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Pentachlorophenol

Chemistry, Pharmacology, and Environmental Toxicology

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Pref

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Contents

I. Usage Patterns and Environmental Fate of Pentachlorophenol

Patterns of Pentachlorophenol Usage in Canada — An Overview
R.A.W. Hoos 3

Patterns of Pentachlorophenol Usage in the United States of America — An Overview
D.P. Cirelli 13

Photolysis of Pentachlorophenol in Water
A.S. Wong and D.G. Crosby 19

Degradation of Pentachlorophenol in Soil, and by Soil Microorganisms
D.D. Kaufman 27

The Fate of Pentachlorophenol in an Aquatic Ecosystem
R.H. Pierce, Jr., and D.M. Victor 41

The Environmental Fate of ^{14}C-Pentachlorophenol in Laboratory Model Ecosystems
P.-Y. Lu, R.L. Metcalf and L.K. Cole 53

II. Pharmacology and Toxicology of Pentachlorophenol

A. Metabolism

Microbial Metabolism of Pentachlorophenol
E.A. Reiner, J.P. Chu and E.J. Kirsch 67

Fate of Pentachlorophenol in the Blue Crab, *Callinectes sapidus*
A.K. Bose and H. Fujiwara 83

Metabolism of Pentachlorophenol in Fishes
K. Kobayashi 89

Studies on the Uptake, Disposition and Metabolism of Pentachlorophenol and Pentachloroanisole in Rainbow Trout (*Salmo gairdneri*)
J.J. Lech, A.H. Glickman and C.N. Statham 107

Dechlorination of Pentachlorophenol *in vivo* and *in vitro*
U.G. Ahlborg 115

Pentachlorophenol in Different Species of Vertebrates after Administration of Hexachlorobenzene and Pentachlorobenzene
G. Koss and W. Koransky 131

B. Comparative Toxicology and Pharmacology

Toxicity of Pentachlorophenol and Related Compounds to Early Life Stages of Selected Estuarine Animals
P.W. Borthwick and S.C. Schimmel 141

Effects of Sodium Pentachlorophenate on Several Estuarine Animals: Toxicity, Uptake and Depuration
S.C. Schimmel, J.M. Patrick, Jr., and L.F. Faas 147

Effects of Dowicide® G-ST on Development of Experimental Estuarine Macrobenthic Communities
M.E. Tagatz, J.M. Ivey and M. Tobia 157

Effects of Pentachlorophenol on the Meiobenthic Nematodes in an Experimental System
F.R. Cantelmo and K.R. Rao 165

Effect of Sodium Pentachlorophenate on the Feeding Activity of the Lugworm, *Arenicola cristata* Stimpson
N.I. Rubinstein 175

Toxicity of Sodium Pentachlorophenate to the Grass Shrimp, *Palaemonetes pugio*, in Relation to the Molt Cycle
P.J. Conklin and K.R. Rao 181

Inhibition of Limb Regeneration in the Grass Shrimp, *Palaemonetes pugio*, by Sodium Pentachlorophenate
K.R. Rao, P.J. Conklin and A.C. Brannon 193

Effect of Sodium Pentachlorophenate on Exoskeletal Calcium in the Grass Shrimp, *Palaemonetes pugio*
A.C. Brannon and P.J. Conklin 205

..... 89

ro-
rdneri)
..... 107

..... 115

zene
..... 131

y Life
..... 141

nimals:
..... 147

..... 157

in an
..... 165

y of
..... 175

..... 181

nonetes
..... 193

n in the
..... 205

Ultrastructural Changes Induced by Sodium Pentachlorophenate in the Grass Shrimp, *Palaemonetes pugio,* in Relation to the Molt Cycle
D.G. Doughtie and K.R. Rao 213

Effects of Sodium Pentachlorophenate and 2,4-Dinitrophenol on Respiration in Crustaceans
A.C. Cantelmo, P.J. Conklin, F.R. Fox and K.R. Rao 251

Effects of Sodium Pentachlorophenate and 2,4-Dinitrophenol on Hepatopancreatic Enzymes in the Blue Crab, *Callinectes sapidus*
F.R. Fox and K.R. Rao 265

Effect of Pentachlorophenol on the ATPases in Rat Tissues
D. Desaiah 277

Effects of Sodium Pentachlorophenate on Survival and Energy Metabolism of Embryonic and Larval Steelhead Trout
G.A. Chapman and D.L. Shumway 285

Results of Two-Year Toxicity and Reproduction Studies on Pentachlorophenol in Rats
B.A. Schwetz, J.F. Quast, P.A. Keeler, C.G. Humiston, and R.J. Kociba 301

III. Chlorophenols and Their Contaminants: Chemistry, Toxicology, Environmental Residues and Environmental Impact

Impurities in Commercial Products Related to Pentachlorophenol
C.-A. Nilsson, Å. Norström, K. Andersson and C. Rappe 313

Genetic Activity of Chlorophenols and Chlorophenol Impurities
R. Fahrig, C.-A. Nilsson and C. Rappe 325

Negative Chemical Ionization Mass Spectrometry: Applications in Environmental Analytical Chemistry
R.C. Dougherty and E.A. Hett 339

Human Exposure to Pentachlorophenol
R.C. Dougherty 351

Survey of Pesticide Residues and Their Metabolites in Urine from the General Population
F.W. Kutz, R.S. Murphy and S.C. Strassman 363

Health Implications of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure in Primates
J.R. Allen and J.P. van Miller 371

Renal Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
J.B. Hook, K.M. McCormack and W.M. Kluwe 381

Environmental Impact of Pentachlorophenol and Its Products—
A Round Table Discussion
P.J. Conklin and F.R. Fox (editors) 389

Index 395

I

Usage

Fate

Results of Two-Year Toxicity and Reproduction Studies on Pentachlorophenol in Rats

B.A. SCHWETZ, J.F. QUAST, P.A. KEELER, C.G. HUMISTON, and R.J. KOCIBA

Abstract—Male and female Sprague-Dawley rats were maintained on diets containing pentachlorophenol (PCP), characterized by a low content of nonphenolic impurities, for up to 24 months. Pentachlorophenol (PCP) was not found to be carcinogenic when administered to rats in their diet on a chronic basis at dose levels sufficiently high to cause mild signs of toxicity (1, 3, 10, or 30 mg/kg/day). Effects at the high dose level included decreased body weight gain (females), increased serum glutamic pyruvic transaminase activity (males and females), and increased urine specific gravity (females). An accumulation of pigment was observed in the livers and kidneys of females at 30 and 10 mg PCP/kg/day and males at 30 mg/kg/day. Ingestion of 3 mg PCP/kg/day or less by females and 10 mg/kg/day or less by males was not associated with significant toxicologic effects. To evaluate the effects on reproduction, rats were fed 3 or 30 mg PCP/kg/day for 62 days prior to mating, during 15 days of mating, and subsequently throughout gestation and lactation. A reduction in the mean body weight was observed among the adult rats at the highest dose level. Except for a significant decrease in neonatal survival and growth among litters of females ingesting 30 mg PCP/kg/day, measures of reproductive capacity were unaffected at both dose levels of pentachlorophenol. Ingestion of 3 mg PCP/kg/day had no effect on reproduction or neonatal growth, survival, or development.

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Introduction

Pentachlorophenol is a registered antimicrobial agent used widely for the preservation of wood. The acute oral LD_{50} of the pentachlorophenol (PCP) used in these studies was approximately 150 mg/kg in rats (unpublished data; Dow Chemical Company, Midland, Michigan). In subchronic toxicity studies conducted on this same pentachlorophenol, no gross pathological or histopathological changes were noted in rats maintained for 90 days on diets providing 3, 10, or 30 mg PCP/kg/day. Increased kidney weights were observed at 30 mg PCP/kg/day and increased liver weights were observed at 10 and 30 mg PCP/kg/day (Johnson *et al.*, 1973). PCP has been found to be toxic to the developing embryo and fetus of rats but was not teratogenic (Schwetz *et al.*, 1974). The purpose of the studies reported herein was to determine the potential of PCP to interfere with the reproductive capacity of rats as well as to evaluate the toxic effects, including carcinogenicity, that might be associated with the chronic ingestion of pentachlorophenol.

Experimental Procedures

Pentachlorophenol was mixed in the diet of the animals and was provided free choice at all times. To evaluate the effects on reproduction, Sprague-Dawley rats (Spartan substrain, Spartan Research Animals, Haslett, Michigan) were fed 0, 3, or 30 mg PCP/kg/day. Each group consisted of 10 males and 20 females. The rats were fed PCP for 62 days prior to mating as well as during 15 days of mating. The males were then separated from the females during gestation and lactation but all rats continued on the test diets. At the time of weaning, all adult and weanling rats were necropsied. The skeletons of the weanlings were prepared and stained for examination.

In the chronic toxicity study, rats were fed 0, 1, 3, 10, and 30 mg PCP/kg/day. Female rats were maintained on the test diets for 24 months but the male rats were terminated after 22 months because of high mortality among the control and the experimental rats. At each dose level, 25 rats of each sex were utilized. An additional two rats of each sex were included at each dose level to provide tissues for chemical analysis. Hematology and urinalysis data were collected at the end of 12 months. Observations at the termination of the study included hematology, clinical chemistry, urinalysis as well as measurement of organ weights, and a gross and microscopic examination of tissues. Observations during the study included measurements of body weights and food consumption at monthly intervals as well as observations for overt alterations in behavior.

The results of chemical analysis of the sample of PCP used in these studies are given in Table 1. This sample was representative of commercially available pentachlorophenol identified as DOWICIDE® EC-7 antimicrobial (Dow Chemical Company). This is a purified grade of pentachlorophenol characterized by a lower content of nonphenolic contaminants than is found in technical grade pentachlorophenol. The test diets were prepared by mixing PCP dissolved in anisole with ground Purina laboratory chow to make a 1% premix. The test diets were then

TABLE 1. Analytical Description of the Pentachlorophenol (PCP) Sample Used in these Studies

Phenolics	*Percent*[a]
Pentachlorophenol	90.4 ± 1.0
Tetrachlorophenol	10.4 ± 0.2
Trichlorophenol	<0.1[c]
Nonphenolics	*ppm*[b]
Dibenzo-*p*-dioxins	
2,3,7,8-tetrachloro-	<0.05[c]
hexachloro-	1.0 ± 0.1
heptachloro-	6.5 ± 1.0
octachloro-	15.0 ± 3.0
Dibenzofurans	
Hexachloro-	3.4 ± 0.4
heptachloro-	1.8 ± 0.3
octachloro-	<1[c]
Hexachlorobenzene	400 ± 40

[a]Average of 4 analyses by gas-liquid chromatography.

[b]Average of 4 analyses by gas chromatography-mass spectrometry.

[c]Concentration in the sample was less than the indicated level of sensitivity for the analytical method.

prepared weekly from the 1% premix. The concentrations of PCP in the diet were adjusted on a monthly basis to maintain the designated dose levels on a mg/kg body weight/day basis according to the food consumption and body weights of the rats. Groups of control rats of each sex received the laboratory chow to which anisole without PCP was added.

In both studies, statistical evaluation of all continuous data consisted of an analysis of variance together with Dunnett's test for comparison of means of experimental and control groups (Steel and Torrie, 1960). Incidence data were analyzed by the Fisher exact probability test (Siegel, 1956). P values less than 0.05 were considered significant.

TABLE 2. Body Weights of Adults and Survival of Neonates of Rats Fed Pentachlorophenol (PCP) in a Reproduction Study

	Dose level (mg PCP/kg/day)		
	0	3	30
	Body weight, g, Mean ± S.D.		
MALES			
Number of rats	10	10	10
Day 0	220 ± 7	225 ± 11	213 ± 8
29	405 ± 28	394 ± 32	374 ± 26
62	501 ± 46	480 ± 44	463 ± 36
169	619 ± 62	590 ± 67	570 ± 42
FEMALES			
Number of pregnant rats	16	17	19
Day 0	187 ± 9	184 ± 11	187 ± 10
29	259 ± 11	259 ± 15	256 ± 16
62	298 ± 13	293 ± 18	287 ± 16
21 postpartum (~ 110 days)	344 ± 21	334 ± 21	308 ± 25[a]
	Reproduction indices (percent)		
Pregnancy	80 (16/20)	85 (17/20)	95 (19/20)
Liveborn pups	97 (174/180)	96 (195/204)	91 (188/206)[b]
24-Hour survival	98 (171/174)	98 (191/195)	96 (180/188)
7-Day survival	96 (167/174)	95 (186/195)	81 (153/188)[b]
14-Day survival	95 (166/174)	94 (183/195)	79 (148/188)[b]
21-Day survival	95 (165/174)	94 (183/195)	76 (142/188)[b]

[a]Significantly different from control by Dunnett's test, $p < 0.05$.
[b]Significantly different from control by the Fisher Exact Probability test, $p < 0.05$.

Effects of PCP on Reproduction in Rats

Toward the end of the study, the mean body weight of the female rats at the high dose level (30 mg/kg/day) was significantly less than that of control rats (Table 2). Daily observation of the male and female adult rats and their litters revealed no treatment-related effect on demeanor or physical appearance. Ingestion of 3 mg PCP/kg/day had no effect on the percent of pregnancy among females or on

TABLE 3. Litter Size and Weight of Rats Fed Pentachlorophenol (PCP) in a Reproduction Study

	Dose level (mg PCP/kg/day)		
	0	3	30
	Litter Size, Mean ± S.D.		
Birth	11.6 ± 3.0	11.5 ± 3.2	9.9 ± 2.1
Day 1	11.4 ± 3.1	11.2 ± 3.3	9.5 ± 1.8
Day 7	11.1 ± 2.9	10.9 ± 3.4	8.1 ± 2.9[a]
Day 14	11.1 ± 2.8	10.8 ± 3.3	7.8 ± 2.8[a]
Day 21	11.0 ± 2.8	10.8 ± 3.3	7.7 ± 2.7[a]
	Neonatal body weight, g, Mean ± S.D.		
Day 1	7.1 ± 0.6	7.0 ± 0.4	6.1 ± 0.7[a]
Day 7	14.1 ± 2.3	13.8 ± 1.4	11.2 ± 2.0[a]
Day 14	26.3 ± 4.1	25.5 ± 3.4	19.9 ± 4.1[a]
Day 21, male	41 ± 9	38 ± 7	30 ± 5[a]
Day 21, female	40 ± 8	38 ± 7	30 ± 5[a]

[a]Significantly different from control by Dunnett's test, $p < 0.05$.

the survival indices of neonates from the time of birth to the end of lactation, 21 days of age. Ingestion of 30 mg PCP/kg/day had no effect on the percent of pregnancy but did cause a significant decrease in the percent of pups that were born alive as well as significantly decreased survival to days 7, 14, and 21 of lactation. Every male in each treatment group was fertile, that is, at least one of the females with each male became pregnant.

The average litter size throughout lactation was not affected by the ingestion of 3 mg PCP/kg/day in the diet (Table 3). The average litter size among rats receiving 30 mg/kg/day was significantly lower than among controls on days 7, 14, and 21 of lactation. The mean neonatal body weight was significantly less than the control value at the high dose level, 30 mg/kg/day, but not at the low dose level, 3 mg/kg/day.

Necropsy of the weanling rats at the time of sacrifice revealed no changes that were visible externally or upon visceral examination that were related to ingestion of PCP. There was a significantly increased number of litters at the high dose level of PCP which showed variations in the development of skeletal structures — lumbar spurs and vertebra with unfused centra. These skeletal variants probably reflect perinatal toxicity rather than an effect on the neonate alone.

As in the previous study on rat embryos (Schwetz *et al.*, 1974) the results of this reproduction study indicate that developing or neonatal rats are more sensitive to the toxicologic effects of PCP than are adult rats. This is further substantiated by an age-related difference in the LD_{50} of PCP in rats — being about 150 mg/kg in adult rats and about 65 mg/kg in 3-4 day old rats (unpublished data, Dow Chemical Company, Midland, Michigan).

The Two-Year Toxicity Study of PCP in Rats

Ingestion of PCP did not affect the demeanor of animals, the mean food consumption or their survival. Hematology measures including the hemoglobin levels, packed cell volume, total erythrocyte counts, and total and differential leukocyte counts were not affected by ingestion of PCP. The mean body weight of the females at the high dose level was significantly less than that of control rats throughout much of the study. The mean of the monthly body weights of the rats during the last twelve months of the study was 428 grams for the female control rats compared to 378 grams for the females at the high dose level, 30 mg/kg/day. There was a significant increase in the serum glutamic pyruvic transaminase activity among the male and female rats at the high dose level at the termination of the study (males: control - 38 ± 16, high dose - 63 ± 13; females: control - 36 ± 8, high dose - 48 ± 15). There was an increase in the specific gravity of urine among the female rats at the high dose level after one year but not at the termination of the study. Among the rats killed at the termination of the study, the weights of the brain, heart, liver, kidneys, and testes of the rats in the experimental groups were comparable to those of the controls.

The incidence of non-tumorous pathologic changes in rats fed PCP are

TABLE 4. Non-tumorous Pathologic Changes in Rats Fed Pentachlorophenol (PCP) for 22 Months (Males) and 24 Months (Females)

	Males					Females				
Dose: mg PCP/kg/day	0	1	3	10	30	0	1	3	10	30
Number of rats examined	27	26	27	27	27	27	27	27	27	27
	Number of rats affected									
GROSS OBSERVATIONS										
Liver — dark, discolored	0	0	0	0	0	0	0	0	2	14
Kidney — dark, discolored	0	0	0	0	0	0	1	0	3	12
MICROSCOPIC OBSERVATIONS										
Liver — brown granular pigment within hepatocytes and reticulo-endothelial cells surrounding the central vein	0	0	0	0	1	0	0	0	8	16
Kidney — brown granular pigment within the tubular epithelial cells	0	0	0	0	0	0	0	0	7	19

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Females		
3	10	30
27	27	27
d		
0	2	14
0	3	12
0	8	16
0	7	19

summarized in Table 4. An accumulation of pigment was observed in the liver and kidneys of the experimental rats. This was grossly recognizable among the female but not male rats as a dark coloration of these organs. Microscopic examination of hematoxylin and eosin stained sections revealed the presence of brown granular pigmented material in these organs - in the liver, primarily in the hepatocytes surrounding the central veins; in the kidneys, primarily in epithelial cells of the proximal convoluted tubules. The material did not stain with any of the following stains: oil red-O, nile blue sulfate, acid fast, Gomori's stain for iron, McManus' Periodic Acid Schiff, Hall's method for bilirubin and Stein's method for bile pigments. Approximately half of the females at the high dose level and a few at 10 mg/kg/day showed the dark colored liver and kidney. This was not observed macroscopically in any of the male rats. Microscopic examination of sections of the liver and kidney revealed the brown pigment in a larger number of the female rats at 10 and 30 mg/kg and in the liver of a single male rat at the high dose level. No other non-tumorous pathologic changes were observed which were related to ingestion of pentachlorophenol.

The results of examinations of tumorous formations in the rats which died spontaneously or were necropsied in a moribund state or at the terminal necropsy are summarized in Table 5. As expected in this strain of rat, the highest incidence of tumors among male rats involved endocrine organs such as pituitary, adrenal, and thyroid glands, testes and pancreas. The frequently occurring tumors among female rats were located in the mammary gland region. The pituitary, thyroid glands, and uterus were the other organs with the most frequently occurring tumorous changes.

TABLE 5. Incidence of Primary Tumors (Based on Histopathological Diagnosis) in Rats Fed Pentachlorophenol (PCP) for 22 Months (Males) and 24 Months (Females)

Dose: mg PCP/kg/day	Males					Females				
	0	1	3	10	30	0	1	3	10	30
Number of rats examined	27	26	27	27	27	27	27	27	27	27
Number of rats with tumors	11	13	13	12	11	27	26	25	25	25
Number of tumors	17	14	17	15	16	62	67	42	63	63
Number of tumors/rats with tumors	1.6	1.1	1.3	1.3	1.4	2.3	2.6	1.7	2.5	2.5
Number of morphologic malignant tumors	1	3	2	1	0	2	7	2	3	2

The highest incidence of tumors among the experimental groups was observed at the lowest dose level of PCP (1 mg/kg/day); however, no tumors were observed in any group of experimental male or female rats at an incidence significantly different from that in the control rats. Rats ingesting diets containing PCP were not submitted for necropsy examination earlier than control rats.

The findings in this chronic toxicity study are consistent with those reported by other workers. Goldstein *et al.*, (1976) have reported on the effects associated with the ingestion of either pure or technical grade PCP in the diet for 8 months by female Sherman rats. At the time of sacrifice, the livers of some of the rats given PCP in the diet were very dark in color. At least some but not all of the pigment appeared to be due to porphyrins since some of the dark livers contained levels of porphyrins no higher than that found in livers of some control rats. Goldstein *et al.*, (1976) concluded that the presence of chlorodioxins in technical grade pentachlorophenol was almost totally responsible for the hepatic effects of PCP. Kimbrough and Linder (1975) observed a prominent brown pigment in the macrophages and Kupffer cells in the livers of rats fed technical grade PCP for three months. The livers of rats fed technical PCP showed more ultrastructural changes than the livers of rats fed pure pentachlorophenol. Previous studies in our own laboratory have also associated toxicological effects in animals with the nonphenolic contaminants in pentachlorophenol (Johnson *et al.*, 1973).

Conclusions

In summary, the following conclusions have been drawn from these studies. In the single generation reproduction study in which PCP was given in the diet at dose levels of 3 and 30 mg/kg/day, there was no significant effect on the fertility of rats but there was a significant decrease in neonatal survival and growth at the high dose level, 30 mg/kg/day. The no-adverse effect dose level of PCP in the reproduction study was 3 mg/kg/day. In the chronic toxicity study in which PCP was given in the diet at dose levels ranging from 1-30 mg/kg/day, there was no carcinogenicity when rats were given dose levels of PCP which were significantly high to cause signs of mild toxicity. The no-adverse-effect dose level of pentachlorophenol in the chronic toxicity study was 10 mg/kg/day among the males and 3 mg/kg/day among the females.

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