EC-7. In female mice, the incidence of hepatocellular adenoma was elevated only at the 600-ppm dose of EC-7 when compared with the control group, and the incidence of hepatocellular carcinoma was not elevated in females treated with either grade of PCP. If incidence of hepatocellular adenoma in female groups treated with tPCP is compared with the combined control groups, then statistical significance is achieved at 100 ppm (p=0.05) and marginal significance at 200 ppm (p=0.06).

Adrenal gland medullary pheochromocytoma occurred in 22% and 51% of male mice receiving each dose of tPCP, respectively, and in 44% and 90% in male mice receiving 200 and 600 ppm EC-7, respectively, but in none of the controls. Pheochromocytoma also developed in 78% of females receiving 600 ppm EC-7 compared with only one or two female mice in the control groups, 100-ppm, and 200-ppm dosed groups. Hemangiosarcomas, which developed primarily in the liver and spleen, were observed in 12% of females receiving 200 ppm tPCP, 16% receiving 600 ppm EC-7 and none in the 70 controls examined. The hemangiosarcomas observed in three females receiving the 100-ppm tPCP or the 200-ppm EC-7 diets were probably related to PCP treatment.

The results of this study showed that tPCP and EC-7, the latter of which contains lower levels of dioxin and furan impurities, induced neoplasms in mice; tPCP was slightly more potent. The NTP (1989) and McConnell et al. (1991) compared the concentrations of hexachlorodibenzo -*p*-dioxin (HxCDD) in tPCP and EC-7 with that known to induce liver tumors in mice and concluded that the carcinogenic response in mice can be attributed primarily to PCP and the impurities contribute only a small part. NTP (1989) concluded that PCP is primarily responsible for the carcinogenicity observed in mice and impurities played only a small part in the neoplastic process, at least in the liver of male mice. NTP further concluded that there was *clear evidence of carcinogenic activity* for male mice receiving tPCP and male and female mice receiving PCP (EC-7) and *some evidence of carcinogenic activity* for female mice receiving tPCP.

Table 10. Treatment-Related Neoplasms in Male B6C3F$_1$ Mice Fed Technical Grade Pentachlorophenol or Dowicide EC-7 for 2 Years							
Organ/Lesions/Statistical Test[a]	Technical Grade PCP			Dowicide EC-7			
	Control	100 ppm	200 ppm	Control	100 ppm	200 ppm	600 ppm
Liver/ Hepatocellular Adenoma							
Overall Rate	5/32[b] (16%)	20/47 (43%)	33/48 (69%)	5/35 (14%)	13/48 (27%)	17/48 (35%)	32/49 (65%)
Adjusted Rate[c]	27.6%	65.1%	88.5%	20.0%	41.6%	53.0%	84.1%
Life Table	p<0.001	N.S.	p<0.001	p<0.001	N.S.	p=0.008	p<0.001
Logistic Regression	p<0.001	p=0.037	p<0.001	p<0.001	N.S.	p=0.007	p<0.001
Fisher Exact/ Cochran-Armitage Trend	p<0.001	p=0.003	p<0.001	p<0.001	N.S.	p=0.027	p<0.001
Liver/ Hepatocellular Carcinoma							
Overall Rate	2/32 (6%)	10/47 (21%)	12/48 (25%)	1/35 (3%)	7/48 (15%)	7/48 (15%)	9/49 (18%)
Adjusted Rate	11.4%	33.2%	39.5%	4.0%	20.2%	24.1%	25.0%
Life Table	N.S.	N.S.	N.S.	N.S.	N.S.	p=0.047	p=0.034
Logistic Regression	p=0.046	N.S.	p=0.049	N.S.	N.S.	p=0.045	p=0.032
Fisher Exact Test/ Cochran-Armitage Trend	0.031	N.S.	p=0.027	N.S.	N.S.	N.S.	p=0.029
Liver/ Hepatocellular Adenoma/Carcinoma							
Overall Rate	7/32 (22%)	26/47 (55%)	37/48 (77%)	6/35 (17%)	19/48 (40%)	21/48 (44%)	34/49 (69%)
Adjusted Rate	35.8%	75.5%	89.6%	24.0%	53.8%	65.5%	87.1%
Life Table	p<0.001	N.S.	p=0.002	p<0.001	p=0.009	p=0.002	p<0.001
Logistic Regression	p<0.001	p=0.015	p<0.001	p<0.001	p=0.015	p=0.001	p<0.001
Fisher Exact/ Cochran-Armitage Trend	p<0.001	p=0.003	p<0.001	p<0.001	p=0.024	p=0.009	p<0.001
Adrenal Gland/ Hyperplasia	1/31 (3%)	10/45 (22%)	10/45 (22%)	1/34 (3%)	19/48 (40%)	13/48 (27%)	1/49 (2%)
Fisher Exact/ Cochran-Armitage Trend	p=0.044	p=0.017	p=0.017	N.S.	p<0.001	p=0.003	N.S.
Adrenal Gland/ Pheochromocytoma/Malignant							
Overall Rate	0/31 (0%)	10/45 (22%)	23/45 (51%)	0/34 (0%)	4/48 (8%)	21/48 (44%)	45/49 (90%)
Adjusted Rate	0.0%	37.9%	84.9%	0.0%	13.8%	67.5%	97.8%
Life Table Test	p<0.001	p=0.021	p<0.001	p<0.001	N.S.	p<0.001	p<0.001
Logistic Regression Test	p<0.001	p=0.017	p<0.001	p<0.001	N.S.	p<0.001	p<0.001
Fisher Exact Test	p<0.001	p=0.003	p<0.001	p<0.001	N.S.	p<0.001	p<0.001

Source: NTP, 1989

[a]p-values for trend tests are under the control column, p-values for pairwise comparisons of dosed groups with controls are in the dosed group columns.

[b]Number of animals with tumors/number of animals examined at the site.

[c]Incidence after adjusting for intercurrent mortality.

Table 11. Treatment-Related Neoplasms in Female B6C3F$_1$ Mice Fed Technical Grade Pentachlorophenol or Dowicide EC-7 for 2 Years							
Organ/Lesions/Statistical Analysis[a]	Technical Grade PCP			Dowicide EC-7			
	Control	100 ppm	200 ppm	Control	100 ppm	200 ppm	600 ppm
Liver/ Hepatocellular Adenoma							
Overall Rate	3/33[b] (9%)	8/49 (16%)	8/50 (16%)	1/34 (3%)	3/50 (6%)	6/49 (12%)	30/48 (63%)
Adjusted Rate[c]	10.7%	19.5%	24.0%	3.4%	10.7%	15.8%	75.0%
Life Table Test	N.S.	N.S.	N.S.	p<0.001	N.S.	N.S.	p<0.001
Logistic Regression Test	N.S.	N.S.	N.S.	p<0.001	N.S.	N.S.	p<0.001
Fisher Exact Test	N.S.	N.S.	N.S.	p<0.001	N.S.	N.S.	p<0.001
Liver/ Hepatocellular Adenoma/Carcinoma							
Overall Rate	3/33 (9%)	9/49 (18%)	9/50 (18%)	1/34 (3%)	4/50 (8%)	6/49 (12%)	31/48 (65%)
Adjusted Rate	10.7%	21.4%	25.9%	3.4%	13.8%	15.8%	77.5%
Life Table Test	N.S.	N.S.	N.S.	p<0.001	N.S.	N.S.	p<0.001
Logistic Regression Test	N.S.	N.S.	N.S.	p<0.001	N.S.	N.S.	p<0.001
Fisher Exact Test	N.S.	N.S.	N.S.	p<0.001	N.S.	N.S.	p<0.001
Adrenal Gland Medulla/ Hyperplasia Fisher Exact/ Cochran-Armitage Trend	0/33 (0%)	4/48 (8%)	2/49 (4%)	2/35 (6%)	1/49 (2%)	5/46 (11%)	17/49 (35%
Adrenal Gland/ Pheochromocytoma/Malignant							
Overall Rate	2/33 (6%)	2/48 (4%)	1/49 (2%)	0/35 (0%)	2/49 (2%)	2/46 (4%)	38/49 (78%)
Adjusted Rate	–	–	–	0.0%	3.6%	5.3%	86.3%
Life Table Test	–	–	–	p<0.001	N.S.	N.S.	p<0.001
Logistic Regression Test	–	–	–	p<0.001	N.S.	N.S.	p<0.001
Fisher Exact Test	–	–	–	p<0.001	N.S.	N.S.	p<0.001
Hemangiosarcoma							
Overall Rate	0/35 (0%)	3/50 (6%)	6/50 (12%)	0/35 (0%)	1/50 (2%)	3/50 (6%)	9/50 (16%)
Adjusted Rate	0.0%	6.8%	17.1%	0.0%	3.6%	7.3%	18.9%
Life Table Test	p=0.013	N.S.	p=0.029	p=0.002	N.S.	N.S.	P=0.016
Logistic Regression Test	p=0.024	N.S.	p=0.036	p<0.001	N.S.	N.S.	P=0.016
Fisher Exact Test	p=0.024	N.S.	p=0.036	p<0.001	N.S.	N.S.	P=0.010

Source: NTP, 1989

[a]p-values for trend tests are under the control column, p-values for pairwise comparisons of dosed groups with controls are in the dosed group columns.

[b]Number of animals with tumors/number of animals examined at the site

[c]Incidence after adjusting for intercurrent mortality.

Umemura et al. (1999) examined the initiating and promoting activity of PCP (98.6% purity) administered in the diet to B6C3F_1 mice. Diethylnitrosoamine (DEN) was administered as the initiator when the promoting activity of PCP was assessed, and phenobarbital (PB) was administered as the promoter when the initiating activity of PCP was assessed. Each group consisted of 20 male mice. Table 12 summarizes the treatment protocol and response of each group to treatment. DEN (20 ppm) in drinking water was administered to four groups of male mice for 13 weeks followed by a 4-week rest period and 500 ppm of PB in drinking water, 300 or 600 ppm of PCP in the diet, or no treatment for 25 weeks to assess promoting activity of PCP. PCP (600 and 1200 ppm) was given in the diet to two groups of male mice for 13 weeks followed by 500 ppm of PB for 29 weeks. PCP (1200 ppm) was given to another group of male mice for 13 weeks followed by no treatment for 29 weeks. Three groups received no treatment during the initiating phase followed by basal diet, 600 ppm PCP, or 500 ppm PB during the promoting phase. Body weights were significantly reduced in mice receiving DEN with or without subsequent PCP or PB treatment; however, 300 and 600 ppm PCP had a dose-related potentiating effect on body weights. Liver weights were increased in mice receiving 600 ppm PCP with or without prior DEN treatment and by PB treatment alone. Liver weights were not increased after administering 1200 ppm PCP for 13 week followed by no treatment for 29 weeks. The incidence of liver neoplasms was significantly higher in mice initiated with DEN and promoted with 600 ppm PCP (72%, $p<0.01$) or 300 ppm PCP (67%, $p<0.05$) than in control mice receiving DEN only (27%). Tumor multiplicity was also significantly increased in PCP-promoted mice (2.22 and 1.27 tumors/mouse, respectively) than in DEN controls (0.33 tumors/mouse). No liver neoplasms developed in mice initiated with PCP and promoted with PB. Umemura et al. (1999) concluded that PCP exerts a promoting effect on liver carcinogenesis that is related to oxidative stress and compensatory cell proliferation.

Table 12. Hepatocellular Neoplasms in B6C3F_1 Mice in Initiation/Promotion Studies

Treatment[a]		Incidences				Tumor Multiplicity
Initiation (13 weeks)	Promotion (25 weeks)	Altered Foci	Adenomas	Carcinomas	Adenoma/ Carcinoma	
Untreated	Basal Diet	0/20	0/20	0/20	0/20	0
Untreated	PCP (600 ppm)	1/19 (5%)	0/19	0/19	0/19	0
Untreated	PB (500 ppm)[b]	8/20 (40%)	0/20	0/20	0/20	0
DEN (20 ppm)	Basal diet	7/15 (47%)	4/15 (27%)	0/15	4/15 (27%)	0.33
DEN (20 ppm)	PB (500 ppm)	6/19 (32%)	10/19 (53%)	1/19(5%)	10/19 (53%)	1.42*
DEN (20 ppm)	PCP (300 ppm)	8/15 (53%)	10/15 (67%)	2/15 (13%)	10/15 (67%)*	1.27*
DEN (20 ppm)	PCP (600 ppm)	13/18 (72%)	13/18 (72%)	4/18 (22%)	13/18 (72%)**	2.22*

Table 12. Hepatocellular Neoplasms in B6C3F$_1$ Mice in Initiation/Promotion Studies						
PCP (600 ppm)	PB (500 ppm)[b]	5/20 (25%)	0/20	0/20	0/20	0
PCP (1200 ppm)	PB (500 ppm)[b]	2/20	0/20	0/20	0/20	0/20
PCP (1200 ppm)	Untreated	2/17(12%)	0/17	0/17	0/17	0/17

Source: Umemura et al., 1999
[a] Vehicle: PCP in feed; DEN and PB in drinking water; a 4-week rest period followed the initiation phase of the study.
[b]No rest period, PB given for 29 weeks.
*p<0.05, **p<0.01

4.2.3.2. Inhalation studies

No long-term inhalation studies were found in the literature searched.

4.3 REPRODUCTION, ENDOCRINE, AND DEVELOPMENTAL STUDIES

4.3.1. Reproduction and Endocrine Studies

Schwetz et al. (1978) conducted a one-generation reproduction study in which groups of 10 male and 20 female Sprague-Dawley rats were administered PCP (EC-7) (90% a.i.) in the diet. Dietary concentrations were adjusted monthly to deliver doses of 0, 3, or 30 mg/kg/day. The test material was administered continuously for 62 days prior to mating and during mating, gestation, and lactation. All animals including pups were sacrificed after the litters were weaned on lactation day 21 (169 days for males and ~110 days for females). Decreased body weight was noted in high dose rats, with an 8% (non-significant) decrease in males and a 10% decrease in females ($p<0.05$) . At 30 mg/kg/day, fewer pups were born alive and survival of pups was decreased throughout lactation leading to decreased litter sizes on days 7, 14, and 21 of lactation. In addition, mean pup weights were significantly decreased by 14–27% at birth and throughout lactation at 30 mg/kg/day PCP compared with the controls. Decreased pup weight gain of 28% and survival of 79% during the first 14 days of lactation is suggestive of a lactational effect of PCP at 30 mg/kg/day. The study authors noted that increased incidences of litters with skeletal variations (lumbar spurs and vertebra with unfused centra) occurred at 30 mg/kg/day compared with control incidences. The LOAEL for this study is 30 mg/kg/day for reproductive and developmental effects; the NOAEL is 3 mg/kg/day.

In a 2-generation reproduction study (Hoberman, 1997), pentachlorophenol (88.9 % a.i.) in corn oil was administered by gavage 7 days/week to groups of 30 male and 30 female Sprague-Dawley rats at doses of 0, 10, 30, and 60 mg/kg/day. F_0 male and female rats were given the test material for at least 70 days prior to mating and during mating, gestation, and lactation until weaning of litters, after which all F_0 animals were sacrificed. F_1 male and female rats were similarly exposed starting at weaning and

continuing through the day before sacrifice. In addition to indices of reproductive performance, parameters of reproductive function (vaginal patency, preputial separation, estrous cycle, and sperm morphology) were also evaluated.

Absolute body weights and body weight gain of 30- and 60-mg/kg/day group F_0 and F_1 parental male rats were significantly decreased by more than 10% compared with controls during the premating period and at 60 mg/kg/day in females during the premating (except for F_0 females), gestation, and lactational periods. No treatment-related effect was observed on body weights or body weight gain in females receiving 30 mg/kg/day. Systemic effects in parental animals (F_0 and F_1male and female rats) included increased liver weight, enlarged liver, and microscopic liver lesions (centrilobular hypertrophy, inflammation, single cell necrosis, or centrilobular pigment) at 30 and 60 mg/kg/day. Centrilobular hypertrophy was also observed at the lowest dose of 10 mg/kg/day; bile duct proliferation was observed in F_0 and F_1 females receiving 60 mg/kg/day.

The fertility index and the number of litters produced for both generations were decreased at 60 mg/kg/day. Days to vaginal patency and preputial separation were significantly increased in F_1 females and males, respectively. The length of the estrous cycle was not significantly affected in either F_0 or F_1 females. Sperm morphology and count were not affected in F_0 males, but testicular spermatid count and testes weight were decreased at 30 and 60 mg/kg/day, and the number of sperm with broken flagella was increased at 60 mg/kg/day in F_1 males. Offspring evaluations showed significantly reduced mean litter size, number of live pups, viability index, and lactation index for F_1 and F_2 pups at 60 mg/kg/day compared with the controls. Body weights of pups were decreased by 10–15% at 30 mg/kg/day throughout lactation and by 11–39% at 60 mg/kg/day. In addition, decreased weight of the liver, brain, spleen, and thymus were observed in F_2 pups at 60 mg/kg/day.
Based on the data in this study, the Systemic NOAEL = 10 mg/kg/day for male and female parental rats. The Systemic LOAEL = 30 mg/kg/day for male and female rats, based on decreased body weight and weight gain in F1 generation parental rats, and adverse testicular effects in F1 male rats (decreased testis weight, decreased spermatid count).

The reproductive NOAEL = 10 mg/kg/day in this study. The reproductive LOAEL = 30 mg/kg/day, based on decreased group mean litter weight.

Beard et al. (1997b) conducted a study using mink to assess the effect of pesticides in a one-generation study. Groups of female 10 mink (9-months old) received 0 or 1 mg/kg/day PCP (purity not stated) in the diet continuously for 3 weeks before mating, during mating, gestation, and lactation of one litter of kits. Each female was mated twice with an untreated male mink, with an interval of 7–8 days between matings. Treatment with 1 mg/kg/day PCP had no effect on clinical signs, body weight gain, or food consumption. No effect was observed on females accepting males during the first mating, but significantly fewer PCP-treated females accepted males during the second mating, resulting in significantly fewer pregnant females. Implantations were not affected by PCP treatment, but only 70% of PCP-treated mink with implantation sites eventually whelped compared with 88% of control. In PCP-treated mink, 46.7% of embryos were lost compared with 40.5% of control embryos which resulted in smaller litter sizes for PCP-treated mink (3.40 vs 4.45 for controls). The presence of uterine cysts in mink treated with PCP may have contributed to the loss of embryos. The study authors noted that the uterine cysts may have been associated with uterine infection and could indicate an immunosuppressive effect of PCP. Additionally, PCP treatment resulted in a longer duration of pregnancy compared with controls. PCP treatment had no effect of serum levels of progesterone, estradiol, cortisol, or thyroxine in

adult female mink at weaning of their litters. Mink are seasonal breeding animals, with induced ovulation and delayed implantation, which according to the investigators may result in these animals being particularly sensitive to PCP. This study showed effects on reproduction at a dose that was an order of magnitude lower that the NOAEL for the two-generation study in rats.

In a second study utilizing mink, Beard and Rawlings (1998) examined reproductive and endocrine function in the second and third generations (designated as F_2 and F_3 generations) mink exposed continuously to PCP. The F_0 females (described in Beard et al., 1997b) were given untreated or PCP-treated feed continuously from 3 weeks before breading until weaning of the F_1 litters 8 weeks post partum. Therefore, the F_1 females were exposed continuously from conception until 3 months after weaning the F_2 generation. The F_2 females were exposed continuously from conception until they reached full adult size at 30 weeks. F_1 and F_2 male generations (6-10 per group) were exposed continuously from conception until sexual maturity (about 42 weeks). Both treated and control F_1 and F_2 females (8-10 per group) were mated with untreated males. PCP had no effect on body weights or food efficiency. The results between generation with regard to mating efficiency, gestation length, whelping date, average litter size, sex ratio, serum estradiol, cortisol, and testosterone levels were inconsistent as reported for the F_0 mink (Beard et al., 1997b) and for the F_1 and F_2 generations suggesting a refractoriness in the response to PCP. The severity of interstitial cell hyperplasia of the testes and cystic hyperplasia of the prostate gland was greater in F_1 males treated with PCP than in controls. Serum thyroxine (T_4) levels were depressed in F_1 and F_2 males and females compared with the respective controls; in addition, thyroid mass (mg/kg b.w.) was also decreased compared with that of the respective controls. Decreased severity of cellular vacuolation of the adrenal cortex was observed in all F_1 females and in F_2 males fed PCP, but the severity was decreased. The description of effects of PCP on the F_0 parents was reported by Beard et al. (1997b).

In study on cattle, McConnell et al. (1980) administered groups of 3 yearling (10–14 months) Holstein cattle 100% aPCP, 10% tPCP/aPCP mix, 35% tPCP/aPCP mix, or tPCP to determine the level of contaminants on the effect of PCP. Each treatment group was given 647 ppm as PCP in feed (20 mg/kg body weight) for 42 days then 491 ppm (15 mg/kg body weight) for 118 days of the study (total treatment time = 160 days). A group of 3 yearlings served as controls. Treatment with aPCP caused statistically significant decreases in serum T_4 (60-71% of control level) and T_3 levels (56-65% of control level). The effect on thyroid hormones is attributable to PCP and not the contaminants, because the hormone levels were similar among all treated groups. The investigators noted that thyroid follicles were smaller and more numerous in animals receiving 100% tPCP; they did not describe the thyroid of animals receiving aPCP.

Beard et al. (1997a) and Beard et al. (1999b) also reported on a study of ram lambs born of ewes maintained on untreated or PCP-treated diets delivering a dose of 1 mg/kg/day PCP (purity not reported) starting at week 5 prior to mating and continuing through weaning of lambs; the lambs were maintained on the same diets as the ewes from weaning until puberty at 28 weeks of age. The rams exhibited no overt signs of toxicity or treatment-related decreases in body weight. Testes diameter was unaffected at 10 and 14 weeks of age, but scrotal circumference measured at intervals between 16 and 26 weeks was significantly increased in PCP-treated rams. There was no effect of PCP on age at puberty, sperm count, or sperm motility at 27 weeks of age. Scores for different measures of sexual behavior were consistently lower in PCP-treated rams than in controls at 26 weeks of age, but the differences were not statistically significant. Thyroxine (T_4) levels were significantly lower than control levels from 6 to 16 weeks, similar from 18 to 26 weeks, and lower again at 28 weeks of age. The response to thyroid-stimulating hormone (TSH) stimulation was unaffected by treatment with PCP. The serum levels of other endocrine

hormones were unaffected by treatment with PCP. Microscopic examination of the testes and epididymides showed seminiferous tubular atrophy, reduced production of spermatocytes in the seminiferous tubules, and reduced density of sperm in the body of the epididymides, but not in the head and tail of the epididymides. The investigators attributed the spermatogenic findings to the reduced thyroid hormone levels.

In a study by Rawlings et al. (1998), Mature ewes in age groups of 1 year, 1–2 years, and 3–4 years and older were given capsules containing 2 mg/kg PCP (99.9% purity) or empty capsule directly into the rumen twice weekly for a total of ~6 weeks. Blood was collected for serum analysis of T_4, LH, FSH, estradiol, progesterone, cortisol, and insulin on day 36 of treatment. A marked decrease in serum T_4 levels was observed in mature ewes at 36 days. In addition to a significant decreased serum T_4 level, PCP-treated ewes had significantly increased serum insulin levels, but no treatment-related changes were observed in cortisol, LH, FSH, estradiol, or progesterone levels. No clinical signs, or treatment-related weight changes were observed during treatment. The only microscopic change observed was increased severity of intraepithelial cysts in both oviducts.

In a one-generation study, groups of 13 ewes (1-3 years old) received an untreated diet or a diet treated with PCP (purity not reported) at a concentration delivering a dose of 1 mg/kg/day (Beard and Rawlings, 1999; Beard et al., 1999a). The ewes were treated for 5 weeks prior to mating (with untreated rams), during gestation, and until 2 weeks after weaning their lambs. The ewes were sacrificed at the end of treatment. Clinical signs, blood hormone levels, ovarian function, embryonic growth, reproductive function, and histopathologic lesions were assessed during the study. No clinical signs or treatment-related decrease in body weight were observed. One PCP-treated ewe died of a cause unrelated to treatment with PCP. No effects on reproductive function were observed (ovulation rate, fertility rate, lambing rate, mean number of lamb born per ewe, and mean gestation rate). The male:female ratio showed an excess of ewe lambs born (5:13). There was a slight, but statistically significant decrease in the weight of ewe lambs at weaning (86% of control weight). Ovarian function (follicle number and corpora lutea size), fetal growth (measured by head diameter), and post-weaning serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and cortisol were not affected by treatment with PCP. However, maximum serum T_4 levels in PCP-treated ewes were significantly lower than in control ewes with or without prior administration of thyroid-stimulating hormone (TSH). The increase in serum T_4 levels compared with pretreatment level was 190% for PCP-treated ewes and 169% for controls.

Jekat et al. (1994) conducted a study to examine the effect of aPCP and tPCP (purity not reported) on thyroid hormones in female Wistar rats maintained on a normal iodine diet (NID) or a low iodine diet (LID) and pretreated with propylthiouracil to exacerbate the thyroid deficiency. Each group of eight female rats was administered 3 mg/kg/day tPCP, 3 or 30 mg/kg/day aPCP, or the vehicle only (0.5% tylose solution). The test materials were administered by gavage, twice a day at 12-hour intervals, 7 days/week for 28 days. Iodine deficiency caused an 182% increase in thyroid weight, decrease in total and free serum T_4 and T_3 levels, decrease in T_4 and T_3 in the thyroid gland, and decrease in the serum and thyroid gland T_4:T_3 ratio. Treatment with 3 mg/kg/day aPCP caused decreases in total serum T_4, free serum T_4, T_4:T_3 ratio in serum, and serum TSH. Treatment with 3 mg/kg/day tPCP caused decreases in serum T_4, serum T_3, T_4 and T_3 in the thyroid, T_4:T_3 ratio in serum, and serum TSH. Except for serum TSH, aPCP caused greater decreases in iodine deficient rats than in normal rats. Because TSH levels were not elevated in response to the reduced thyroid hormone levels, the investigators concluded that PCP interfered with thyroid hormone regulation at the hypothalamic and pituitary level. They also stated that peripheral interference with thyroid hormone metabolism was suggested by the greater reduction in

T_4 compared with T_3. The study authors concluded that the NOEL for this study was 3 mg/kg/day. However, thyroid hormone levels were clearly reduced at this dose suggesting that this study did not establish a NOAEL.

4.3.2. Developmental Toxicity Studies

In a study conducted by Schwetz et al. (1974), doses of 0, 5, 15, 30, and 50 mg/kg/day commercial grade (88.4% a.i.) or purified (>98% a.i.) pentachlorophenol prepared in corn oil were administered by gavage to groups of pregnant Sprague-Dawley rats on gestation days 6-15 inclusive. For purified pentachlorophenol, the number of rats per group was as follows: control, 33 rats; 5 mg/kg, 15 rats; 15 mg/kg, 18 rats; 30 mg/kg/, 20 rats; 50 mg/kg, 19 rats. For the commercial grade of pentachlorophenol: 5 mg/kg, 18 rats; 15 mg/kg, 17 rats; 30 mg/kg, 19 rats; 50 mg/kg, 15 rats. Additional groups of rats were administered 0 or 30 mg/kg/day pentachlorophenol (type of a.i. not specified) on days 8-11 or 12-15 of gestation.
Maternal toxicity from purified pentachlorophenol was evidenced by decreased maternal weight gain at the 30 and 50 mg/kg dose groups for days 6-21 of gestation (74% decrease vs control). For the commercial grade, weight gain was decreased 43% at the 50 mg/kg dose, and by 22% at the 30 mg/kg dose. Weight gain appeared more significantly affected by purified pentachlorophenol. No other significant signs of maternal toxicity were observed. Fetal incidence of resorption was significantly increased at 30 and 50 mg/kg purified and commercial grade pentachlorophenol. The report stated that the fetal and litter incidence was also significantly increased at 15 mg/kg commerical grade pentachlorophenol, but the fetal incidence (7 and 8% at control and 15 mg/kg/day) as well as the litter incidence (55 and 64% at control and 15 mg/kg/day) did not appear biologically meaningful. Fetal body weight was reported significantly decreased for commerical grade pentachlorophenol at 30 and 50 mg/kg/day and at 30 mg/kg/day for purified pentachlorophenol, but actual values were not reported. Crown-rump length was significantly decreased at 30 mg/kg/day purified pentachlorophenol. The litter incidence of subcutaneous edema, lumbar spurs, and supernumerary, lumber or fused ribs was significantly increased at 30 and 50 mg/kg commercial grade pentachlorophenol, but the data did not indicate a dose-response, i.e. the number of litters affected with subcutaneous edema, rib and vertebral abnormalities were greater at 30 mg/kg than at 50 mg/kg for the commercial grade of pentachlorophenol and for the purified pentachlorophenol. The number of litters at the high dose of purified pentachlorophenol was also severely limited (only 2 litters at this dose). Resorptions were significantly increased when pentachlorophenol (both grades) was administered on gestation days 8-11, but not on gestation days 12-15.
Based on the results of this study, the Maternal NOAEL can be considered as 15 mg/kg/day, based on body weight effects observed at 30 mg/kg/day, for both grades of pentachlorophenol. The Developmental NOAEL would appear to differ according to grade of pentachlorophenol used. Limited data for purified pentachlorophenol at the 50 mg/kg/dose hampers evaluation of a NOAEL and LOAEL for this grade. For the commercial grade of pentachlorophenol, the NOAEL can be considered as 15 mg/kg/day, and the LOAEL as 30 mg/kg/day, based on decreased fetal body weight and crown-rump length. The responses observed at the low dose of commercial grade pentachlorophenol for fetal anomalies (i.e. lumber spurs, anomalous ribs, subcutaneous edema) do not show a dose-response pattern at the higher doses of pentachlorophenol, and are also limited by reduced number of litters at the high dose.

Larsen et al. (1975) reported that groups of 10 pregnant CD Sprague-Dawley derived rats administered 60 mg/kg aPCP (>99% purity) in olive oil by gavage on GD 8, 9, 10, 11, 12, or 13 and maintained until GD 20 showed increases in body temperature of 0.5 to 0.8°C and fetuses exhibited

developmental effects. Controls received olive oil only. The percentages of resorptions for controls ranged from 2.0% to 11.6% and for treated dams 1.6% to 13.5%. The fetuses from dams receiving aPCP on days 8, 9, 10, and 12 weighed 12% to 20% less than those from controls; the weight of fetuses from dams treated on day 11 and 13 were similar to those of controls. There was a small increase in the percentage of fetuses with malformations: 2% after treatment on GD 8 and 5.8% after treatment on GD 9. No malformations were observed in control fetuses. The investigators attributed the fetal effects to maternal toxicity because other studies have indicated that only very small amounts of PCP cross the placental barrier.

In a study conducted by Welsh et al. (1987), groups of male and female Sprague-Dawley rats (20/group) were placed on diets containing purified pentachlorophenol at dose levels of 0, 60, 200, or 600 ppm (0, 4, 13, and 43 mg/kg/day reported for females; no actual intake data for males). These test diets were administered for 181 days. At the end of the subchronic phase, male and female rats were mated for teratological evaluation following subchronic exposure to pentachlorophenol. Body weight gain in maternal rats exposed to PCP was significantly decreased at the high dose (76% from control). Pregnancy rates were low in all dose groups (77.5, 55, 84.2, and 85 for the 0, 60, 200, and 600ppm dose groups, respectively) but, according to the report, there was no effect on fertility. Decreased number of viable fetuses (due to early death) was observed at the 600 ppm dose level of PCP, as well as an increase in total litter resorptions. Body weight of fetuses appeared decreased at the 200 ppm dose level; analysis at the 600 ppm dose level was not complete, due to an alteration in the sex ratio at this dose (100% male sex ratio at this dose as reported). There were no reported alterations in external or sternebral observations at any dose level tested in this study. Increased incidence of misshapen centra was reported at 200 ppm PCP, but the high dose could not be analyzed due to inadequate numbers of fetuses. The incidence of total skeletal variations was reported increased at the 200 ppm dose level for PCP. The results of this study demonstrate toxicity of PCP at 200 ppm (13 mg/kg/day) in the form of increased percentage of female rats with 2 or more resorptions. However, this study is hampered by a lack of fetal data at the high dose, and inconsistent and low percentages of pregnancy at each dose level of PCP tested. The data appear to point to a definitive toxic effect of PCP at the 43 mg/kg/day dose level on both maternal and fetal rats, with decreased weight gain in maternal rats, and decreased viable fetuses, increased early deaths , and increased resorptions at the high dose.

Similar, but less severe effects have been observed in Crl:CD BR VAF/plus rats administered tPCP (88.9% a.i.) by gavage (Hoberman, 1994b). Groups of 25 pregnant rats were administered tPCP in corn oil at doses of 0, 10, 30, and 80 mg/kg/day on GD 6-15 inclusive and sacrificed for maternal and fetal examinations on GD 21. The mean maternal body weight gain was reduced by 15% at 80 mg/kg/day. Developmental toxicity was observed at 80 mg/kg/day. Effects included increased numbers of dams with resorptions (85% vs 41% for controls) along with decreased litter size (86% of control) and reduced fetal body weights (79% of control). Litters from dams treated with 80 mg/kg/day had significantly increased incidences of visceral (27% vs 5% for controls) and skeletal malformations/variations (96% vs 27% for controls) (hydrocephaly, diaphragmatic hernia, and dilation of renal pelvis, and vertebral and sternebral anomalies). This study in rats showed similar effects as those observed in Sprague-Dawley rats (Welsh et al., 1987), but this strain does not appear to be as sensitive or tPCP is not as toxic to the fetus as aPCP. The LOAEL for this study is 80 mg/kg/day for developmental toxicity, the NOAEL is 30 mg/kg/day. The maternal LOAEL and NOAEL are the same as that established for developmental toxicity.

Hoberman (1994a) reported on a developmental toxicity study in which inseminated New Zealand White rabbits (20 rabbits/dose) were administered tPCP (88.9% a.i.) by gavage at doses of 0, 7.5, 15, and 30 mg/kg/day on gestation days 6-18 inclusive. The dams were sacrificed for maternal and fetal examinations on GD 29. No maternal deaths or signs of maternal toxicity at any dose level. Maternal body weight gain and food consumption showed very slight, but statistically significant decreases for GD 6-12 and GD 9-12, respectively, at 30 mg/kg/day. The decrease in weight gain was too small to be considered adverse. In this study, treatment with PCP up to 30 mg/kg/day did not result in developmental effects in rabbits. Since rabbits did not receive the 80-mg/kg/day dose as did the rats in the Hoberman (1994b) study, it is not possible to compare the sensitivity of rabbits with that of the CD rat. The LOAEL for developmental toxicity in the rabbit could not be established and the NOAEL for was ≥30 mg/kg/day. The LOAEL for maternal effects was 30 mg/kg/day based on reduced body weight gain; the NOAEL was 15 mg/kg/day.

4.4 OTHER STUDIES

4.4.1. Genetic Toxicity Studies

4.4.1.1. In vitro studies

TPCP (90.6% purity) in concentrations up to 30 µg/plate did not induce mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without the microsomal fraction (S9) from Aroclor 1254 induced rat or hamster liver (NTP, 1989, 1999). Gopalaswamy and Nair (1992) reported that PCP was positive in the Ames test in the presence of S9. In a review of the genotoxicity of PCP, Seiler (1991) noted that PCP does not induce mutations in bacteria, Drosophila, or mammalian cells in vitro.

NTP (1989, 1999) reported that tPCP (91.6% purity) at concentrations ranging from 3–30 µg/mL produced a weak positive response in Chinese hamster ovary cells (CHO) for induction of sister chromatid exchange (SCE) without added S9 from Aroclor 1254-induced rat liver. The response was negative in the presence of the S9 fraction. In the chromosome aberration test, tPCP produced a weak positive response with added S9 at concentrations of 80 and 100 µg/mL; the response was negative without S9.

Ehrlich (1990) showed that PCP (purity not reported) is not effective in inducing single strand breaks in Chinese hamster ovary (CHO) cells, whereas its metabolite, tetrachloro-*p*-hydroquinone (TCpHQ), is very effective. PCP at a concentration of 10 µg/mL failed to induce single strand breaks after incubating with CHO cells for 2 hours; this concentration was only slightly toxic to the cell after 3 days. A concentration of 20 µg/mL stopped growth of CHO cells after incubation of 2 days. TCpHQ at a concentrations of 2, 5, and 10 µg/mL caused a dose-related increase in single strand breaks. The toxicity tests showed that 5 µg/mL of TCpHQ inhibited growth of CHO cells, 10 µg/mL stopped growth, and 20 µg/mL killed the cells.

Jansson and Jansson (1986) reported that forward mutations (6-thioguanine resistance) were not induced in V79 Chinese hamster cells incubated for 24 hours with 6.25–200 µg/mL PCP (>99.5% purity). The assay system did not include exogenous metabolic activation. Cell survival was ≥27% of

the control. Jansson and Jansson (1991) demonstrated that the metabolite, TCpHQ, incubated 24 hours with V79 Chinese hamster cells induced 6-thioguanine resistance at concentrations of 20–60 μM, suggesting that TCpHQ is at least partly responsible for genotoxic activity of PCP. Dahlahus et al. (1996) reported that oxidative stress (DNA single-strand breaks and formation of 8-OH-dG) was not induced in V79 cells incubated with 25 μM PCP. The PCP metabolites TCpHQ and tetrachloro-*p*-benzoquinone (TCpBQ) induced both lesions, but another metabolite tetrachloro-*o*-hydroquinone (TCoHQ) did not.

No effect was observed on the frequency of SCE or chromosome aberrations in human lymphocytes taken from healthy male subjects and cultured with technical grade sodium-PCP (85% purity) at concentrations up to 90 mg/L (Ziemsen et al., 1987). Cell division was slowed when the cells were incubated with PCP at initiation of culture, but not when it was added 24 hours after initiation of culture.

4.4.1.2. In vivo studies

Chromosomes in peripheral lymphocytes of 22 male workers engaged in the manufacture of PCP (8 workers) or sodium-PCP (14 workers) were analyzed for chromosome aberrations; all 22 workers were smokers (Bauchinger et al., 1982; Schmid et al., 1982). Airborne PCP concentrations during the 3 years before the analysis showed 18/67 measurements <0.01 mg/m^3 and 10/67 measurements >0.5 mg/m^3 for the PCP workplace and 7/55 measurements <0.1 mg/m^3 and 8/55 measurements >0.5 mg/m^3 for the sodium-PCP workplace. The results for the workers exposed to PCP were compared with a group of 22 controls matched for age and social environment; 9 were smokers and 13 nonsmokers. The frequency of chromosome type aberrations (dicentrics and acentrics) were increased in PCP-exposed workers compared with the controls. The frequency of chromatid type aberrations (breaks and exchanges) were not significantly increased compared with controls. A comparison of the SCE frequency in PCP workers who were all smokers with that of control smokers and control nonsmokers subgroups showed that the SCE frequency could be attributed to smoking and not PCP exposure.

Ziemsen et al. (1987) studied the frequency of SCE and chromosome aberrations in the lymphocytes of 20 adult workers occupationally exposed to airborne PCP at concentrations ranging from 1.2–180 μg/m^3 for 3–34 years. Fourteen workers were smokers and six were nonsmokers. Blood PCP concentrations ranged from 23–775 μg/L serum. No exposure-related effect was observed on the frequency SCEs or chromosome aberrations in these 20 workers. Some workers were exposed to PCP via inhalation to dry PCP (96% pure) dust, technical water soluble sodium-PCP (85% pure), or finished PCP solutions.

The NTP (1999) reported protein adducts of chlorinated quinones and semiquinones and oxidative DNA damage in tissue samples from F344 rats after 7 months of dosing with 1000 ppm (60 mg/kg/day) dietary aPCP (99% purity), The level of hemoglobin adducts was elevated in male and female rats. Liver protein adducts of tetrachloro-1,4-benzoquinone, tetrachloro-1,2-benzoquinone, tetrachloro-1,4-semibenzoquinone, and tetrachloro-1,2-semibenzoquinone were formed in male rats, and the level of 8-hydroxyguanosine in liver DNA was elevated twofold in treated male rats compared with controls.

A bone marrow micronucleus test utilizing male and female CD-1 mice dosed with tPCP (88.9% purity) by gavage with 24, 60, or 120 mg/kg for males and 10, 50, or 100 mg/kg for females produced no

increases in the frequency of micronuclei (Xu, 1996). Bone marrow cells were harvested 24, 48, and 72 hours after dosing.

Daimon et al. (1997) conducted an in vivo/in vitro study which showed that PCP did not induce SCE in hepatocytes isolated from male Fischer injected intraperitoneally (i.p.) with 10 mg/kg PCP. In addition, PCP did not cause an increase in the number of cells in S-phase, the mitotic index, chromosome aberrations, or DNA adduct levels.

Sai-Kato et al. (1995) studied the influence of PCP on formation of an oxidative DNA lesion, 8-hydroxydeoxyguanosine (8-OH-dG) in the liver of $B6C3F_1$ mice after a single or repeated doses. Groups of five male mice received PCP by gavage at doses of 0, 30, 60, or 80 mg/kg as a single administration or repeated administration for 5 days. The livers were excised and analyzed for 8-OH-dG 6 hours after the single dose or after the last dose (repeated exposure). The formation of 8-OH-dG was significantly increased at the two highest doses after a single exposure and all doses after repeated exposures; a clear dose-response relationship was also observed with both treatments. The increase in 8-OH-dG formation after a single dose was 1.4- and 1.7-fold at 60 or 80 mg/kg, respectively, compared with that of the control and 1.5-, 1.9, and 1.9-fold increases after repeated exposures to 30, 60, or 80 mg/kg, respectively. Sai-Kato et al. (1995) also showed that formation of 8-OH-dG is specific for liver, because a single dose of 60 mg/kg resulted in no significant increase in 8-OH-dG levels in kidney or spleen.

Umemura et al, (1996) demonstrated that feeding PCP (98.6% purity) to male $B6C3F_1$ for 2 or 4 weeks at concentrations of 41, 86, and 200 mg/kg/day resulted in dose-dependent increases in 8-OH-dG formation the liver. The increases were also statistically significant at all doses. There was an increase in 8-OH-dG levels in the liver between 2 and 4 weeks. In addition, the labeling index and the DNA content of the liver were significantly elevated at 2 and 4 weeks in mice receiving all doses. The labeling index was not increased between 2 and 4 weeks except for a slight increase at 86 mg/kg/day. The liver DNA content at 86 and 200 mg/kg/day was also slightly increased between 2 and 4 weeks. These results support those obtained by Sai-Kato et al. (1995).

In another study, Umemura et al. (1999) fed mice 600 or 1200 ppm PCP (98.6% purity) for 8 weeks and noted that the oxidative lesion 8-OH-dG in liver DNA was statistically increased to 2.5- and 3.8-fold at 600 and 1200 ppm, respectively, compared with the control level. La et al. (1998) reported that Fischer-344 rats fed PCP for 27 weeks had a twofold increase in the 8-OH-dG DNA lesion in liver. Another lesion that co-migrated with the adduct formed with tetrachloro-1,4-benzoquinone was also noted but at an absolute level threefold lower than that of the oxidative lesion.

In conclusion, PCP exposure is associated with oxidative damage and weak clastogenic effects in mammalian systems in vivo. A metabolite of PCP, TcpHQ, is genotoxic in mammalian cells.

4.4.2. Immunotoxicity Studies

McConnachie and Zahalsky (1991) reported that 38 individuals exposed to PCP in PCP-treated log homes for various times ranging from 0-13 years had activated T-cells, autoimmunity, functional immunosuppression, and B-cell disregulation. The exposed individuals consisted of 17 females 9-60 years of age (mean - 30.1 years) and 21 males 8-60 years of age (mean - 31.8 years). The exposed group was compared with a control group consisting of 129 individuals, 81 of whom were females 11-50 years of age and 39 males 24-67 years of age Blood serum PCP concentrations ranged from 0.01-3.40 ppm; the

blood of 17 individuals was not analyzed for PCP content. In addition, females, but not the males, exhibited significantly increased natural killer cell function.

Daniel et al. (1995) studied the immune response using peripheral lymphocytes from 188 patients exposed to PCP-containing pesticides for more than 6 months. Of the patients tested, the mitogenic response was found to be impaired in 65%. The likelihood of an impaired response was greatest in patients with blood PCP levels >10 µg/L (68%) and particularly for those with levels >20 µg/L (71%). Only 50% of patients with blood levels <10 µg/L had impaired immune response. The impaired response persisted for up to 36 months in some patients. Patients with impaired mitogenic response were also likely to have significantly elevated interleukin-8 (IL-8) levels (3.2-fold) and increased proportion of peripheral monocytes (+18%) compared with patients with normal response. The study authors concluded that PCP-exposed patients had moderate to severe immune dysregulation involving T and B lymphocytes. They further noted that immune dysfunction may explain chronic infection, chronic fatigue, and hormonal dysregulation seen in PCP-exposed patients.

Holsapple et al. (1987) administered PCP by gavage to groups of eight female $B6C3F_1$ mice at doses of 0 (control), 10, 30, or 100 mg/kg t-PCP (purity not reported) or 100 mg/kg EC-7 (purity not reported) for 14 consecutive days. Spleen cells were harvested, cultured and exposed to three antigens (lipopolysaccharide, DNP-Ficol, and sheep red blood cells (SRBC) on day 15. Neither t-PCP nor EC-7 affected the antibody response in the splenic cells immunized in vitro to LPS, DNP-Ficoll, or SRBC. In another experiment, animals were treated as described above, but on day 10 or 11, the mice were immunized with SRBC and sacrificed on day 15. The response of IgM-producing spleen cells was decreased in a dose related manner with t-PCP; the lowest dose of 10 mg/kg resulted in statistically significant reductions of 44% and 31% on day 4 (peak response) and day 5, respectively, compared with the control response. The LOAEL for immunotoxicity in mice was 10 mg/kg tPCP the lowest dose tested.

Kerkvliet et al. (1985b) conducted a study to examine the effect of tPCP on the humoral immune response. They administered 15, 30, 60, or 120 mg/kg tPCP (86% purity) to $B6C3F_1$ mice by gavage 2 days before challenge with SRBC; the peak splenic IgM antibody response was measured 5 days after challenge. The 120-mg/kg dose was given in two 60-mg/kg fraction in two consecutive days because a single 120-mg/kg dose was lethal to about one-half the group of 32 animals. A dose-related immunosuppressive effect was observed; the dose suppressing the immune response by 50% (ID_{50}) relative to controls was 83 mg/kg. The same doses of aPCP (99%) had no effective on the IgM antibody response. The investigators tested three contaminant fractions from tPCP at doses equivalent to that of the tPCP ID_{50} dose and found that the chlorinated dioxin/furan fraction had a significant immunosuppressive effect, whereas chlorinated phenoxyphenol and the chlorinated diphenyl ether fractions were ineffective. They compared the immunosuppressive effect of tPCP in two strains of mice (B6C3F1 and DBA/2) and observed that the tPCP has a greater immunotoxic effect in B6C3F1 mice than in DBA/2 mice. The antibody response was suppressed by 28% in B6C3F1 mice administered 10 ppm tPCP and by 75% at 250 ppm; compared with no significant suppression at 10 ppm and only 45% at 250 ppm in DBA/2 mice. The investigators attributed the difference in the two strains to Ah-receptor responsiveness in B6C3F1 mice and Ah-nonresponsiveness in DBA/2 mice. The LOAEL for immunotoxicity for this study was 30 mg/kg; the NOAEL was 15 mg/kg.

White and Anderson (1985) demonstrated that tPCP (90.4% purity) administered to $B6C3F_1$ mice by gavage for 14 days inhibited the functional activity of complement measured by the microtiter hemolytic assay. The classical complement, spontaneous autoactivation, and alternative pathways were

inhibited at 100 mg/kg (high dose); 10 and 30 mg/kg (low and mid doses) PCP resulted in less pronounced effects. Animals returned to control diet after the 14-day treatment period showed only a partial recovery by 30 days postexposure. Animals treated with 100 mg/kg of EC-7 (91.0% purity, which contains almost no dibenzodioxin/dibenzofuran contaminants) exhibited no effects on complement levels. The investigators concluded that a contaminant or contaminants are responsible for the effect on the complement system.

In another study, Kerkvliet et al (1985a) examined the sensitivity of T-cells, macrophage, and natural killer cells in naive and interferon-induced mice to tPCP. tPCP (86% purity) was administered in the diet to female C57BL/6J (B6) mice at concentrations of 100, 250, or 500 ppm for 8 weeks. Immune function tests included T-cell (Concanavalin A and phytohemaglutinin (PHA) induced) and B-cell mitogenesis (lipopolysaccharide induced) (B-cell mitogen), mixed lymphocyte response (proliferation and cytotoxicity), spontaneous and boosted natural killer cytotoxicity, and phagocytic activity of resident, thioglycollate-induced, and tumor activated peritoneal macrophages. As with other studies with tPCP, body weight was not affected, but the relative liver weights were significantly increased at all doses. The only effect of tPCP was the mixed lymphocyte proliferative response to allogeneic stimulation, but there was no effect on the generation of cytotoxic effector cells measured by response to P815 mastocytoma cells. The peak proliferative response of mixed lymphocyte cultures did not show a clear dose-response relationship. The T- and B-cell mitogenic response, natural killer cell activity (spontaneous and boosted), macrophage phagocytic activity, and bone marrow cellularity were not affected by exposure to tPCP. The investigators noted the differences in response of humoral and cell-mediated immunity to inhibitory effects of tPCP, i.e., humoral immunity was affected by tPCP but cellular immunity was not affected.

Exon and Koller (1983) conducted a study in rats in which they examined the effects of PCP on cell-mediated immunity, humoral immunity, and macrophage function. Groups of male and female Sprague-Dawley rats were administered 0, 5, 50, or 500 ppm aPCP (97% purity) continuously in the diet from weaning until 3 weeks after parturition; offspring were continued on same treatment as parents until 13 weeks of age. Immune response was examined in the offspring. Cell-mediated immunity measured by delayed-type hypersensitivity reaction and humoral immunity measured by antibody production to bovine serum albumin were significantly depressed at all doses. A clear dose-response relationship, however, was not seen for either endpoint. Macrophage function measured by the ability to phagocytize sheep red blood cells showed a dose-related increase that was statistically significant at 50 and 500 ppm. In addition, there was an increase in the number of macrophages harvested from the peritoneal exudate. In contrast to the lack of effect of aPCP in adult rodents, aPCP exposure from the time of conception to 13 weeks of age of the offspring produced effects on both humoral and cell mediated immunity.

Kerkvliet et al. (1982a) assessed the humoral immune response in groups of random-bred Swiss-Webster female mice fed tPCP (86% purity) at concentrations of 0, 50, 250, or 500 ppm and in B6 female mice fed 0, 50, 100, or 250 ppm for 8 weeks. In a separate experiment, groups of Swiss-Webster female mice were fed 0 or 250 ppm tPCP with serial sacrifice at 2 week intervals during the 8-week feeding and an 8-week recovery period to determine the time of onset and recovery from PCP-induced toxicity. In addition, groups of B6 female mice were fed 0 or 1000 ppm aPCP (>99%) for 8 weeks to assess the effect of a fourfold higher dose of aPCP as compared with tPCP on immune function. The effect of tPCP on the primary and secondary splenic antibody response to T-dependent sheep red blood cells (SRBC) in Swiss-Webster mice was measured using the hemolytic antibody isotope release (HAIR) assay. The direct effect of tPCP on B cells in B6 mice was measured using the splenic hemolytic plaque assay and the serum antibody response to the T-independent antigen, 2,4-dinitrophenyl-

aminoethylcarbamylmethyl-Ficoll (DNP-Ficoll). tPCP caused dose-dependent suppression of the primary and secondary T-dependent immune responses in Swiss-Webster mice and the T-independent immune response in B6 mice. The kinetics of the response, peak of the response, and/or the magnitude of the pre-peak and post-peak antibody response to SRBC was affected by tPCP at all doses. The IgM response was more sensitive to tPCP exposure than the IgG response. A serial sacrifice study in Swiss-Webster mice showed that significant immunosuppression was evident after only 2 weeks of treatment and persisted for the 8-week treatment and recovery periods. In contrast to tPCP, aPCP at a fourfold higher dose than tPCP had no effect on humoral immune response in mice.

A study conducted in $B6C3F_1$ mice assessed the immunotoxic effect of PCP administered in the diet at 200, 600, or 1800 ppm for tPCP; 200, 600, or 1200 ppm for DP2 and EC7; and 200, 500, or 1500 ppm for aPCP (NTP, 1989) for 6 months. Immunotoxicity was determined by measuring the hemagglutinin titer and quantitating plaque-forming cells (PFC) in response to immunization with sheep red blood cells. The results showed marked decreases in PFC antibody to SRBCs mice treated with tPCP or DP-2: 89% reduction at 200 ppm tPCP, 57% at 600 ppm tPCP, and 85, 56, and 45% reductions at 1200, 600, and 200 ppm DP-2, respectively. The hemagglutinin titers showed a similar response, but were less consistent due to the lack of sensitivity to the test (NTP, 1989). No effects were noted for EC-7 or aPCP.

Forsell et al. (1981) observed no treatment-related effect on immune function in lactating cattle fed commercial PCP (85–90% purity) for up to 146 days. Two groups of four female Holstein-Friesian cattle received control diet throughout or PCP-treated diets corresponding to a dose of 0.2 mg/kg/day for 75–84 days followed by 2.0 mg/kg/day for 56–62 days. Immunologic parameters measured included peripheral T- and B-cell populations, serum IgG, IgA, and IgM levels, mitogen-induced lymphocyte blastogenesis, and antibody response to SRBC.

McConnell et al. (1980) reported decreased IgG2 and IgM levels in serum of Holstein yearlings (10–14 months old) fed 647 ppm as PCP in feed (20 mg/kg/day) for 42 days decreased to 491 ppm (15 mg/kg/day) for 118 days (total treatment time = 160 days). They tested 100% aPCP, 10% tPCP/aPCP mix, 35% tPCP/aPCP mix, and 100% tPCP. IgG2 levels decreased as the proportion of tPCP increased. The decrease in IgM levels did not show a dose-related trend. Lymphocyte proliferation in response to Concanavalin A and pokeweed mitogen was increased in calves treated with tPCP. The increase was time and dose related.

Kerkvliet et al. (1982b) studied the effect of tPCP and aPCP on susceptibility of mice to tumor growth and viral infection; these tests assessed the function of cytotoxic T-cells and phagocytic macrophages. Male B6 mice were administered aPCP (>99% pure) or tPCP (86% pure) in the diet at concentrations of 0, 50, or 500 ppm for 12 weeks before testing for immune competence. In vivo immunotoxicity tests included (1) growth of transplanted syngeneic 3-methylcholanthrene (MCA)-induced sarcoma cells, (2) susceptibility to Maloney sarcoma virus (MSV) inoculation followed by challenge with MSV-transformed tumor cells (MSB), and(3) susceptibility to encephalomyocarditis virus (EMCV) infection. Progressive tumor growth was not affected by aPCP; the incidence was 35% for controls and 31 and 40% for the 50- and 500-ppm groups, respectively. The incidence of progressive tumor growth in tPCP-treated animals was significantly increased to 67% at 50 ppm and 82% at 500 ppm. After MSV inoculation all animals developed primary tumors that regressed but at a slower rate in mice treated with 500 ppm tPCP. The tumor reappeared in 55% of the 500-ppm tPCP mice and an additional two mice developed secondary tumors after challenge with MSB for a total of 73%. Secondary tumors developed in only 19% of controls, 45% of 50-ppm tPCP mice, and ≤18% of aPCP-

treated mice. Splenic tumors were observed in MSB challenged animals administered PCP: 22% and 44% at 50 and 500 ppm aPCP, respectively; 50% at 50 ppm tPCP, but none in the remaining 500-ppm tPCP-treated animals. In contrast to increased tumor susceptibility, susceptibility to EMCV virus-induced mortality was not significantly affected by either aPCP or tPCP. Of particular interest is the observation that PCP-treated mice showed significant depression of T-lymphocyte cytolytic activity and enhancement of macrophage phagocytosis after tPCP treatment but not after aPCP treatment, but these immune effects could be the result of exposure to the dioxin-like contaminants of PCP.

4.4.3. Neurotoxicity Studies

4.4.3.1. In Vitro Studies

Igisu et al. (1993) demonstrated that acetylcholinesterase activity in human erythrocytes is inhibited by PCP at temperatures ranging from 13°C to 37°C.

Using isolated sciatic nerve-sartorius muscle preparations from toads, Montoya and Quevedo (1990) demonstrated a dose-dependent irreversible reduction of endplate potential at the neuromuscular junction using pentachlorophenol concentrations between 0.01-0.1 mM. The origin and purity of the pentachlorophenol used in this study was not known.

Axonal conduction, using an *in vitro* preparation of toad de-sheathed sciatic nerve, was shown to be blocked (concentration-time dependent) irreversibly by pentachlorophenol (Sigma chemical; unknown purity but likely analytical grade) at concentrations ranging from 0. 3 to 10 mM (Montoya et al., 1988). In its ionized form, it appears that pentachlorophenol did not reach the site of action as effectively. Pentachlorophenol was more potent (approximately 2-fold) in causing axonal conduction block than procaine. The ED_{50} for pentachlorophenol was 1 mM. Pentachlorophenol was also able to cause a dose-time dependent ganglionic synaptic transmission block (also irreversible) at concentrations ranging from 0.003 to 0.03 mM. Pentachlorophenol is believed to have an effect during depolarization as it would interfere with Ca^{++} influx (Montoya and Quevedo, 1990).

4.4.3.2. In Vivo Studies

Savolainen and Pekari (1979) studied the neurochemical effects of tPCP and the body burden of chlorophenols on male Wistar rats administered tPCP (sodium salt, 86.1% PCP and 2.4% tetrachlorophenol (TCP)) in drinking water at a concentration of 20 mg/L for 3–14 weeks; one group was allowed to recover for 4 weeks. Each group consisted of five rats. PCP and TCP levels in the liver and brain (PCP only) remained stable between 3 and 14 weeks, whereas the levels in perirenal fat continued to increase during the treatment time. PCP and TCP levels in liver, brain, and fat decreased during the 4-week recovery period. Neurochemical studies showed that acid proteinase, superoxide dismutase, and NADPH diaphorase activities in the right cerebral hemisphere were significantly increased at 8, 14, or 18 weeks, respectively. NADPH diaphorase was significantly decreased in the right hemisphere at 3 weeks. Glutathione peroxidase in the right hemisphere was not significantly affected. Glutathione and superoxide dismutase were significantly decreased in glial cells at 7 and 12 weeks. Glutathione was not affected in neuronal cells and glutathione peroxidase was not affected in glial cells. The study authors concluded that treatment with tPCP caused transient biochemical effects in the rat brain and the effects were associated with body burden of chlorophenols and possibly dibenzodioxin and dibenzofuran contaminants.

Villena et al. (1992) examined the microscopic lesions in nerves of rats receiving PCP under different experimental conditions. This study also included an examination of lesions in kidney and liver. Groups (number not reported) of male Wistar rats were given drinking water containing PCP at concentrations of 0.3 mM for 60 days, 1.0 mM for 60 days or 90 days, 3.0 mM for 120 days, or drinking water without added PCP. Sciatic nerves were examined by electron and light microscopy. No effects were seen in rats given 0.3 mM or 1.0 mM for 60 days. Exposure to 1.0 mM PCP for 90 days or 3.0 mM PCP for 120 days caused changes in myelin sheath of about 10% of type A and B nerve fibers; the effect was more severe in animals receiving the highest dose. Visible damage to the sciatic nerve fibers was characterized by variable degrees of dissociation of the myelin sheath including complete dissociation, profound invagination of the myelin, advanced degeneration of the neuroglial coat, variable losses of neurotubule neurofilaments and other axoplasmic components. The solubility of PCP in water is only 80 mg/L (Budavari et al., 1996); the sodium salt, however, is freely soluble in water. The investigators did not state whether the animals were treated with tPCP, aPCP, or a sodium salt. The investigators noted that interference with food intake (malnutrition) can impair myelin development in maturing animals, but they did not investigate whether PCP caused effects on body weights, food or water consumption, or clinical signs in this study.

Special tests were conducted in ten male and ten female $B6C3F_1$ mice to assess the neurobehavioral effect of PCP administered in the diet at 200, 600, or 1800 ppm for tPCP; 200, 600, or 1200 ppm for DP2 and EC7; and 200, 500, or 1500 ppm for aPCP (NTP, 1989) for 6 months. Neurobehavioral effects were assessed at weeks 5 and 26. The battery of tests included the presence or absence of autonomic signs; pinnal, corneal, and righting reflexes; spontaneous motor activity, acoustical startle response; visual placement response; grip strength; and rotarod tests. The only neurobehavioral effects observed were dose-related decreases in motor activity and rotarod performance in males receiving tPCP for 5 weeks and dose related increases in motor activity and startle response in females receiving all four grades and males receiving tPCP for 26 weeks.

4.5 SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS AND MODE OF ACTION — ORAL AND INHALATION

No animal data are available to evaluate the consequences of long-term inhalation exposure to PCP. Toxicokinetic studies show that PCP is efficiently absorbed from the respiratory tract after single or repeated exposures and that a large portion of the PCP found in the body is unmetabolized parent compound (Hoben et al., 1976b). Human test subjects have been shown to excrete unmetabolized or conjugated forms of PCP after ingestion (Braun et al., 1979; Uhl et al., 1986). However, both animal and human data indicate the formation of phase I metabolites of PCP, including the tetrahydroquinone metabolite of PCP.

The liver is the primary target for noncancer effects of exposure to PCP. Numerous short- and/or long-term oral studies show that PCP is toxic to the liver of rats, mice, dogs, and pigs. Liver toxicity is generally manifested by increased absolute and/or relative weights and a wide spectrum of microscopic lesions. Liver toxicity in long-term studies in rats was manifested primarily by pigment accumulation

(Schwetz et al., 1978), chronic inflammation at high doses and cystic degeneration at lower doses in males (NTP, 1999); female rats were not as sensitive as males in the NTP study. Liver toxicity in mice exposed orally to PCP was manifested primarily by necrosis, cytomegaly, chronic active inflammation, and bile duct lesions (NTP, 1989). Liver toxicity in mice was more severe than that observed in rats at similar doses, and could be based in part on differences in biotransformation of PCP. However, rats were treated with aPCP, whereas mice received either tPCP or EC-7 grades of PCP, which are higher in chlorinated dibenzodioxins and dibenzofuran contaminants, which could contribute to the severity of the response in mice. The NTP (1989) studies showed very little difference between the toxicity of tPCP and EC-7 in mice, except for bile duct hyperplasia, which appeared to be associated with impurities in tPCP at the lower concentration. Liver lesions in the dog (Mecler, 1996), were similar to those observed in the mouse (NTP, 1989), but the doses inducing the lesions in the dog were much lower than those that induced these lesions in the mouse (1.5 mg/kg/day compared with 17-18 mg/kg/day for the mouse). Neither study established a NOAEL and the incidence of some liver lesions approached 100% in mice receiving the lowest dose suggesting that a smaller difference in toxicity may have been observed if the mice had been tested at lower doses. Studies utilizing domestic animals showed that pigs, but not cattle, exhibited liver lesions similar to those observed in mice. The pig exhibited liver toxicity as a lower dose (10 vs 17-18 mg/kg/day for the mouse) and for a shorter duration (30 days vs 2 years) than the mouse. Other nonneoplastic targets identified in long-term studies include the kidney where pigment deposition in the proximal convoluted tubules was observed in rats (NTP, 1999), spleen, mammary gland, and olfactory epithelium of the nose in mice, and the stomach of dogs

A two-generation reproductive toxicity study in rats showed that exposure to tPCP is associated with decreased fertility, delayed puberty, testicular effects , decreased litter size, decreased viability, and decreased pup weights in rats at a dose of 30 mg/kg/day (Hoberman, 1997). These effects occurred at the same doses causing systemic toxicity in parental animals. Reproductive toxicity assessed in mink given 1 mg/kg/day showed evidence of reproductive toxicity in the parental generation, but not in the F_1 generation.

The available developmental toxicity studies in rats and rabbits showed that rats are more sensitive than rabbits. Developmental toxicity is a more sensitive endpoint than maternal toxicity occurring at doses three to six times lower than the doses that caused maternal toxicity manifested as decreased weight gain in the rat. Developmental toxicity studies also showed that aPCP is as toxic or more toxic to the fetus than tPCP (Schwetz et al., 1974; Welsh et al., 1987). The highest doses utilized in the developmental toxicity resulted in severe toxicity to the fetus as well as and maternal toxicity at the highest or two highest levels. Malformations were not induced in either study at doses that were not maternally toxic. Nevertheless, in both studies, developmental toxicity related to growth retardation occurred at doses lower than those causing maternal toxicity.

Several studies showed that treatment with PCP affected the levels of circulating thyroid hormones, T_3 and T_4. Serum T_3 and T_4 levels were decreased by aPCP and tPCP in rats (Jekat et al., 1994), cattle (McConnell et al., 1980), ram and ewe lambs (Beard et al., 1997a; Beard et al, 1999a, Beard and Rawlings, 1999), and mature ewes (Rawlings et al., 1998). PCP treatment did not affect the degree to which TSH stimulated thyroid hormone levels (Beard and Rawlings, 1999; Beard et al., 1999b). The effect on serum thyroid hormone levels was attributed to PCP and not its impurities. PCP was postulated to interfere with thyroid hormone regulation at the hypothalamic/pituitary level and possibly peripheral thyroid hormone metabolism (Jekat et al., 1994). The effect of PCP on thyroid hormone levels suggest that it causes endocrine disruption.

Studies examining the immunotoxic effects of PCP showed that the humoral response and complement activity in mice were impaired by tPCP but not by aPCP when administered to adult animals (Holsapple et al., 1987; Kerkvliet et al., 1982a, 1985a,b; NTP, 1989). Treatment of mice from the time of conception to 13 weeks of age resulted in impaired humoral and cell mediated immunity (Exon and Koller, 1983). Human studies showed that immune response was impaired in patients who had blood PCP levels >10 µg/L, in particular those whose levels were >20 µg/L (Daniel et al., 1995; McConnachie and Zahalsky, 1991).

In vitro neurotoxicity studies showed that PCP causes a dose-dependent irreversible reduction in endplate potential at the neuromuscular junction and interferes with axonal conduction in the sciatic nerve from the toad (Montoya and Quevedo, 1990Montoya et al., 1988). An NTP (1989) study in mice showed only decreased motor activity in rotarod performance in male rats treated with tPCP for 5 weeks and increases in motor activity and startle response in females receiving purified and technical grade PCP for 26 weeks. Another in vivo study showed that treatment of rats with PCP for up to 14 weeks caused biochemical effects in the rat brain (Savolainen and Pekari, 1979). The most definitive study showed that rats receiving PCP in drinking water for at least 90 days had marked morphological changes in sciatic nerves (Villena et al., 1992).

4.6. WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION

A large body of human data as noted in section 4.2 of this document are available for assessing the association of exposure to PCP and disease outcome, but few structured epidemiologic studies with credible exposure assessments and appropriate controls have been performed. Route of exposure is difficult to identify, because of the high potential for simultaneous dermal and inhalation exposure. In spite of the uncertainties, limitations, and weaknesses with the human studies a reasonably strong argument can be made that exposure to PCP is associated with increased risk of soft tissue sarcoma (STS) and non-Hodgkin's lymphoma (NHL). Increased risks of developing STS were reported in six studies, although statistical significance was achieved only in three. Only one of five studies reporting increased risks of NHL achieved statistical significance. Increased risks have been reported for lymphatic cancer, and hematopoietic cancer. Many of these effects may in fact be the result of exposure to the dioxin-like contaminants of PCP.

Five animal studies are available for assessing the carcinogenicity of PCP in animals. The study by BRL (1968) showed no carcinogenic response in male and female $B6C3F_1$ and $B6AKF_1$ mice

administered PCP (Dowcide-7) at dietary concentrations of 130 ppm for up to 18 months. BRL (1968) also reported that Dowcide-7 administered as a single subcutaneous injection was ineffective in eliciting a carcinogenic response. Schwetz et al. (1978) reported no carcinogenic response in male and female Sprague-Dawley rats administered EC-7 in the diet at dose up to 30 mg/kg/day for 22–24 months. An NTP (1989) feeding study in $B6C3F_1$ mice showed that tPCP and EC-7 caused statistically significant increases in the incidences of hepatocellular adenoma/carcinoma and adrenal gland pheochromocytoma in males and females and the incidence of hemangiosarcoma in female mice. tPCP was slightly more effective than EC-7, which contain no or very low levels of chlorinated dibenzodioxins and dibenzofurans, suggesting that the impurities may have enhanced the carcinogenic effect in mice. In the chronic feeding study in rats (NTP, 1999), only aPCP was tested, and there was no evidence of carcinogenicity in male and female rats administered diets containing 10, 20, or 30 mg/kg/day PCP, nor in female rats administered 60 mg/kg/day PCP. There was, however, some evidence for carcinogenicity in male rats administered the 60 mg/kg/day PCP dietary dose (increased incidence of mesothelioma and nasal squamous cell carcinoma).

NTP (1989) concluded that there was *clear evidence of carcinogenic activity* for male $B6C3F_1$ mice fed diets containing tPCP as shown by increased incidences of adrenal medullary and hepatocellular neoplasms and *some evidence of carcinogenic activity* for female $B6C3F_1$ mice as shown by increased incidences of hemangiosarcomas and hepatocellular neoplasms. There was *clear evidence of carcinogenic activity* for male $B6C3F_1$ mice exposed to PCP (EC-7) as shown by increased incidences of adrenal medullary and hepatocellular neoplasms and *clear evidence of carcinogenic activity* for female $B6C3F_1$ mice as shown by increased incidences of adrenal medullary and hepatocellular neoplasms and hemangiosarcomas.

Under EPA's carcinogen risk assessment guidelines of 1986, PCP is classified as Group B2 (*probable human carcinogen*) based on inadequate evidence from human studies and adequate evidence from animal studies. The lack of exposure data rendered the human studies inadequate for associating STS and NHL with exposure to PCP. Animal studies showed that tPCP, which contained chlorinated dibenzodioxin and dibenzofuran impurities, and EC-7, which contained very low concentrations or no detectable impurities, induced hepatocellular and adrenal medullary neoplasms and hemangiosarcomas in mice and mesotheliomas in male rats. In addition, aPCP promoted hepatocellular neoplasms in mice initiated with DEN. PCP appears to be a weak clastogen, but not a mutagen. In addition, it induces oxidative lesions in DNA. EPA (IRIS Online Database, 2000) has concluded that the human evidence for carcinogenicity of PCP is inadequate, but the animal evidence is sufficient, thus placing PCP in the B2 class (probable human carcinogen).

Under EPA's proposed risk assessment guidelines (U.S. EPA, 1996a), PCP is *likely to be carcinogenic to humans by the oral route*. This weight of evidence is based on unequivocal evidence of carcinogenicity from oral studies in male and female mice, positive evidence of hepatocellular tumor promoting activity in mice, suggestive evidence from an oral study in male rats, suggestive evidence from human epidemiologic studies showing increased risks of STS and NHL associated with PCP exposure. tPCP contain impurities, particularly chlorinated dibenzodioxins and chlorinated dibenzofurans, which may contribute to the carcinogenic activity of tPCP.

The mode of action of PCP is not well understood. PCP is not mutagenic in bacterial systems. It is a weak clastogen and it induces oxidative damage to DNA. The metabolite, TCpHQ is mutagenic in mammalian cells and has been identified as a metabolite in both humans and experimental animals. Therefore, the dose-response assessment should adopt both linear and nonlinear default approaches.

4.7. SUSCEPTIBLE POPULATIONS

4.7.1. Possible Childhood Susceptibility

The available developmental toxicity studies showed that PCP is very toxic to the developing fetus. Total resorptions occurred at doses at which reductions in maternal body weight gain were observed (Schwetz et al., 1974; Welsh et al., 1987). It should be noted that effects on maternal body weight gain were due in part to the total litter resorptions. Growth retardation, manifested by reduced fetal body weights and delayed ossifications at various sites in rats, occurred at doses of PCP that did not elicit maternal toxicity (reductions in weight gain).

In two studies utilizing cattle, severe toxicity including death occurred within 5 days of dosing 7-day old bull calves with 20 mg/kg/day PCP (Hughes et al., 1985); the severe toxicity resulted in lowering the dose to 10 mg/kg/day for the remainder of the study. In addition, severe toxicity (moribundity) was noted in calves treated with 10 mg/kg/day for up to 42 days. No deaths occurred among 10–14 month old yearling administered 20 mg/kg aPCP or tPCP for 42 days (McConnell et al., 1980) suggesting greater sensitivity of the newborn calves to PCP than the yearlings. Hughes et al. (1985) reported that the steady state concentration of PCP in serum of calves was more than twice that of adults administered the same dose (10 mg/kg/day). Hughes et al. (1985) stated that they could not conclude that the toxicity of PCP in calves vs older cattle corresponded directly with blood PCP concentration, but they did note that calves appeared somewhat more sensitive than adult cattle.

A human study conducted on residents of in log homes made with PCP-treated wood showed that children age 2 to 15 had serum PCP levels 1.7 to 2 times higher than that of adults in the same household (Cline et al., 1989). The difference was attributed to difference in the ventilation rate to body weight ratio. These results suggest a toxicokinetic difference in children and adults.

4.7.2. Possible Gender Differences

In the stop-exposure study, aPCP (1000 ppm) administered to female Fischer 344 rats for 1 year followed by 1 year without treatment did not elicit a carcinogenic response; whereas malignant mesotheliomas were observed in 18% of males receiving aPCP under the same conditions compared with only 2% of male controls. There was also an increase in the incidence of nasal squamous cell carcinomas for the male rats in the stop exposure study. tPCP or EC-7 administered to male and female $B6C3F_1$ mice elicited a carcinogenic response in both sexes, but the incidences for males were somewhat higher than those for females with one exception. Females had a higher incidence of hemangiosarcomas than did males. These studies suggest a small sex difference in the carcinogenic response for rats and possibly a site-specific difference for mice.

5. DOSE-RESPONSE ASSESSMENT

5.1. ORAL REFERENCE DOSE (RfD)

5.1.1. Choice of Principal Study and Critical Effect

The primary target for PCP toxicity is the liver. Liver toxicity was observed in animals after short- and long-term exposure to PCP and in multiple species: mouse (NTP, 1989), rat (NTP, 1999), dog (Mecler, 1996), and pigs (Greichus et al., 1979). Liver toxicity was manifested by a number of effects consisting of hepatocytomegaly, hepatocellular degeneration, inflammation, and bile duct lesions. Of the species tested, the dog appears to be the most sensitive; liver toxicity was observed after administration of only 1.5 mg/kg/day tPCP for 1 year (Mecler, 1996).

Although effects of toxicologic relevance were observed at the 1.5 mg/kg/day dose level (increased liver weight in female dogs, increased incidence of pigmentation of the liver, and increased incidence of lymphocytic mucosal inflammation of the stomach in both sexes), the derivation of an NOAEL is possible with the use of an extra uncertainty factor of 3x to account for the lack of a definitive NOAEL. This practice is consistent with published Agency policy (EPA, 1993). In addition, it is noted that the liver of dogs is also a target organ of pentachlorophenol induced toxicity, similar to that observed in other species. Thus, the endpoints in this present study can be used to support an RfD. Previously, the RfD was determined from a chronic toxicity study in rats in which pigmentation of the liver and kidneys was observed at a dose of 10 mg/kg/day. As similar effects were observed at a lower dose level in the present study, use of an extra uncertainty factor in determining the RfD would make the present study acceptable for risk characterization purposes.

5.1.2. RfD Derivation

The RfD Approach: The LOAEL for liver toxicity in dogs administered PCP was 1.5 mg/kg/day. Uncertainty factors (UF) of 10 for intraspecies variation, 10 for interspecies variation, and 3 for use of a LOAEL (total UF = 300) were applied to the LOAEL. The resulting RfD is 0.005 mg/kg/day. This value agrees with that derived by EPA's Office of Prevention, Pesticides and Toxic Substances (U.S. EPA, 1999b) but differs from the value of 0.03 mg/kg/day reported in the current IRIS Database (U.S. EPA, 1999a). The current IRIS value was based on the rat oral chronic study by Schwetz et al. (1978) that established a NOAEL of 3 mg/kg/day for liver toxicity and used a 100-fold uncertainty factor applied to the NOAEL. Thus, the differences in the RfD values lie in the selection of the effect level and the use of different uncertainty factors between the two studies.

$$RfD = \frac{LOAEL}{UF} = \frac{1.5\,mg/kg/day}{300} = 0.005\,mg/kg/day$$

$$UF = 10_A \times 10_H \times 3_L = 300$$

One study supporting this RfD is the developmental toxicity utilizing rats (Schwetz et al., 1974) where developmental effects were observed at 15 mg/kg/day with commercial pentachlorophenol, and the NOAEL for this grade of pentachlorophenol was 5 mg/kg. Applying 10-fold uncertainty factors for

intraspecies and interspecies variability and an additional uncertainty factor for estimating a NOAEL from the LOAEL yields an RfD of 0.005 mg/kg/day, similar to the RfD value derived from the dog study.

The Benchmark Dose Approach The benchmark dose approach was also applied to the developmental toxicity data (Schwetz et al., 1974). Doses of 0, 5, and 15 mg/kg/day were associated with litter incidences of 6/31 (19%), 9/15 (60%), and 13/18 (72%). The linearized multistage, gamma, quantal linear, and Weibull models were utilized to calculate the lower 95% confidence limit on the benchmark dose (BMDL) based on a benchmark response (BMR) of 10%. Global86 computer program (Howe et al. (1986) was used for the linearized multistage model and EPA's Benchmark Dose Software, Version 1.1b (http://www.epa.gov/ncea/bmds.htm) was used for the gamma, quantal linear, and Weibull models. The BMDL was 0.8 mg/kg/day for each of the four models. Applying an uncertainty factor of 100 (10 for intraspecies variation and 10 for interspecies variation) yields an RfD of 0.008 mg/kg/day.

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

No data were available for deriving an inhalation reference concentration.

5.3. CANCER ASSESSMENT

5.3.1. Choice of Study/Data With Rationale and Justification

Epidemiologic data strongly suggest an association between exposure to PCP and development of STS and NHL; however, the lack of adequate exposure estimates render these studies unsuitable for deriving cancer risk estimates for PCP.

Two well-conducted studies provided data for the carcinogenicity of PCP in laboratory animals: one study utilizing B6C3F_1 mice and another study utilizing Fischer 344 rats (NTP, 1989). In the mouse study, the carcinogenicity of tPCP, which contained appreciable amounts of chlorinated dibenzodioxins and dibenzofurans, was compared with the carcinogenicity of EC-7, which contained no or very low levels of dioxins and furans. Only purified PCP or aPCP was tested in the rat study. Both tPCP and EC-7 were carcinogenic in the mouse, and aPCP showed some evidence of carcinogenicity in the male rat. Hepatocellular adenomas/carcinomas and adrenal medullary pheochromocytomas developed in male mice treated with tPCP or EC-7, hepatocellular adenomas/carcinomas and hemangiosarcomas developed in female mice treated with tPCP or EC-,7 and adrenal medullary pheochromocytoma also developed in female mice treated with EC-7. Mesiotheliomas and nasal squamous cell carcinomas developed in rats treated with aPCP.

The induction of the neoplasms in rats (mesotheliomas and nasal squamous cell carcinomas) may be related to oxidative damage to cells caused by PCP, which can be measured by the production of 8-OH-dG lesions in DNA (U.S. EPA, 1999b). Oxidative lesions are prominent in liver of mice administered PCP as a single dose or as repeated doses ((Sai-Kato et al., 1995). Further, no significant increase in the oxidative lesion occurred in the kidney and spleen of mice as was observed in the liver, indicating some specificity for the liver in mice (Sai-Kato et al., 1995). In addition, protein adducts as indications of tissue dose showed qualitative and quantitative differences in the mouse and rats, possibly explaining the differences in carcinogenicity of PCP in the mouse compared with that of the rat. Formation of tetrachloro-1,4-benzoquinone and tetrachloro-1,2-benzoquinone were the prominent reactive metabolites detected in mouse liver, whereas tetrachloro-1,2-benzoquinone metabolite was not detected in the liver of the rat (Lin et al., 1997, 1999).

The mouse studies have been selected for dose-response assessment. Based on available data (see Table 4), it appears that humans were more similar to the rats and mice than the monkey suggesting that mouse data are appropriate for deriving lifetime cancer risk estimates for humans. Because PCP is not mutagenic but appears to have clastogenic activity both linear and nonlinear modes of action are considered for dose-response assessment for PCP.

5.3.2. Dose-Response Data

The data for mesotheliomas in the rat study were not utilized for dose-response assessment because the statistical analysis did not show a significant dose-related trend. Therefore, oral cancer risk estimates were calculated based on the incidences of hepatocellular neoplasms, adrenal medullary neoplasms, and hemangiosarcomas that developed in mice treated with tPCP or EC-7. Each site was considered separately, but the data for tPCP and EC-7 were combined. The data were combined because the two grades of PCP induced neoplasms at the same anatomical sites. tPCP, however, appeared to be slightly more potent than EC-7, suggesting some enhancing activity due to the impurities. The combined incidences of neoplasms in mice treated with tPCP and EC-7 are presented below:

$B6C3F_1$ Male Mice	Tumor Incidence[b]		
Administered Dose (mg/kg/day)[a]	Hepatocellular neoplasms	Adrenal Medullary Neoplasms	Hemangiosarcomas/ Hemangiomas
0	13/67	0/65	–
18 (2.59)	45/95	14/93	–
36 (5.18)	58/96	44/93	–
118 (16.98)	34/49	45/49	–
$B6C3F_1$ Female Mice			
0	4/67	2/68	0/70
17 (2.45)	13/99	4/97	4/100
34.5 (4.96)	15/99	3/95	9/100
114)16.40)	31/48	38/49	9/50

[a]Average dose for tPCP and EC-7
[b]Combined incidences for animals treated with tPCP and EC-7.

5.3.3. Dose Conversion

The mice were administered PCP by the dosed feed method. Weight-normalized doses were presented by NTP (1989). Animals doses were converted to human equivalent doses (HED) by applying body weight to 3/4-power to extrapolate from animals to humans. The default body weights of 0.030 kg for the mouse and 70 kg for human were utilized for the conversion. The equation is as follows:

$$HED = \left(Animal \quad Dose \quad (mg / kg / day \times \left(Animal \quad Wt. \Big/ Human \quad Wt. \right)^{1/4} \right)$$

$$HED = \left(Animal \quad Dose \quad (mg/kg/day) \times \left({}^{0.030kg}\!/_{70kg} \right)^{1/4} \right)$$

5.3.4. Extrapolation Method(s)

Three low-dose extrapolation methods were considered for deriving cancer risk values for PCP. The first was EPA's 1986 methodology in which the linearized multistage model was used to extrapolate the dose-response data to low doses to estimate the slope factor (U.S. EPA, 1986a). The second and third methods were based on EPA Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996) and used the linearized multistage or benchmark dose models to derive the LED_{10} (point of departure), i.e., the lower 95% confidence limit on the dose associated with a 10% extra risk. The 10% risk was selected because this response level is within the range of experimental detection applying appropriate statistical analysis. The second method involved linear extrapolation in which cancer risk values were derived by extending a straight line from the point of departure (LED_{10}) to the origin (zero dose/zero response). The third method was nonlinear extrapolation, which applies a margin of exposure (MOE) analysis to key data. Where available key data should consist of precursor events to carcinogenesis (U.S. EPA, 1996). The LED_{10} is compared to expected environmental exposure; the ratio between the LED_{10} and environmental exposure is the MOE. The MOE should be sufficiently large to assure protection of sensitive human subpopulations at the expected environmental concentrations. If a biological threshold is indicated by the data then uncertainty factors can be applied to the LED_{10} to calculate a RfD; this dose should represent no appreciable risk of cancer. Dose-response data for precursor events are not available for PCP-induced carcinogenesis; therefore, the MOE analysis is deferred until such data are available.

5.3.5. Oral Slope Factor and Carcinogenicity Unit Risk

Oral slope factors (lifetime estimates of unit cancer risk) are presented in Table 13. Slope factors were calculated using the linearized multistage model (LMS; GLOBAL86 Computer Program) and the Benchmark Dose Software, Version 1.1b. The Benchmark Software package includes the following models: gamma hit, logistic, multistage, probit, quantal linear, quantal quadratic, and Weibull. Logarithmic transformation of dose data can transform the logistic and probit models to log-logistic and log-probit models, respectively. Slope factors presented in Table 13 were derived by low-dose extrapolation by the LMS model (q_1*) or drawing a straight line from the point of departure (LED_{10} for LMS model or BMDL for Benchmark dosed approach) to the origin ($0.1/LED_{10}$. Only the results of models that gave adequate fits to the data are presented in the table. An adequate fit for the data was determined by a probability of $p>0.05$ and visual inspection of the graphs.

The slope factors for PCP ranged from 1.9×10^{-1} to 1.5×10^{-2} per (mg/kg)/day. The geometric mean of all the values in Table 13, excluding the slope factors derived from the full data set for hemangiosarcomas in female mice, was 4.6×10^{-2} per (mg/kg)/day. These data show that the lifetime risk values derived from the male mouse data exceeded the values derived from female mouse data for all tumor types. These results also showed that for each tumor type, the lifetime cancer risks were largely independent of the model applied to the data. The recommended slope factor for PCP is 1.8×10^{-1} per (mg/kg)/day. This value is the average slope factor derived from the incidence of hepatocellular neoplasms in male mice.

The above calculated unit risk value varies only slightly from that derived previously by EPA [1.2×10^{-1} per (mg/kg)/day]. That estimation of unit risk was based upon the combination of the incidence of

hemangiosarcomas in female mice receiving technical grade pentachlorophenol and the incidence of hepatocellular adenomas/carcinomas, pheochromocytomas, and hemangioma/hemangiosarcoma combined in female mice receiving Dowicide EC-7 (U.S. EPA, 1999b). The California Department of Pesticide Regulation (Cal EPA, 1998), in their final risk characterization document on pentachlorophenol, used the U.S. EPA's Science Advisory Board recommendation that only hemangiosarcoma incidence be used in calculation of the cancer unit risk, with a resulting estimated unit risk of 1.6×10^{-2}. This estimate is 7.5-fold lower than the EPA's, and is based upon the use of only one tumor site as mentioned (hemangiosarcoma) as well as the use of only tumor data from the Dowicide EC-7 study and not the use of pooled tumor incidence data as was done by the EPA. Nonetheless, both Cal EPA as well as U.S. EPA recognize pentachlorophenol as a positive carcinogen. The International Agency for Research on Cancer (IARC, 1999) has also classified pentachlorophenol as a Group 2B (probable) human carcinogen.

Table 13. Lifetime Human Cancer Risk Estimates Based on Incidences of Hepatocellular Neoplasms, Adrenal Pheochromocytomas, and Hemangiosarcomas/Hemangiomas in the mouse (NTP, 1989)

Model	Oral Slope Factors (risk per (mg/kg)/day)				
	Hepatocellular neoplasms		Pheochromocytomas		Hemangiosarcoma/ Hemangiomas
	Male[a]	Female	Male	Female	
LMS (q_1*)	1.9×10^{-1}	3.6×10^{-2}	1.1×10^{-1}	inadequate fit	2.2×10^{-2}
LMS ($0.1/LED_{10}$)	1.8×10^{-1}	3.7×10^{-2}	1.1×10^{-1}	inadequate fit	2.1×10^{-2}
Benchmark Dose Models					
Gamma Hit	1.8×10^{-1}	3.6×10^{-2}	8.3×10^{-2}	1.5×10^{-2}	2.0×10^{-2} (2.6×10^{-2})[b]
Logistic	Inadequate fit	2.4×10^{-2}	Inadequate fit	1.7×10^{-2}	Inadequate fit
Multistage	1.5×10^{-1}	3.6×10^{-2}	1.1×10^{-1}	Inadequate fit	(2.7×10^{-2})[b]
Probit	Inadequate fit	2.6×10^{-2}	Inadequate fit	1.9×10^{-2}	Inadequate fit
Quantal Linear	1.8×10^{-1}	Inadequate fit	1.3×10^{-1}	Inadequate fit	2.0×10^{-2} (2.6×10^{-2})[b]
Quanta Quadratic	Inadequate fit	2.1×10^{-2}	Inadequate fit	Inadequate fit	Inadequate fit
Weibull	1.8×10^{-1}	3.6×10^{-2}	9.1×10^{-2}	Inadequate fit	2.0×10^{-2} (2.6×10^{-2})[b]

[a]High dose automatically dropped by GLOBAL 86 Computer program to obtain an adequate fit; the high-dose was also dropped (not automatically) to obtain adequate fits for the benchmark dose models.
[b]Numbers in parenthesis are the slope factors for hemangiosarcomas after dropping the high-dose from the analysis.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

Numerous short- and/or long-term oral studies in experimental animals show that PCP is toxic to the liver. Liver toxicity is generally manifested by increased absolute and/or relative weight accompanied in some cases by microscopic lesions. In long-term studies in rats, liver toxicity was manifested primarily by accumulation of pigment (Schwetz et al., 1978), or chronic inflammation and cystic degeneration (NTP, 1999). Liver toxicity in mice was manifested primarily by necrosis, cytomegaly, chronic active inflammation, and bile duct lesions (NTP, 1989). The increased severity of liver toxicity observed in mice vs. rats could be based in part on differences in biotransformation of PCP (Lin et al., 1997), but it is also noted that in the mouse studies, the PCP test material used contained higher concentrations of chlorinated dibenzodioxin/dibenzofuran contaminants, which could contribute to the severity of the liver response. Liver toxicity in the dog (Mecler, 1996) was similar to that of the mouse, but the doses causing toxicity were lower than those inducing toxicity in the mouse (i.e. 1.5 mg/kg/day in the dog vs. 17-18 mg/kg/day in the mouse). Studies using domestic and/or farm animals showed that pigs, but not cattle, exhibited similar liver toxicity as that observed in mice. Other target organs of non-neoplastic toxicity include the kidney of rats, where pigment deposition in the proximal comvoluted tubules were observed (NTP, 1999), as well as the spleen, mammary gland, and olfactory epithelium in mice, and the stomach of dogs.

Developmental toxicity studies showed that toxicity to the fetus occurred at doses equivalent or below those causing maternal toxicity (Schwetz et al., 1974; Welsh et al., 1987). However, these data have several limitations that preclude definitive assessment. In the Schwetz study, the fetal responses observed (lumbar spurs, anomalous ribs, subcutaneous edema) do not show a dose-response pattern at higher doses, and the characterization of the response is limited by the reduced number of litters at the high dose. In the Welsh study, inconsistent and low pregnancy rates were observed at each dose level of PCP tested, and there is also a lack of fetal data at the high dose. In addition, data submitted to and reviewed by the Agency on the developmental and reproductive toxicity of PCP (in support of the reregistration of this pesticide chemcial) show no special sensitivity of offspring to the toxicity of PCP.

In Position Document 4 (USEPA, 1984), the Agency required a teratogenicity / fetotoxicity warning on the labels for all uses of pentachlorophenol and salts of pentachlorophenol. This labeling was based on results obtained from literature studies using pentachlorophenol (Schwetz et al, 1974 [see above]; Larsen et al., Environmental Lett. 10(2): 121-128, 1975 [see above]; Fahrig et al., In K.R. Rao (Ed.), Pentachlorophenol: Pentachlorophenol Chemistry, Pharmacology, and Environmental Toxicology, pp. 325-338, 1978) in which toxicity to the developing fetus was observed. These toxic responses (decreased body weight, fetal resorption increase, decreased crown-rump length) were observed in the presence of maternal toxicity, or were implied to be an indirect effect of maternal toxicity. The more recent data submitted and reviewed by the Agency as also summarized above supports this same conclusion. The Agency recognizes (EPA Position Document 2/3, p. 261) that “pure penta is not a teratogen.” However, it is recognized that the contaminants hexachlorodioxin and 2,3,7,8 tetrachlorodioxin are considered teratogenic chemicals. For this reason, and with the knowledge that hexachlorodioxin is a contaminant of pentachlorophenol, the label warning on pentachlorophenol formulations is supported.

Disruption of endocrine homeostasis has been observed from administration of PCP. Several studies have reported decreased serum thyroxine and triiodothyronine levels in rats (Jekat et al, 1994), cattle (McConnell et al., 1980), ram and ewe lambs (Beard et al., 1997a; Beard et al., 1999a; Beard and Eawlings, 1999), and mature ewes (Rawlings et al., 1998) after administration of PCP. The effect is

postulated to be due to interference with tyroid hormone regulation at the hypothalamic/pituitary level and possibly increased peripheral thyroid hormone metabolism (Jekat et al., 1994). The effect of PCP on thyroid hormone homeostasis has been attributed to PCP and not to contaminants.

Studies examining the immunotoxic effects of PCP showed that the humoral response and complement activity in mice were impaired by tPCP but not by aPCP when administered to adult animals (Holsapple et al., 1987; Kerkvliet et al., 1982a, 1985a,b; NTP, 1989). Treatment of mice from the time of conception to 13 weeks of age resulted in impaired humoral and cell mediated immunity (Exon and Koller, 1983). Human studies showed that immune response was impaired in patients who had blood PCP levels >10 µg/L, in particular those whose levels were >20 µg/L (Daniel et al., 1995; McConnachie and Zahalsky, 1991). Immunotoxic effects of PCP appear to be mediated in part through the presence of the dioxin/furan contaminants within PCP.

In vitro neurotoxicity studies showed that PCP causes a dose-dependent irreversible reduction in endplate potential at the neuromuscular junction and interferes with axonal conduction in the sciatic nerve from the toad (Montoya and Quevedo, 1990Montoya et al., 1988). An NTP (1989) study in mice showed only decreased motor activity in rotarod performance in male rats treated with tPCP for 5 weeks and increases in motor activity and startle response in females receiving purified and technical grade PCP for 26 weeks. Another in vivo study showed that treatment of rats with PCP for up to 14 weeks caused biochemical effects in the rat brain (Savolainen and Pekari, 1979). The most definitive study showed that rats receiving PCP in drinking water for at least 90 days had marked morphological changes in sciatic nerves (Villena et al., 1992).

Studies examining the mutagenicity of PCP have shown that in large part, PCP is non-mutagenic in a variety of test systems, with the exception of one published report (Gopalaswamy and Nair, 1992), in which PCP was reported positive for mutagenicity in the Ames Salmonella assay. In contrast to data on PCP, data for the tetrahydroquinone metabolite of PCP (THQ) show positive mutagenic effects in Chinese hamster ovary cells (Jansson and Jansson, ..), an increase in micronuclei using V79 cells (Jansson and Jansson), covalent binding to DNA (Witte et al.,) and induction of DNA single-strand breaks (Witte et al.,). THQ has been thought to be involved in some or all of the mutagenic and carcinogenic effects of PCP.

Pentachlorophenol has been classified as a B2 (probable) human carcinogen, based upon inadequate evidence in humans and sufficient evidence in animals. Animal studies with PCP in mice show clear evidence of adrenal medullary and hepatocellular neoplasms as well as increased incidence of hemangiosarcomas and hemangiomas. The recommended slope factor (q1*) of 1.8×10^{-1} differs only slightly from the previously calculated value of 1.2×10^{-1} , and is based upon the different tumor data sets used to calculate unit risk. Whereas before the combined incidence of hemangiosarcomas in female mice and hepatocellular adenoma/carcinoma, pheochromocytoma, and hemangioma/hemangiosarcoma were used to calculate unit risk, the current unit risk was derived from the incidence of hepatocellular neoplasms in male mice.

6. REFERENCES

Ahlborg, U.G., Lindgren, J.-E., and Mercier, M. 1974. Metabolism of pentachlorophenol. Arch. Toxicol. 32:271-281.

Ahlborg, U.G., Larsson, K., and Thunberg, T. 1978. Metabolism of pentachlorophenol in vivo and in vitro. Arch. Toxicol. 40:45-53.

Allan, R.E., 1994. Phenols and phenolic compounds. In: Patty's Industrial Hygiene and Toxicology, 4th ed., Vol. 2, Pt. B, G.D. Clayton and F.e. Clayton, Eds., John Wiley & Sons, Inc. pp. 1567-1630.

ATSDR (Agency for Toxic Substances and Disease Registry). 1999. Toxicological Profile for Pentachlorophenol (Update). U.S. Department of Health and Human Services, Atlanta, GA

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

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

Beard, A.P., Bartlewski, P.M., Rawlings, N.C. 1999a. Endocrine and reproductive function in ewes exposed to the organochlorine pesticides lindane or pentachlorophenol. J. Toxicol. Environ. Health (Part A) 56:23-46.

Beard, A.P., Bartlewski, P.M., and Chandolia, R.K., Honaramooz, A., Rawlings, N.C. 1999b. Reproductive and endocrine function in rams exposed to the organochlorine pesticides lindane and pentachlorophenol from conception. J. Reprod. Fert. 115:303-314.

Beard, A.P., Bartlewski, P.M., and Chandolia, R.K., Honaramooz, A., Rawlings, N.C. 1997a. Pituitary, thyroid and testis function in rams exposed to organochlorine pesticides from conception. Biol. Reprod. 56 (Suppl. 1): 200.

Beard, A.P., McRae, A.C., and Rawlings, N.C. 1997b. Reproductive efficiency in mink (Mustela vison) treated with the pesticides lindane, carbofuran and pentachlorophenol. J. Reprod. Fert. 111:21-18.

Begley, J., Reichert, E.L., Rashad, M.N. and Klemmer, H.W. 1977. Association between renal function tests and pentachlorophenol exposure. Clin. Toxicol. 11:97-106.

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

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

Braun, W.H., Blau, G.E., and Chenoweth, M.B. 1979. The metabolism/pharmacokinetics of pentachlorophenol in man, and a comparison with the rat and monkey. In: Toxicology and Occupational Medicine, New York, Elsevier, pp. 289-296.

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

BRL (Bionetics Research Labs, Inc.) 1968. Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals. Volume I. Carcinogenic Study. Prepared for National Cancer Institute, Bethesda, MD. PB223159.

Budavari, S, O'Neil, M., Smith, A., Heckelman, P.E., and Kinneary, J.F. 1996. The Merck Index: An Encyclopedia of Chemical, Drugs, and Biologicals. 12th ed., Merck & Co., Inc., Whitehouse Station, N.J. p. 1222.

Casarettt, L.J., Benevue, W.L., Yauger, W.L., et al. 1969. Observations on pentachlorophenol in human blood and urine. Am. Ind. Hyg. Assoc. J. 30: 360-366.

Chhabra, R.S., Maronpot, R.M., Bucher, J.R., et al. 1999. Toxicology and carcinogenesis studies of pentachlorophenol in rats. Toxicol. Sci. 48:14-20. hardcopy

Cline, R.E., Hill, R.H., Phllips, D.L., and Needham, L.L. 1989. Pentachlorophenol measurements in body fluids of people in log homes and workplaces. Arch. Environ. Contam. Toxicol. 18:475-481.

Cook, S.J., Beard, A.P., McRae, A.C., and Rawlings, N.C. 1997. Fertility in mink (*Mustela vison*) exposed to pesticides from conception. Biol. Reprod. 56(Suppl. 1):200.

Dahlahus, M., Almstadt, E., Henschke, P., Luettgert, S., and Appel, K.E. 1996. Oxidative DNA lesions in V79 cells mediated by pentachlorophenol metabolites. Arch. Toxicol. 70:457-460.

Daimon, H.; Sawada, S., Asakura, S. and Sagami, F. 1997. Inhibition of sulfotransferase affecting in vivo genotoxicity and DNA adducts induced by safrole in rat liver. Teratog. Carcinog. Mutag. 17:327-337.

Daniel, V., Huber, W., Bauer, K., and Oplez, G. 1995. Impaired in vitro lymphocyte responses in patients with elevated pentachlorophenol (PCP) blood levels. Arch. Environ. Health 50:287-292.

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

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.

Engst, R., Macholz, R.M., Kujawa, M., Lewerenz, H.-J., and Plass, R. 1976. The metabolism of lindane and its metabolites gamma-2,3,4,5,6-pentachlorocyclohexene, pentachlorobenzene, and pentachlorophenol in rats and the pathways of lindane metabolism. J. Environ. Sci. Health. B11:92-117.

Exon, J.H. and Koller, L.D. 1983. Effects of chlorinated phenols on immunity in rats. Int. J. Immunopharmac. 5:131-136.

Forsell, J.H., Shull, L.R., Kateley, J.R. 1981. Subchronic administration of technical pentachlorophenol to lactating dairy cattle: immunotoxicologic evaluation. J. Toxicol. Environ. Health. 8:543-558.

Gopalaswamy, U.V. and Nair, C.K. 1992. DNA binding and mutagenicity of lindane and its metabolites. Bull. Environ. Contam. Toxicol. 49:300-305.

Greichus, Y.A., Libal, G.W., and Johnson, D.D. 1979. Diagnosis and physiologic effects of pentachlorohenols on young pigs. Part. 1. Effects of purified pentachlorophenol. Bull. Environ. Contam. Toxicol. 23:418-422.

Hoben, H.J., Ching, S.A., and Casarett, L.J. 1976a. A study of inhalation of pentachlorophenol by rats III. Inhalation toxicity study. Bull. Environ. Contam. Toxicol. 15:463-465.

Hoben, H.J., Ching, S.A., and Casarett, L.J. 1976b. A study of inhalation of pentachlorophenol by rats IV. Distribution and excretion of inhaled pentachlorophenol. Bull. Environ. Contam. Toxicol. 15:466-474.

Hoberman, A.M. 1994a. Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of Pentachlorophenol Administered Orally Via Stomach Tube to New Zealand White Rabbits. Study conducted by Argus Research Laboratories for the Pentachlorophenol Task Force, submitted under MRID 43091701 (Unpublished).

Hoberman, A.M. 1994b. Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of Pentachlorophenol Administered Orally Via Gavate to Crl:CD®BR VAF/Plus® Presumed Pregnant Rats. Study conducted by Argus Research Laboratories for the Pentachlorophenol Task Force, submitted under MRID 43091702 (Unpublished).

Hoberman, A.M. 1997. Oral (Gavage) Two-Generation (One Litter Per Generation) Reproduction Study of Pentachlorophenol in Rats. Study conducted by Argus Research Laboratories, Horsham, PA for the Pentachlorophenol Task Force, submitted under MRID 44464101.

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

Howe, R.B.; Crump, K.S.; Van Landingham, C. (1986) GLOBAL 86, A Computer Program to Extrapolate Quantal Animal Toxicity Data to Low Doses. Prepared under subcontract 2-251U-2745 to Research Triangle Institute Contract 68-01-6826. U.S. EPA, Washington, D.C.

HSDB (Hazardous Substance Data Bank). 1999. Online Database.

Hughes, B.J., Forsell, J.H., Sleight, S.D., Kuo, C., and Shull, L.R. 1985. Assessment of pentachlorophenol toxicity in newborn calves: clinicopathology and tissue residues. J. Anim. Sci. 61:1587-1603.

IARC (International Agency for Research on Cancer). 1991. Pentachlorophenol. In: Occupational Exposures in Insecticide Application, and some Pesticides, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 53. IARC, Lyon, France. pp. 371-402.

Igisu, H., Hamasaki, N. and Ikeda, M. 1993. Highly cooperative inhibition of acetylcholinesterase by pentachlorophenol in human erythrocytes. Biochem. Pharmacol. 46:175-177.

Jakobson, K. and Yllner, S. 1971. Metabolism of 14C-pentachlorophenol in the mouse. Acta Pharmacol. Toxicol. 19:513-524.

Jansson, K. and Jansson, V. 1986. Inability of chlorophenols to induce 6-thioguanine-resistant mutants in V79 Chinese hamster cells. Mutat. Res. 171:165-168.

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

Jansson, K and Jansson, V. 1992. Induction of micronuclei in V79 Chinese hamster cells by tetrachlorohydroquinone, a metabolite of pentachlorophenol. Mutat. Res. 279:205-508.

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

Johnson, R.L., Gehring, J, Kociba, R.J., and Schwetz, B.A. 1973. Chlorinated dibenzodioxins and pentachlorophenol. Environ. Health Perspect. 5:171-175.

Jones, R.D., Winter, D.P, and Cooper, A.J. 1986. Absorption study of pentachlorophenol in persons working with wood preservatives. Human Toxicol. 5:189-194.

Jorens, P.G., Janssens, J.J., Van Tichelen, W.I., et al. 1991. Pentachlorophenol concentrations in human cerebral fluid. NeuroToxicol. 12:1-8.

Juhl, U., Witte, I., and Butte, W. 1985. Metabolism of pentachlorophenol to tetrachlorohydroquinone by human liver homogenate. Bull. Environ. Contam. Toxicol. 35:596-601.

Kerkvliet, N.I., Baecher-Steppan, L., Claycomb, A.T., Craig, A.M., and Sheggeby, G.G. 1982a. Immunotoxicity of technical pentachlorophenol (PCP-T): Depressed humoral immune responses to T-dependent and T-Independent antigen stimulation in PCP-T exposed mice. Fund. Appl. Toxicol. 2:90-99.

Kerkvliet, N.I., Baecher-Steppan, L. and Schmitz, J.A. 1982b. Immunotoxicity of pentachlorophenol (PCP): increased susceptibility to tumor growth in adult mice fed technical PCP-contaminated diets. Toxicol. Appl. Pharmacol. 62:55-64.

Kerkvliet, N.I., Brauner, J.A., Baecher-Steppan, L. 1985a. Effects of dietary technical pentachlorophenol exposure on T cell, macrophage and natural killer cell activity in C57Bl/6 mice. Int. J. Immunopharmac. 7:239-247.

Kerkvliet, N.I., Brauner, J.A., and Matlock, J.P. 1985b. Humoral immunotoxicity of polychlorinated diphenyl ethers, phenoxyphenols, dioxins and furans present as contaminants of technical grade pentachlorophenol. Toxicology. 36:307-324.

Kimbrough, R.D. and Linder, R.E. 1975. The effect of technical and 99% pure pentachlorophenol on the rat liver. Light microscopy and ultrastructure. Toxicol. Appl. Pharmacol. 33:131-132..

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

Kinzell, J.H., Ames, N.K., Sleight, S.D., et al. 1981. Subchronic administration of technical pentachlorophenol to lactating dairy cattle: performance, general health, and pathologic changes. J. Dairy Sci. 64:42-51.

Knudsen, I, Verschuuren, H.G., Den Tonkelaar, E.M., Kroes, R., and Helleman, P.F.W. 1974. Short-term toxicity of pentachlorophenol in rats. Toxicology. 2:141-152.

La, D.K., Lin, P.H., and Swenberg, J.A. 1998. Analysis of DNA adducts in rats chronically exposed to pentachlorophenol. Proc. Am. Assoc. Cancer Res. 39:330. (Abstract)

Larsen, R.V., Born, G.S., Kessler, W.V., Shaw, S.M., and Van Sickel, D.C. 1975. Placenta transfer and teratology of pentachlorophenol in rats. Environ. Lett. 10:121-128.

Larsen, R.V., Kirsch, L.E., Shaw, S.M., Christian, J.E., and Born, G.S. 1972. Excretion and tissue distribution of uniformly labeled 14C-pentachlorophenol in rats. J. Pharm. Sci. 61: 2004-2006.

Lin, P-H., Waidyanatha, S., Pollack, G.M., Rappaport, S.M. 1997. Dosimetry of chlorinated quinone metabolites of pentachlorophenol in the livers of rats and mice based upon measurement of protein adducts. Toxicol. Appl. Pharmacol. 145:399-408.

Lin, P.-H., Waidyanatha, S., Pollack, G.M., Swenberg, J.A., and Rappaport, S.M. 1999. Dose-specific production of chlorinated quinone and semiquinone adducts in rodent livers following administration of pentachlorophenol. Toxicol. Sci. 47:126-133.

McConnachie, P.R. and Zahalsky, A.C. 1991. Immunological consequences of exposure to pentachlorophenol. Arch. Environ. Health. 46:249-253.

McConnell, E.E., Huff, J.E., Hejtmancik, M., Peters, A.C., and Persing, R. 1991. Toxicology and carcinogenesis studies of two grades of pentachlorophenol in B6C3F1 mice. Fund. Appl. Toxicol. 17:519-532.

McConnell, E.E., Moore, J.A., Gupta, B.N., et al. 1980. The chronic toxicity of technical and analytical pentachlorophenol in cattle. I. Clinicopathology. Toxicol. Appl. Pharmacol. 52:468-490.

Mecler, F.C. 1996. Pentachlorophenol: Fifty-Two Week Repeated Dose Chronic Oral Study of Pentachlorophenol Administered Via Capsule to Dogs. Study conducted by TSI Mason Labs for the Pentachlorophenol Task Force (Study No. 2-J31). Submitted under MRID 43982701 (Unpublished).

Montoya, G.A. and Quevedo L. 1990. The effects of pentachlorophenol (PCP) at the toad neuromuscular junction. Comp. Biochem. Physiol. 96C:193-197.

Montoya, G.A., Roa, J.; Cruz, F., Villena, F., and Pezo, P. 1988. The actions of phenol and pentachlorophenol (PCP) on axonal conduction, ganglionic synaptic transmission, and he effect of pH changes. Comp. Biochem. Physiol. 89C:377-382.

National Research Council. 1983. Risk assessment in the Federal Government: managing the process. Washington, DC: National Academy Press.

Norris, J.M. 1972. Acute Toxicological Properties of XD-8108.00L Antimicrobial. Studies conducted by Dow Chemical Co. and submitted under MRID 00101715.

NTP (National Toxicology Program). 1989. Toxicology and Carcinogenesis Studies of Two Pentachlorophenol Technical-Grade Mixtures (CAS No. 87-86-5) in B6C3F1 Mice (Feed Studies). NTP TR 349. U.S. Department of Health and Human Services, Research Triangle Park, NC.

NTP (National Toxicology Program). 1999. Toxicology and Carcinogenesis Studies of Pentachlorophenol (CAS No. 87-86-5) in F344/N Rats (Feed Studies). NTP TR 483. U.S. Department of Health and Human Services, Research Triangle Park, NC.

Osheroff, M.R., Horvath, C.,, Abrams, K.L., et al. 1994. Ninety-one Day Repeated Dose Dermal Toxicity Study of Pentachlorophenol in Sprague-Dawley Rats. Study conducted by TSI Mason Labs for the Pentachlorophenol Task Force (Study No. 2-J27). Study submitted under MRID 43182301 (Unpublished).

Parker, C.E., Jones, W.A., Matthews, H.B., McConnell, E.E., and Hass, J.R. 1980. The chronic toxicity of technical and analytical pentachlorophenol in cattle. Toxicol. Appl. Pharmacol. 55:359-369.

Ratcliffe, J.M. 1981. Lead in Man and the Environment. John Wiley and sons, New York, p. 27 (cited by Cline et al., 1989)

Rawlings, N.C., Cook, S.J., and Waldbillig, D. 1998. Effects of the pesticides carbofuran, chlorpyrifos, dimethoate, lindane, triallate, trifluralin, 2,4-D, and pentachlorophenol on the metabolic endocrine and reproductive endocrine system in ewes. J. Toxicol. Environ. Health (Part A) 54:21-36.

Reigner, B.G., Gungon, R.A., Hoag, M.K., and Tozer, T.N. 1991. Pentachlorophenol toxicokinetics after intravenous and oral administration to rat. Xenobiotica. 21:1547-1558.

Reigner, B.G., Rigod, J.F., and Tozer, T.N. 1992a. Disposition, bioavailability, and serum protein binding of pentachlorophenol in the B6C3F1 mouse. Pharm. Res. 9:1053-1057.

Reigner, B.G., Gungon, R.A., Bois, F.Y., Zeise, L., Tozer, T.N. 1992b. Pharmacokinetic concepts in assessing intake of pentachlorophenol by rats after exposure through drinking water. J. Pharm. Sci. 81:1113-1118.

Renner, G. and Mucke, W. 1986. Transformations of pentachlorophenol. Toxicol. Environ. Chem. 11:9-29.

Renner, G., Hopfer, C., Gokel, J.M., Braun, S., and Mucke, W. 1987. Subacute toxicity studies on pentachlorophenol (PCP), and isomeric tetrachlorobenzenediols tetrachlorohydroquinone (TCH), tetrachlorocatecol (TCC), and tetrachlororesorcinol (TCR). Toxicol. Environ. Chem. 15:301-312.

Roy. Soc. Chem. 1992. The Agrochemicals Handbook. Update3–December 1992, 3rd ed., Pentachlorophenol. Cambridge, England.

Rozman, T., Ballhorn, K, Rozman, C., Klassen, C., and Greim, H. 1982. Effect of cholestyramine on the disposition of pentachlorophenol in Rhesus monkeys. J. Toxicol. Environ. Health. 10:277-283.

RTECS. 1999. Registry of Toxic Effects of Chemical Substances. Online Database, maintained by the National Institute for Occupational Safety and Health.

Sai-Kato, K., Umemura, T., Takagi, A., et al. 1995. Pentachlorophenol-induced oxidative DNA damage in mouse liver and protective effect of antioxidants. Fd. Chem. Toxicol. 33:877-882.

Savolainen H. and Pekari, K. 1979. Neurochemical effects of peroral administration of technical pentachlorophenol. Res. Commun. Chem. Pathol. Pharmacol. 23:652-657.

Schmid, E., Bauchinger, M., and Dresp, J. 1982. Chromosome analyses of workers from a pentachlorophenol plant. Prog. Clin. Biol. Res. 109:471-477.

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

Schwetz, B.A., Quast, J.F., Keeler, P.A., Humiston, C.G., and Kociba, R.J. 1978. Results of two-year toxicity and reproduction studies on pentachlorophenol in rats. In Pentachlorophenol: Chemistry, Pharmacology, and Environmental Toxicology, Ed. K.R. Rao, Plenum Press, New York. pp. 301-309.

Seiler, J.P. 1991. Pentachlorophenol. Mutat. Res. 257:27-47.

Thompson, T.S. and Treble, R.G. 1996. Pentachlorophenol levels in human urine. Bull. Environ. Contam. Toxicol. 56:520-526.

Treble, R.G. and Thompson, T.S. 1996. Normal values for pentachlorophenol in urine samples collected from a general population. J. Anal. Toxicol. 20:313-317.

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

Umemura, T., Sai-Kato, K., Takagi, A., Hasegawa, R., and Kurodawa, Y. 1996. Oxidative DNA damage and cell proliferation in the livers of B6C3F1 mice exposed to pentachlorophenol in their diet. Fund. Appl. Toxicol. 30:285-289.

Umemura, T., Kai, S., Hasegawa, R., et al. 1999."Pentachlorophenol (PCP) produces liver oxidative stress and promotes but does not initiate hepatocarcinogenesis in B6C3F(1) mice. Carcinogenesis. 20:1115-1120.

U.S. EPA. 1986a. Guidelines for carcinogen risk assessment. Fed. Regist. 51(185):33992-43003.

U.S. EPA. 1986b. Guidelines for health risk assessment of chemical mixtures. Fed. Regist. 51(185):34014-34025.

U.S. EPA. 1986c. Guidelines for mutagenicity risk assessment. Fed. Regist. 51(185):34006-34012.

U.S. EPA. 1988. Recommendations for and documentation of biological values for use in risk assessment. Office of Health and Environmental Assessment, Washington, DC. EPA 600/6-87/800. NTIS PB88-179874/AS.

U.S. EPA. 1991. Guidelines for developmental toxicity risk assessment .Fed. Regist. 56(234):63798-63826.

U.S. EPA. 1994a. Interim policy for particle size and limit concentration issues in inhalation toxicity: notice of availability. Fed. Regist. 59(206):53799.

U.S. EPA. 1994b. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1994c. Peer review and peer involvement at the U.S. Environmental Protection Agency, signed by U.S. EPA Administrator, Carol M. Browner, dated June 7, 1994.

U.S. EPA. 1995a. Guidance on risk characterization. Memorandum of the U.S. EPA Administrator, Carol Browner, dated March 21, 1995.

U.S. EPA. 1995b. Proposed guidelines for neurotoxicity risk assessment. Fed. Reg. No. 191 819 60(192): 52032-52056.

U.S. EPA. 1995b. Use of the benchmark dose approach in health risk assessment. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA/630/R-94/007.

U.S. EPA. 1996a. Proposed guidelines for carcinogen risk assessment. Office of Research and Development. Fed. Regist. 61(79):17960-18011.

U.S. EPA. 1996b. Reproductive toxicity risk assessment guidelines. Fed. Reg. 61 (212):56274-56322.

U..S. EPA. 1998a. Guidelines for neurotoxicity risk assessment. Fed. Regist. 63(93):26926-26954.

U.S. EPA. 1998b. U.S. Environmental Protection Agency. Science policy council handbook: peer review. Prepared by the Office of Science Policy, Office of Research and Development, Washington, DC. EPA/100/B-98/001.

U.S. EPA. 1999a. IRIS (Integrated Risk Information System). Online Database. Office of Research and Development and National Center for Environmental Assessment, Washington, D.C. http://WWW.EPA.GOV/ngispgm3/iris/

U.S. EPA. 1999b. Pentachlorophenol. Integrated RED Science Document. Office of Prevention, Pesticides and Toxic Substances, Washington, DC.

van Ommen, B., Adang, A., Muller, F., and van Bladeren, P.J. 1986. The microsomal metabolism of pentachlorophenol and its covalent binding to protein and DNA. Chem-Biol. Interact. 60:1-11.

Villena, F., Montoya, G., Klaasen, R., Fleckenstein, and Suwalsky, M. 1992. Morphological changes on nerves and histopathological effects on liver and kidney of rats by pentachlorophenol (PCP). Comp. Biochem. Physiol. 101C:353-363.

Welsh, J.J., Collins, F.X., Black, T.N., Graham, S.L., and O'Donnell, M.W., Jr. 1987. Teratogenic potential of purified pentachlorophenol and pentachloroanisole in subchronically exposed Sprague-Dawley rats. Fd. Chem. Toxicol. 25;163-177.

Wester, R.C., Maibach, H.I., Sedik, L., et al. 1993. Percutaneous absorption of pentachlorophenol from soil. Fund. Appl. Toxicol. 20:68-71.

White, K.L., Jr. and Anderson, A.C. 1985. Suppression of mouse complement activity by contaminants of technical grade pentachlorophenol. Agents Action. 16:385-392.

Witte, I., Juhl, U., and Butte, W. 1985. DNA-damaging properties and cytotoxicity in human fibroblasts of tetrachlorohydroquinone, a pentachlorophenol metabolite. Mutat. Res. 145:71-75.

Xu, J. 1996. In vivo test for chemical induction of micronucleated polychromatic erythrocytes in mouse bone marrow cells. Study conducted by SITEK Research Laboratories for the Pentachlorophenol Task Force. Submitted under MRID 43911301 (Unpublished).

Yuan, J.H. et al. 1994. Toxicokinetics of pentachlorophenol in the F344 rat. Gavage and dosed feed studies. Xenobiotica 24:553-560.

Ziemsen, G., Angerer, J., and Lehnert, B. 1987. Sister chromatid exchange and chromosomal breakage in pentachlorophenol (PCP) exposed workers. Int. Arch. Occup. Environ. Health. 59:413-417.