

A Morbidity Study of Former Pentachlorophenol-production Workers

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Pentachlorophenol (PCP) is a pesticide that was once widely used for wood preservation. Commercial PCP contained impurities including higher chlorinated dibenzo-*p*-dioxins (CDDs) and chlorinated dibenzofurans (CDFs). We investigated the effects of occupational exposure to PCP and its CDD and CDF contaminants on the skin, liver, porphyrin metabolism, and central and peripheral nervous systems. In 1986 we conducted a medical survey of 366 workers who had been engaged in the production of PCP at a single plant between 1938 and 1978. The referent group consisted of 303 workers from the same plant who were not exposed to these or related compounds. Exposure was determined from computerized personnel records. The medical survey included an administered questionnaire, medical record review, physical examination by dermatologists, internists, and neurologists, and analysis of 24-hr urine for quantitative porphyrins among other tests. In this paper we present the results of analyses of the general health, chloracne, and porphyrin metabolism end points. The general health status of PCP workers was similar to unexposed workers, but 17.8% of PCP workers had evidence of current or past chloracne. PCP workers with chloracne had significantly higher mean urinary excretion of coproporphyrins (117.0 vs. 90.6 µg/24 hr) than unexposed workers after controlling for potential confounders. Workers with chloracne who had worked with both PCP and polychlorinated biphenyls had significantly higher mean urinary excretions of hepta-, penta-, and coproporphyrins than unexposed workers. We conclude that occupational exposure to PCP is associated with chloracne and biochemical abnormalities which may persist years after exposure. **Key words:** chlorinated dibenzo-*p*-dioxins, chloracne, dibenzofurans, occupational exposures, pentachlorophenol, porphyrins. *Environ Health Perspect* 106:401–408 (1998). [Online 5 June 1998] <http://ehpnet1.niehs.nih.gov/docs/1998/106p401-408/hryhorczuk/abstract.html>

Pentachlorophenol (PCP) is a pesticide that was once widely used for wood preservation. Major uses included commercial wood treatment in the lumber industry and slime control in the pulp and paper industry. The sodium salt of PCP (NaPCP) was also used in wood preservation as a sap stain control agent. Minor uses have included various nonindustrial applications as a herbicide, antimicrobial, and disinfectant.

From 1984 to 1988, the U.S. EPA issued a series of strict regulatory controls over the manufacture, use, and disposal of PCP (1). Commercial pentachlorophenol had contained a variety of impurities including higher chlorinated dibenzo-*p*-dioxins (CDDs) and chlorinated dibenzofurans (CDFs). One of these compounds, hexachlorodibenzo-*p*-dioxin (HxCDD), was found to be a carcinogen and reproductive toxin in laboratory animals (2). Production of PCP in the United States ceased in 1992.

Acute poisoning by PCP in exposed workers produces a characteristic syndrome of hyperpyrexia caused by uncoupling of oxidative phosphorylation (3). The chronic effects of exposure to PCP have been studied in PCP production workers (4–10), PCP formulators (11), wood treatment workers

(12,13), sprayers (11), and sawmill workers (14–16). Several studies have demonstrated that exposure to commercial PCP can produce chloracne (4,8–10,17,18). Some studies have observed irritant effects on the eyes and upper respiratory tract (4,16), peripheral sensory neuropathy (5,10), reversible renal impairment (12), decreased bilirubin (8,11), increased serum glutamate dehydrogenase (GLDH) (6), increased urinary excretion of porphyrins (10), decreased hematocrit and white blood cell count (15), and increased frequency of chromosome alterations in lymphocytes (7).

In 1986, Northwestern University conducted a comprehensive morbidity study of past and present workers at a chemical plant in southwestern Illinois who had been engaged in the production of PCP as well as lower chlorinated phenols and esters of chlorophenoxy acids. This plant was also a major producer of polychlorinated biphenyls (PCBs). The purpose of this study was to determine if workers who had been engaged in the production of PCP, chlorinated phenols, and chlorophenoxy acid esters suffered any long-term health effects as a result of their past exposure to these compounds and their CDD and

CDF contaminants. The primary hypotheses of this study were that exposures to these compounds may be associated with chloracne, liver dysfunction, disorders of porphyrin metabolism, neurobehavioral disturbances, disorders of lipid metabolism, and peripheral neuropathy.

This paper presents the results of the analyses of general health status, chloracne, and porphyrin metabolism for the group of workers who had ever been engaged in the production of PCP ("ever PCP"). We also present the results of analyses for the subgroup of these workers who produced PCP but did not produce lower chlorinated phenols or esters of chlorophenoxy acids ("only PCP"), as well as the respective subgroups of workers with chloracne ("ever PCP, chloracne" and "only PCP, chloracne"). The results of analyses for the other exposure subgroups and effects on other organ systems will be presented in subsequent papers.

Materials and Methods

Plant history and process description. The chemical plant whose employees were examined in this study produced pentachlorophenol from 1938 to 1978. In 1986, at the time of the survey, the plant used more than 75 raw materials to produce 22 different intermediate chemical products. The major raw materials included chlorine, phosphorus, and benzene. Major products included lower

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chlorinated benzenes, nitrochlorobenzene, *o*-nitrophenol, nitroaniline, PCl_3 , P_2S_5 , chlorine bleaches, and detergent materials. The plant had produced lower chlorinated phenols from 1931 to 1983, polychlorinated biphenyls from 1936 to 1977, and esterified 2,4,5-trichlorophenoxyacetic acid (brought in from another facility) from 1960 to 1971.

Pentachlorophenol was produced by direct chlorination of phenol, *o*-chlorophenol, *p*-chlorophenol, 2,4-dichlorophenol, and/or 2,4,6-trichlorophenol in the presence of an aluminum catalyst. The major changes in production between 1938 and 1978 were related to the form of the finished product. The physical forms of PCP included flakes from 1938 to 1963, a 40% solution from 1938 to 1943, prills between 1963 and 1978, and blocks between 1972 and 1978. From 1938 to 1975, molten PCP was reacted with caustic soda to produce NaPCP. The NaPCP was produced as briquettes from 1938 to 1956 and as pellets from 1954 to 1975.

The company began measuring levels of CDDs in PCP produced at this plant in 1972. That year the total CDD content in a batch of PCP was determined by the company to be 2,500 ppm. The concentrations of CDDs and CDFs in samples of PCP produced at the study plant are given in Table 1.

Description of study populations. The exposed worker populations in this study were defined as all workers who were alive at the time of sample selection and who met one of the following definitions of exposure: 1) hourly production workers who had been engaged in the production of PCP for 3 or more days between 1938 and 1978; 2) hourly production workers who had been engaged in the production of mono- and dichlorophenols between 1931 and 1983; 3) hourly production workers who had been engaged in the esterification of 2,4,5-T and 2,4-D between 1960 and 1971. Employment in these departments was ascertained from a computerized plant personnel records database maintained by the company. PCP and lower chlorinated phenols (*o*-chlorophenol, *p*-chlorophenol, and 2,4-dichlorophenol) were produced in physically adjacent departments from 1938 to 1978, creating opportunities for cross-exposure. From 1969 to 1978 these departments were merged into a single administrative unit, and separation of exposure (PCP vs. lower chlorinated phenols) was based on job titles rather than on departmental classifications.

An internal audit of the computerized personnel records database revealed an overall error rate of 2.3% on occupational exposure variables. An external audit revealed that approximately 9% of exposed workers

could be missed by relying on this database alone. The plant medical department had maintained a registry of workers who were undergoing medical surveillance for chloracne beginning in 1970. Twenty-nine production workers on this chloracne registry who met the definition of exposure were included in the exposed group. Maintenance and other workers who were noted to have chloracne on these plant medical records, with the exception of workers who were exclusively engaged in the production of PCBs or chlorinated benzenes, were also included as a separate exposure subgroup. These workers were included as a separate subgroup because, before 1983, personnel records did not specify the departmental assignments of maintenance workers.

The unexposed comparison population was defined as workers who had ever been employed at this same plant on or after 1931, who were alive at the time of sample selection, and who met the following definitions of no exposure: 1) had not worked in any of the exposed departments; 2) had not worked in maintenance; 3) had not worked in other departments with potential exposure to CDDs and CDFs (PCBs, chlorinated benzenes, derivatives of 2,4-dichlorophenol, or the analytical laboratory); 4) did not work in departments immediately adjacent to chlorophenol production. A sample of these unexposed workers was selected by taking all active, retired, and transferred workers together with a random sample of

terminated workers frequency-matched to the exposed population on age and length of employment.

We located 647 of the 763 eligible exposed workers (85%), and 473 of those located participated in the medical examination (73%). We located 445 of the 559 eligible unexposed workers (80%), and 303 of those located participated in the medical examination (68%).

This paper presents the results of the analyses of general health status, chloracne, and porphyrin metabolism for the group of workers who had been engaged in the production of pentachlorophenol. Of the 473 exposed workers in this study, 366 (77%) were engaged in the production of pentachlorophenol. Seventy-three (19.9%) of these workers had been exposed between 3 and 29 days, 76 (20.8%) between 30 and 89 days, 65 (17.8%) between 90 and 179 days, 73 (19.9%) between 180 and 364 days, and 79 (21.6%) for 365 or more days. Sixty-five (17.8%) of these workers had either a history of a doctor's diagnosis of chloracne, plant medical record evidence of chloracne, or physical examination evidence of chloracne at the time of dermatologic exam. Eighty-four (23.0%) of the PCP workers had also worked in the production of lower chlorinated phenols; 26 (7.1%) had worked in the production of esters of 2,4-D and 2,4,5-T. In addition, 57 (15.6%) of the PCP workers had worked in the production of polychlorinated biphenyls, and

Table 1. Impurities in technical pentachlorophenol

Component	NTP ^a (%)	Reference	O'Malley et al. (9) ^b	
			Mean	Range
Phenols				
Trichloro	0.01%	NS	NS	
Tetrachloro	3.8%	3.0%	NS	
Dibenzo- <i>p</i> -dioxins				
Tetrachloro	—	<0.1 ppm	NS	
Pentachloro	NS	<0.1 ppm	NS	
Hexachloro	10.1 ppm	8 ppm	29 ppm	1–260 ppm
Heptachloro	296 ppm	520 ppm	217 ppm	23–540 ppm
Octachloro	1,386 ppm	1,380 ppm	721 ppm	15–1,880 ppm
Dibenzofurans				
Tetrachloro	NS	≤4 ppm	NS	
Pentachloro	1.4 ppm	40 ppm	NS	
Hexachloro	9.9 ppm	90 ppm	324 ppm	190–470 ppm
Heptachloro	88 ppm	400 ppm	336 ppm	80–670 ppm
Octachloro	43 ppm	260 ppm	220 ppm	130–430 ppm
Hydroxydiphenyl ethers				
Heptachloro	0.11%	NS	NS	NS
Octachloro	1.91%	NS	NS	NS
Nonachloro	3.56%	NS	NS	NS
Hydroxydibenzofurans				
Hexachloro	0.16%	NS	NS	NS
Heptachloro	0.47%	NS	NS	NS
Hexachlorobenzene	50 ppm	NS	NS	NS

NS, not specified.

^aNTP sample: industry composite of technical-grade pentachlorophenol prepared from material supplied by three U.S. manufacturers.

^bFor dibenzo-*p*-dioxins $n = 25$; for dibenzofurans, $n = 8$.

114 (31.1%) of the PCP workers and 40 (13.2%) of the unexposed workers had also worked in the chloralkali plant with potential exposure to elemental mercury.

Measurement of health outcomes. The study protocol was reviewed and approved by the Institutional Review Boards of the participating institutions. Participants provided informed consent before examination, and the investigators assured the confidentiality of individual test results.

The health status of participants was measured through a comprehensive medical examination that included a complete medical and reproductive history, physical examinations, electrocardiogram, spirometry, chest X ray, quantitative sensory testing, neurobehavioral evaluation, and blood, urine, and saliva tests. Reported conditions were verified through a review of hospital, plant medical, and vital records. Obtainability rates for these records were 95% for birth records of offspring, 57% for medical records after date of first employment, and 50% for requested plant medical records. The majority of missing plant medical records were older, inactive files that had been archived and lost. All available records were reviewed and coded by trained record review technicians. All on-site data collection personnel, other than the medical interviewer administering the occupational and environmental history questionnaire, were blinded to the participants' exposure status. The interviewer who administered this questionnaire was not allowed to share any work history information with other examiners. Editing, reduction, and entry of all health outcome data were also done with the research staff blinded to the participants' exposure status.

The medical history questionnaire was developed with the assistance of the University of Illinois Survey Research Laboratory and was administered in person by trained interviewers. Portions of the questionnaire were adapted from previously used survey instruments, including the National Center for Health Statistics' Health Interview Survey (19), the NIOSH Dioxin Morbidity Study Questionnaire (20), British Medical Research Council's Respiratory Questionnaire (21), the Multiple Risk Factor Intervention Trial Questionnaire (22), and the Swedish Questionnaire 16 (23). Each participant received a physical examination by a trained board-certified internist, dermatologist, and neurologist.

The general health status of participants was determined by both self-reporting and internists' physical examination. Participants were asked to rate their health as excellent, good, fair, or poor compared to most people their own age. They were also asked to recall the number of days over the previous 12

months that they had been hospitalized, missed work or usual activities due to illness, or visited a doctor's office or clinic. Self-rating of health was treated as a categorical variable (excellent or good vs. fair or poor) in logistic regressions. Other self-reported general health variables were treated as dichotomous or continuous. Internists rated the general appearance of participants as normal, acutely ill, or chronically ill.

Medical history of chloracne was defined as a positive response to the question, "Did a doctor ever tell you that you had chloracne, which is a type of acne caused by chemicals?" on the medical history questionnaire. Participants were also asked to respond to the questions, "Has there ever been a time when your skin seemed unusually dark for you, even though you hadn't had excessive sun exposure?" and "Have you ever been bothered by excess hair growth?" Plant medical record chloracne was coded as positive if the O'Malley score (9) was 1–3 and negative if the score was 4–6.

Dermatologists were asked to rate to what extent the participant's examination was consistent with the diagnosis of chloracne on a five-point scale (1 = very unlikely to 5 = highly likely). Participants with scores of 4 or 5 were coded as positive for chloracne on dermatologic examination. Dermatologists were also asked to determine if participants had hyperpigmentation or hypertrichosis.

The history of porphyria was determined by asking participants, "Have you ever been told by a doctor that you had porphyria?" The history of symptoms suggestive of porphyria was determined by asking participants, "Have you ever had a medical condition in which you had unusual blistering of sun-exposed skin combined with dark, reddish urine?" Dermatologists were asked to rate on a five-point scale (1 = very unlikely to 5 = highly likely) the extent to which the participant's dermatologic examination was consistent with a diagnosis of porphyria cutanea tarda.

Each participant was asked to begin a 24-hr urine collection for quantitative porphyrins after providing a spot morning urine on the day of the examination. These samples were submitted to the Mayo Clinic for analysis. Urinary porphobilinogen was measured spectrophotometrically after complexation with Erlich's reagent by a modification of the method of Schwartz et al. (24). Quantitative porphyrins were analyzed using high performance liquid chromatography (25).

Data were analyzed for completeness and accuracy at several stages in the data collection and analysis. On-site quality control

clerks, as well as Survey Research Laboratory supervisors, provided continuous monitoring of the completeness and consistency of the data collection. Participants were reinterviewed where discrepancies were found. Logical consistency constraints were added to data input screens to minimize data entry error. Each week a 10% random sample of entered data was checked against the original data. If the preestablished 0.1% error threshold was exceeded, all data entered during that week were reentered and rechecked for accuracy.

A subgroup of 24-hr urine samples was split into two specimens, and both specimens were submitted blind to the laboratory for subsequent analysis. Coefficients of variation for urinary porphyrins were high, especially for those porphyrins present in only trace amounts. The coefficient of variation for coproporphyrins was 17.38%, uroporphyrins 41.60%, heptaporphyrins 70.56%, and pentaporphyrins 81.87% (hexaporphyrins were not detected in any of the split samples).

Data analysis. The health status of the unexposed workers was compared to the health status of the ever PCP workers, only PCP workers, ever PCP workers with chloracne, and only PCP workers with chloracne. Workers were classified as having had chloracne if they had a chloracne score of 1–3 on plant medical records, a chloracne score of 4 or 5 on dermatologic examination, or had reported a doctor's diagnosis of chloracne on the medical history questionnaire.

The statistical significance of the unadjusted comparisons of categorical variables was assessed using either the Fisher's Exact test or the chi-square test. The test for trend was used to examine the odds of selected health outcomes with increasing days of exposure. The statistical significance of the unadjusted comparisons of continuous variables was assessed using either Student's *t*-test or nonparametric tests. Adjustment for confounding was performed using stratification as well as either linear or multiple logistic regression. *A priori* regression models were constructed using known risk factors for specific outcome variables and factors found to be significantly associated with these outcome variables in preliminary analyses conducted on the unexposed population. Exposure was analyzed both as a dichotomous variable (exposed yes/no) and as a continuous variable using days of exposure in production of PCP. All statistical analyses were performed using SAS software (26). Confounding and effect modification from other chemical exposures at the plant on selected health outcomes was controlled through stratification (PCBs) and regression analysis (mercury).

Internist's assessment of general physical appearance was treated as a dichotomous variable (normal vs. acutely or chronically ill) in logistic regressions. Regression models of the general health status outcome variables included age, sex, race, schooling, employment status, and exposure. The statistical significance of a trend of increasing odds of having chloracne with increasing days of exposure (3–29, 30–89, 90–179, 180–364, and ≥ 365 days) was assessed using the test for trend. Comparisons of mean urinary uroporphyrin, coproporphyrin, and porphobilinogen were performed using Student's *t*-test and linear regression using nontransformed outcome variables. Comparisons of mean urinary penta-, hexa-, and heptaporphyrins were performed using nonparametric tests; these variables were log transformed in the regression models to adjust for skewness in their distributions. Multiple linear regressions of urinary porphyrins and abnormal values of 24-hr urine porphyrins (using Mayo Clinic normal values) were adjusted for age, gender, race, current alcohol consumption, past mercury exposure, and serum ferritin after excluding workers who used estrogens. The potential confounding and/or modifying effects of PCB exposure on urinary porphyrin excretion were controlled for through stratification.

Results

Demographic characteristics. Demographic characteristics of the exposed and unexposed groups are presented in Table 2. The distributions of workers by current employment status in each of the PCP exposure groups were significantly different from the distribution of the unexposed workers. The unexposed group had a lower percentage of retired workers and a higher percentage of terminated than the exposure subgroups. Ever PCP workers were also significantly older (58.6 vs. 51.5 years), were more frequently male (97.0 vs. 92.4%), had lower household income, and had more pack-years of smoking (19.5 vs. 14.9 pack-years) than unexposed workers. The only PCP workers were also significantly older (59.7 years) and had lower household income than unexposed workers. PCP workers with chloracne (ever PCP, chloracne) were also significantly older (54.8 years) and had more pack-years of smoking (23.6 pack-years) compared to unexposed workers. The only PCP workers with chloracne had significantly less alcohol consumption (20.8 vs. 35.8 ounces/month) than unexposed workers. There were no significant differences between any of the exposure groups and unexposed workers with regard to race.

General health. After adjusting for the effects of age, gender, race, years of schooling, and employment status, there were no significant differences between the unexposed group and any of the PCP exposure subgroups with respect to self-perception of health, self-reported hospitalizations over the past 12 months, or self-reported doctor/clinic visits over the past 12 months (data not shown). Ever PCP workers were more likely to report staying home due to illness over the past 12 months (adjusted OR = 1.47, $p = 0.042$), but there was no significant difference in the mean number of days they stayed at home due to illness (ever PCP 6.6 days vs. unexposed 4.9 days). There were no significant differences between the unexposed group and the ever PCP, chloracne or only PCP, chloracne subgroups with regard to these same general health indicators after adjustment. Also, there were no significant differences, either unadjusted or adjusted, between unexposed and any of the PCP exposure subgroups with regard to the internist's assessment of their general physical appearance.

Chloracne. Sixty-five (17.8%) of the 366 ever PCP workers had either a history of a doctor's diagnosis of chloracne (42 workers), evidence of chloracne on plant medical

records (41 workers), or evidence of current chloracne at the time of dermatologic exam (14 workers). The percentage of ever PCP workers with chloracne by medical history, plant medical records, or dermatology exam increased with duration of exposure (5.5% for those who worked 3–29 days, 6.6% for 30–89 days, 15.4% for 90–179 days, 24.7% for 180–364 days, and 35.4% for those who worked for 1 or more years; $p < 0.001$). There were no significant differences in self-reported hyperpigmentation or hyperpigmentation found on dermatologic examination between the unexposed workers and workers in either of the chloracne groups.

Porphyrins. None of the workers in this study reported a doctor's diagnosis of porphyria. There were no significant differences between any of the exposure groups and the unexposed group with respect to symptoms of reddish urine and blistering skin. Three workers in the ever PCP, chloracne group were found to have hypertrichosis on dermatologic exam compared to one in the unexposed group (4.6% vs. 0.3%, $p = 0.019$). Two workers in the only PCP, chloracne group were found to have hypertrichosis on dermatologic examination (6.5% vs. 0.3%; $p = 0.024$). These two workers also accounted for a significantly

Table 2. Demographic characteristics by exposure subgroups

Characteristic	Unexposed (<i>n</i> = 303)		Ever PCP (<i>n</i> = 366)		Ever PCP, chloracne (<i>n</i> = 65)		Only PCP (<i>n</i> = 260)		Only PCP, chloracne (<i>n</i> = 31)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Sex										
Male	280	92.4	355	97.0**	63	96.9	250	96.2	30	96.8
Female	23	7.6	11	3.0	2	3.1	10	3.9	1	3.2
Race										
White	255	84.2	320	87.4	56	86.2	227	87.3	28	90.3
Black	47	15.5	44	12.0	8	12.3	32	12.3	3	9.7
Other	1	0.3	2	0.6	1	1.5	1	0.4	0	0.0
Household income (thousands)										
<10	12	4.0	27	7.5*	3	4.7	20	7.8#	2	6.7
10–19	53	17.5	87	24.0	9	14.1	79	30.7	6	20.0
20–29	58	19.2	81	22.4	15	23.4	49	19.1	4	13.3
30–39	88	29.0	89	24.6	25	39.1	57	22.2	13	43.3
40–49	55	18.2	43	11.9	4	6.3	29	11.3	2	6.7
≥ 50	37	12.2	35	9.7	8	12.5	23	9.0	3	10.0
Employment status										
Active	96	31.7	91	24.9#	29	44.6**	42	16.2#	11	35.5#
Transferred	10	3.3	34	9.3	7	10.8	28	10.8	5	16.1
Retired	27	8.9	127	34.7	20	30.8	89	34.2	9	29.0
Terminated	170	56.1	114	31.1	9	13.8	101	38.9	6	19.4
Age (years)										
Mean	51.5		58.6#		54.8*		59.7#		56.2	
SD	15.0		10.5		10.9		10.3		11.5	
Range	25–86		29–79		31–73		29–79		31–73	
Pack-years smoked										
Mean	14.9		19.5**		23.6*		18.4		17.7	
SD	20.9		22.6		26.1		21.7		19.6	
Current alcohol consumption (ounces/month)										
Mean	35.8		30.6		30.4		30.5		20.8*	
SD	60.9		54.0		45.0		57.0		35.4	

Abbreviations: PCP, pentachlorophenol; SD, standard deviation.
* $0.01 < p \leq 0.05$; ** $0.001 < p \leq 0.01$; # $p \leq 0.001$.

higher prevalence of history of excess hair growth in the only PCP, chloracne subgroup (6.5% vs. 0.7%; $p = 0.045$).

A comparison of 24-hr urine porphyrins by exposure subgroups is presented in Table 3. After excluding workers on estrogens and adjusting for age, gender, race, current alcohol consumption, past mercury exposure, and serum ferritin, there were no significant differences between the unexposed group and the ever PCP or only PCP groups with respect to mean urinary excretion of porphyrins or percent abnormal excretion with either dichotomous exposure or days of exposure. Workers in the ever PCP, chloracne group had a higher mean urinary excretion of coproporphyrin (113.2 μg vs. 90.6 μg ; $p = 0.0002$) and a higher percentage of abnormal coproporphyrin excretion (67.7% vs. 44.0%; $p = 0.001$) compared to unexposed workers in the unadjusted analyses. These differences remained statistically significant in the adjusted analyses. Ever PCP, chloracne workers also had a significantly higher mean urinary excretion of heptaporphyrin compared to unexposed workers (4.0 μg vs. 3.2 μg ; $p = 0.0355$) in the adjusted analysis. Workers in the only PCP, chloracne group also had a significantly higher urinary excretion of coproporphyrin compared to unexposed workers [117.0 μg vs. 90.6 μg in both the unadjusted ($p = 0.029$) and adjusted ($p = 0.004$) analyses]. The two workers in the only PCP, chloracne group

who also had hypertrichosis had mild coproporphyrinuria (149 μg and 136 $\mu\text{g}/24$ hr) with normal urinary excretion of uroporphyrins. The percentage of abnormal urinary coproporphyrin excretion in the only PCP, chloracne group was also higher than in unexposed workers (61.3% vs. 44.0%), but this difference was not statistically significant in either the unadjusted or adjusted analyses.

Table 4 presents mean, median, and percent abnormal urinary excretion of porphyrins by PCP exposure subgroup stratified on PCB exposure. The eight workers in the ever PCP, chloracne subgroup who had also worked in the PCB department had greater mean 24-hr urinary excretion of uroporphyrin (38.9 μg vs. 24.9 μg ; $p = 0.09$), heptaporphyrin (7.0 μg vs. 3.2 μg ; $p < 0.01$), pentaporphyrin (8.4 μg vs. 2.3 μg ; $p < 0.01$), and coproporphyrin (167.3 μg vs. 90.6 μg ; $p < 0.001$) than the unexposed group in multivariable analysis. The percentage of abnormal urinary excretion of coproporphyrins was significantly different from unexposed workers in the ever PCP, chloracne workers who had not also worked with PCBs (63.2% vs. 44.0%). The four workers in the only PCP, chloracne subgroup who had also worked in the PCB department had significantly greater 24-hr urinary excretion of heptaporphyrin (5.5 μg vs. 3.2 μg ; $p < 0.05$), pentaporphyrin (13.3 μg vs. 2.3 μg ; $p < 0.001$); and coproporphyrins (215.3 μg vs. 90.6 μg ;

$p < 0.001$) than the unexposed group in multivariable analysis.

Discussion

The purpose of this morbidity study was to determine if workers who had been engaged in the production of PCP suffered any long-term health effects as a result of their exposures to PCP and its CDD and CDF contaminants. The time since last exposure ranged from 8 to more than 30 years. As PCP has an elimination half-life of 30.2 hr (27), these workers were unlikely to have significant residual body burdens of PCP. Some CDDs and CDFs, however, have long elimination half-lives and appreciable levels can persist many years after exposure (28). This study was designed to measure the prevalence of persistent effects years after exposure and not the incidence of reversible health effects during or shortly after exposure. Our primary hypotheses included those health effects that some investigators have reported in dioxin-exposed individuals many years after exposure, specifically chloracne (4,8–10,29–38), liver dysfunction (6,20,31,33,35,39), disorders of porphyrin metabolism (10,35,37,40,41), neurobehavioral disturbances (35,36,42–45), disorders of lipid metabolism (32,35,43,46,47), and peripheral neuropathy (4,5,10,31,35,42, 48–51). The analyses in this paper focus on general health status, chloracne, and disorders of porphyrin metabolism.

In our study, 17.8% of workers who had ever been engaged in the production of PCP had evidence of chloracne by medical history, plant medical records, or dermatologic exam. Chloracne resolved in the majority of affected workers: only 11.3% of those who reported a doctor's diagnosis of chloracne still had chloracne at the time of dermatologic exam. The odds of developing chloracne increased with duration of exposure.

O'Malley et al. (9) reviewed the plant medical records of workers who had been engaged in the production of PCP between 1951 and 1978 at this plant. Seven percent of the workers had evidence of chloracne on plant medical records, compared to 8.8% in our only PCP, chloracne group. O'Malley et al. did not find a significant trend between standardized incidence ratios of chloracne and duration of exposure. The differences in our results for trend between duration of exposure and chloracne may be due to differences in the selection of intervals for duration of exposure. We found a significant trend in the odds of developing chloracne during the first year of exposure using time intervals of 3–29, 30–89, 90–179, 180–364, and ≥ 365 days. O'Malley et al. selected time intervals ranging from < 0.5 to ≥ 10 years.

Table 3. Comparison of 24-hr urine porphyrins by exposure subgroup^a

Urinary porphyrin (μg)	Unexposed (n = 295)	Ever PCP (n = 357)	Ever PCP, chloracne (n = 64)	Only PCP (n = 253)	Only PCP, chloracne (n = 30)
Uroporphyrin					
Mean	24.9	25.0	27.9	23.6	22.9
Median	21	21	23.5	20	21
% Abnormal ^b	8.8	9.0	10.9	7.5	3.3
Hepta					
Mean	3.2	3.9	4.0*	3.5	3.0
Median	2	2	3	2	3
% Abnormal	1.0	2.5	3.1	1.6	0.0
Hexa					
Mean	1.2	1.3	1.3	1.3	1.6
Median	1	1	1	1	1
% Abnormal	1.7	1.1	1.6	1.6	3.3
Penta					
Mean	2.3	2.3	3.3	2.3	4.2
Median	1	1	2	1	2
% Abnormal	12.8	10.2	18.5	8.9	22.6
Copro					
Mean	90.6	91.9	113.2**	90.9	117.0**
Median	85.5	85.5	110	82.5	114
% Abnormal	44.0	40.1	67.7**	36.8	61.3
Porphobilinogen					
Mean	1.09	1.07	1.15	1.04	1.06
Median	1	1	1.1	0.95	0.9
% Abnormal	6.0	4.4	4.6	3.1	0.0

PCP, pentachlorophenol.

^aAll p -values adjusted for age, gender, race, current alcohol, mercury exposure, and ferritin after excluding workers who used estrogens. Penta-, hexa-, and hepta- log transformed; uro- and coproporphyrin and porphobilinogen not transformed.

^bAbnormal for males defined as uro > 46 ; hepta > 13 ; hexa > 5 ; penta > 4 ; copro > 96 . Abnormal for females defined as uro > 22 ; hepta > 9 ; hexa > 4 ; penta > 3 ; copro > 60 . Abnormal porphobilinogen > 2 for males and females.

* $0.01 < p \leq 0.05$; ** $p \leq 0.01$.

Table 4. Comparison of 24-hr urine porphyrins by PCP/PCB exposure subgroup^a

Urinary porphyrin (μg)	Unexposed (n = 295)	Ever PCP		Ever PCP, chloracne		Only PCP		Only PCP, chloracne	
		PCB (n = 57)	No PCB (n = 307)	PCB (n = 8)	No PCB (n = 56)	PCB (n = 37)	No PCB (n = 221)	PCB (n = 4)	No PCB (n = 26)
Uroporphyrin									
Mean	24.9	28.3	24.4	38.9	26.4	23.4	23.6	29.5	21.9
Median	21	24	21	38.5	22	24	19	30.5	20
% Abnormal ^b	8.8	12.3	8.3	25.0	8.9	5.4	7.9	0.0	3.9
Hepta									
Mean	3.2	5.4	3.6	7.0**	3.6	3.4	3.5	5.5*	2.7
Median	2	3	2	5	3	2	2	5	2
% Abnormal	1.0	7.0	1.6	12.5	1.8	2.7	1.4	0.0	0.0
Hexa									
Mean	1.2	1.2	1.3	1.4	1.3	1.1	1.3	1.8	1.5
Median	1	1	1	1	1	1	1	1	1
% Abnormal	1.7	0.0	1.3	0.0	1.8	0.0	1.9	0.0	3.9
Penta									
Mean	2.3	2.9	2.2	8.4**	2.6	2.8	2.2	13.3**	2.8
Median	1	1	1	2.5	1	1	1	6.5	1
% Abnormal	12.8	12.3	9.8	37.5	15.8	8.1	9.1	50.0	18.5
Copro									
Mean	90.6	90.1	92.2	167.3**	105.6	92.1	90.7	215.3**	102.4
Median	85.5	89	85	121	104	84	82	194.5	105
% Abnormal	44.0	42.1	39.7	100.0	63.2*	40.5	36.2	100.0	55.6
Porphobilinogen									
Mean	1.09	0.9	1.1	1.05	1.16	0.9	1.07	1.0	1.07
Median	1	0.9	1	1.1	1.1	0.9	1	1	0.9
% Abnormal	6.0	3.5	4.6	0.0	5.3	2.7	3.2	0.0	0.0

Abbreviations: PCP, pentachlorophenol; PCB, polychlorinated biphenyls.

^aAll *p*-values adjusted for age, gender, race, current alcohol, mercury exposure, and ferritin after excluding workers who used estrogens. Penta-, hexa-, and hepta- log transformed; uro- and coproporphyrin and porphobilinogen not transformed.^bAbnormal for males defined as uro >46; hepta >13; hexa >5; penta >4; copro >96. Abnormal for females defined as uro >22; hepta >9; hexa >4; penta >3; copro >60. Abnormal porphobilinogen >2 for males and females.*0.01 < *p* ≤ 0.05; ** *p* ≤ 0.01.

Chloracne has also been observed in PCP production workers at other plants (4,8,10) and in a worker with prolonged exposure to PCP-treated wood (18). Technical PCP has been shown to produce chloracne in a rabbit ear model, whereas pure PCP does not (52).

Our PCP workers with chloracne had significantly elevated mean urinary excretions of coproporphyrin compared to the unexposed workers after control for potential confounders. There were no significant differences in the urinary excretion of uroporphyrins, and none of participants had a history of porphyria cutanea tarda. The pattern of porphyrin excretion in our workers with chloracne is consistent with subclinical, low-grade coproporphyrinuria.

Studies of porphyrin metabolism in TCDD-exposed individuals have yielded conflicting results. In the two plants where workers had clinical porphyria (35,37), hexachlorobenzene may have been a confounding exposure (53). Calvert et al. (54) did not find significant associations between serum levels of TCDD and porphyria cutanea tarda, uroporphyrinuria, or coproporphyrinuria in a cohort of workers who had been exposed to chemicals contaminated with TCDD more than 15 years earlier. Residents of Seveso have been found to have

subclinical coproporphyrinuria compared to controls (41). The only documented cases of porphyria cutanea tarda among Seveso residents occurred in a family with congenital uroporphyrinogen decarboxylase (UROD) deficiency (40).

Studies of PCP-exposed workers have also yielded conflicting results. Baxter (8) found no abnormalities in the urinary excretion of coproporphyrin, uroporphyrin, and δ-aminolevulinic acid (ALA) among workers engaged in the production of PCP at a plant in the United Kingdom. Cheng et al. (10) found higher excretion of urinary porphyrins and ALA among Chinese workers engaged in the production of PCP than in controls. At the plant studied by Cheng et al., PCP was produced through a series of steps involving hexachlorocyclohexane, trichlorobenzene, and hydroxylation of hexachlorobenzene. Pines et al. (55) found higher mean urinary excretion of coproporphyrin and ALA in workers employed in wood processing and furniture manufacture compared to controls. Workers in this pilot study, however, were exposed not only to technical PCP but also to solvents used in wood finishing. Coproporphyrinuria has also been observed in workers with high serum concentrations of PCBs (56).

Animal studies are consistent with the induction of porphyrinuria by exposure to contaminants present in technical PCP. Goldstein et al. (57) compared the porphyrinogenic effect of technical (contaminated with CDDs and CDFs) versus pure PCP in female rats. Rats fed 500 ppm of technical PCP for 8 months had significant elevations in urinary excretion of coproporphyrin, uroporphyrin, and ALA compared to controls, whereas pure PCP was not porphyrinogenic. Technical PCP, however, did not increase the activity of ALA synthetase in this study, although dioxins such as TCDD are believed to exert their porphyrinogenic effect through induction of ALA synthetase as well as inhibition of UROD (58).

In our study, urinary porphyrin excretion was highest among the subgroups of workers with chloracne who had worked with both PCP and PCBs. Results of recent animal studies suggest a possible synergistic interaction between certain PCB congeners and TCDD in producing hepatic porphyrin accumulation. Van Birgelen et al. (59) observed an 800-fold increase in hepatic porphyrin accumulation in female Sprague-Dawley rats that were coadministered PCB 153 and TCDD in a 13-week feeding study. Van Birgelen et al. hypothesize that the synergistic interaction observed in their animal studies may be due to the combined effects of Ah-receptor-mediated induction of CYP1A2, which may play a role in the oxidation of uroporphyrinogen III to uroporphyrin III, together with possible induction of ALA synthetase. These animal data are consistent with our observation of elevated urinary porphyrin excretion among workers with chloracne who had worked with both PCP and PCBs. The contaminants present in the technical PCP produced at the study plant are listed in Table 1. Potential porphyrinogens include the chlorinated dibenzodioxins and chlorinated dibenzofurans. An alternative explanation may be contamination of technical PCP with hexachlorobenzene. Although hexachlorobenzene was not measured in the PCP produced at this plant, an industry composite of technical-grade pentachlorophenol prepared from material supplied by three U.S. manufacturers contained low concentrations of hexachlorobenzene (50 ppm), which is a known porphyrinogen in humans (2). We were unable to test for statistical interaction between PCP and PCB exposure on urinary porphyrin excretion in our study because we did not have a separate study group exposed to PCBs alone.

Mean porphyrin levels in our unexposed group were higher than those of many, but not all, previous studies (60).

Differences among these studies may be due to variations in laboratory procedures, a possibility supported by the high coefficients of variation of our porphyrin assays. An alternative explanation is exposure to other porphyrinogens, such as alcohol or other chemicals at the plant. Both of these factors would tend to bias the results toward the null hypothesis.

The major limitations of this study are reliance on historical personnel records and chloracne as measures of exposure, potential confounding from other chemical exposures, use of prevalence rather than incidence as our predominant measure of disease frequency, and low power in the subgroup analyses. Although direct bioassay of PCDDs and PCDFs in adipose tissue or serum is the most reliable index of exposure, this was not technically or logistically feasible in the present study. Fingerhut et al. (61) found that serum levels of 2,3,7,8-TCDD were related to duration of employment in workers engaged in the production of 2,4,5-trichlorophenol and 2,4,5-trichlorophenoxyacetic acid. Neuberger et al. (62) found higher serum levels of 2,3,7,8-TCDD in production workers with chloracne compared to unexposed referents, whereas Beck et al. (63) found little correlation between adipose PCDD or PCDF concentrations and incidence of chloracne in exposed workers. Chloracne may be a marker of both exposure and susceptibility in exposed workers.

A limitation inherent in the cross-sectional design is the use of prevalence rather than incidence as a measure of disease frequency. If exposure affects survival or ability to participate in the examination due to illness, then this could bias the results toward the null hypothesis. The long lag times between last exposure and time of medical examination limit our ability to study past events. Finally, the small numbers of individuals in our highest exposure groups (ever and only PCP, chloracne), limit our ability to detect significant differences due to low study power, and negative results should be interpreted with a consideration of the potential for beta error.

Despite these limitations, this is the largest morbidity study of pentachlorophenol production workers conducted to date and provides important information on the health status of workers with past exposure to PCP and its CDD and CDF contaminants. Overall, the general health status of these PCP-exposed workers was similar to unexposed workers. The major clinical effect we observed in PCP-exposed workers was chloracne. The other finding we believe is consistent with current knowledge of the effects of exposure to CDDs and CDFs is elevation in urinary excretion

of coproporphyrins in persons with chloracne. The high urinary excretion of uroporphyrin, hepta-, penta-, and coproporphyrins among the subgroup of workers with chloracne who had worked with both PCP and PCBs suggests a possible interaction between compounds present in technical PCP and PCBs on porphyrin metabolism.

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The focus of the meeting will be on new developments in the handling and elimination of potential toxic xenobiotics by epithelial tissues, particularly kidney and liver. Presentations on intestinal and blood-brain barrier drug and xenobiotic transport will also be included. In addition to invited platform presentations by international leaders in this field, an open poster session will be held on the afternoon of August 24, 1998. Attendees (including college students) are encouraged to present posters, and poster boards will be available. To be eligible to participate in the poster session, an abstract must be submitted to Ms. Brenda Deck, Conference Coordinator, NIEHS, PO Box 12233, MD F1-03, Research Triangle Park, NC 27709 no later than August 1, 1998. The deadline for registration is August 15, 1998.

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