Department of Medicine

Wesley Pavilion 296
250 East Superior Street
Chicago, Illinois 60611-2950
(312) 908-2252

Warren H. Wallace, MD
Program Director
Internal Medicine Residency

02257 E

May 5, 1994

James J. Collins, Ph.D.
Director, Epidemiology
& Health Information Services
Monsanto Company
800 N. Lindbergh Blvd. (A2SL)
St. Louis, MO 63167

Dear Dr. Collins:

Enclosed is the most recent draft of our paper "A morbidity study of chemical workers who had been engaged in the production of pentachlorophenol." Under separate cover, copies are being sent to the members of our peer review committee. We have marked our changes to the earlier draft in italics to expedite your review. The changes include 1) an expanded discussion of exposure classifications in Depts 236 and 237; 2) an additional paragraph and introductory sentence on study limitations which discusses incomplete follow-up and low power in subgroup analyses; 3) addition of a reference on tremor; 4) additional analyses of GGT with attention to outliers; and 5) a sentence addressing the potential of contamination of technical PCP with hexachlorobenzene.

As you know, the geographic proximity of Departments 236 and 237 from 1938 to 1978 and their integration into a single administrative unit between 1969 and 1978 have made separation of these exposures difficult. While we believe that we have sufficiently detailed information on job title to separate these exposures, we want our readers to appreciate that "Only" is a relative rather than absolute classification. The paragraph which we have added provides the reader with this information.

We have added an additional paragraph and introductory sentence to our discussion of study limitations to emphasize that the major limitations of the study, in addition to exposure assessment, are incomplete follow up of the cohorts and low study power, especially in the subgroup analyses. While these limitations are self-evident to epidemiologists, we felt they merit re-emphasis for the general reader. For example, the risk of beta error in our crude analysis of abnormal vibration sensation on physical exam among the Only PCP chloracne group compared to the unexposed is greater than 0.80.

We have also included a reference by Klawans in which he reports his observation of tremor in workers exposed to chlorinated phenols. Our inclusion of the Klawan's reference does not change our original assessment regarding tremor: since this finding was not one of our a priori hypotheses, we believe that causal inferences must await data from other studies.

When the paper was presented to Monsanto's external Biohazards Committee and their internal health and safety staff, several questions were raised which we felt merited further analysis of our data. Specifically, this group asked 1) were any outliers accounting for the difference in mean GGT between the Ever and Only PCP chloracne group (recall that Only PCP is a subset of Ever PCP)? 2) was GGT associated with current chloracne (as measured by positive dermatologic exam)? and 3) could potential contamination of technical pentachlorophenol with hexachlorobenzene be accounting for the elevated coproporphyrins among PCP workers with chloracne?

Our re-analysis of our GGT results revealed that the differences in mean GGT between the Ever (52.6 u/l) and Only (74 u/l) PCP chloracne groups were strongly influenced by two outliers (GGT > 3 times upper limit of normal, i.e. greater than 195 u/l) in the Only PCP chloracne group. The first outlier (GGT = 640 u/l) was an employee who had cancer which had probably metastasized to the liver. He was one of two individuals in the Only PCP chloracne group who had abnormal liver consistency on physical examination. The results of the GGT analysis after removal of this individual are follows:

| Chloracne | Unexposed | Ever PCP Chloracne | Only PCP |
|---|---|---|---|
| Mean GGT (u/l) | 35.8 | 43.4 | 55.1 |
| Adjusted p | | NS | 0.0397 |
| % > 65 u/l | 7.6% | 12.5% | 20.0% |
| Adjusted p | | NS | 0.0033 |

The second outlier (GGT = 570 u/l) did not have a medical reason for exclusion. Regression diagnostic methods were used to determine the influence of this worker's GGT value on parameter estimation. This particular observation exerted strong influence in terms of parameter estimation, and we decided to examine the effect on our results of removing both outliers. The effects of removing both of these individuals from our GGT analysis are as follows:

| Chloracne | Unexposed | Ever PCP Chloracne | Only PCP |
|---|---|---|---|
| Mean GGT (u/L) | 35.8 | 35.1 | 37.4 |
| Adjusted p | | NS | NS |
| % > 65 u/l | 7.6% | 11.1% | 17.9% |
| Adjusted p | | NS | 0.0140 |

Removal of both outliers results in a reduction in the difference in mean GGT between the Only PCP Chloracne and unexposed groups with loss of statistical significance in the adjusted analysis. The difference in % > 65 u/l, however, remained statistically significant.

Our review of the second outlier's medical history and his MEHI work record revealed a discrepancy between his recollection of his date of onset of chloracne and his start date in Department 236. On his administered medical history questionnaire he stated that he recalled the onset of his chloracne to be in 1962 ("In what year did a doctor first tell you that you had chloracne?"). He reported that the chloracne appeared on his face, he did not have a biopsy, and the chloracne did not clear up. On our physical examination he was noted to have an acneiform eruption with open comedones on his cheeks, temples, periorbital, and crowfeet areas. Our dermatologist, blinded to his exposure status, gave him a chloracne score of 3 ("In your opinion, to what extent is this subject's examination consistent with the diagnosis of chloracne? 1=very unlikely to 5= highly likely) which did not meet our definition of current chloracne (score of 4 or 5).

His MEHI work record indicated that he began working in Department 236 in 1963. On his administered work history questionnaire (separate interviewer from the medical history questionnaire), he indicated his first date of employment in Department 236 as "1963 estimated." Abstracts of his plant medical records indicated that he did not have evidence of chloracne on his first Monsanto physical. Furthermore, he did not work in any Departments which we have hitherto considered as exposed.

We have attempted to follow-back this individual for more information but have learned that he is deceased. In our judgement, the imprecision inherent in recalling dates of chloracne 25 years after their occurrence does not warrant labeling this case as a misclassification. We believe that his chloracne was related to the PCP exposure for the following reasons: 1) the discrepancy between his recall of chloracne and MEHI record of work in Department 236 could be as short as 2 months; 2) his recall of his date of first employment at the Krummrich plant was in error by one year; 3) he did not have evidence of chloracne on his first Monsanto physical examination; 4) he did not work in Departments 237 or 268 prior to working in Department 236. We have also re-reviewed dates of chloracne against MEHI and self-reported work histories for other workers with chloracne to resolve any other temporal discrepancies.

We have revised the paper to take into account the influence of these outliers on the GGT analysis. Specifically, we have presented the results 1) with no exclusions; 2) excluding the outlier with metastatic liver cancer; and 3) excluding both outliers. We have changed the results section of the abstract to present the differences in percent abnormal GGT which remain significant after excluding both outliers.

In a related question, we were asked whether serum GGT was associated with current chloracne (dermatologist's chloracne score of 4 or 5). The following tables compare mean and percent abnormal GGT between current (Derm Positive) and past (Derm Negative) chloracne cases. The comparisons are presented for both the Ever PCP Chloracne workers and the Only PCP Chloracne workers.

| | Ever PCP Chloracne (N=65) | | |
|---|---|---|---|
| | Derm Positive | Derm Negative | p |
| Mean GGT (u/l) | 55.9 | 40.6 | 0.444 |
| % > 65 u/l | 14.3 | 13.7 | 0.957 |
| | Only PCP Choracne (n=31) | | |
| Mean GGT (u/l) | 33.9 | 90.4 | 0.140 |
| % > 65 u/l | 11.1 | 27.3 | 0.329 |

These analyses did not exclude the outliers, both of whom were derm negative for chloracne.

We were also asked whether the coproporphyrinuria might be due, at least in part, to contamination of technical PCP with hexachlorobenzene. The only data available to us on levels of hexachlorobenzene in technical pentachlorophenol comes from a National Toxicology Program Technical Report on "Toxicology and Carcinogenesis Studies of Two Pentachlorophenol Technical-Grade Mixtures). NTP used an industry composite prepared from material supplied by Monsanto Industrial Chemical Co., Reichhold Chemicals, Inc., and Vulcan Materials Co. which contained, among other impurities, 50 ppm of hexachlorobenzene. Since hexachlorobenzene is a potential contaminant of technical pentachlorphenol, and since it is recognized as a potent porphyrinogen, we cannot exclude the possibility that it contributed to the coproporphyrinuria observed in our study group. We unfortunately do not have information on levels of hexachlorobenzene in the Monsanto product alone.

We will be contacting you to discuss the logistics of the review process. We are preparing papers on other health endpoints in the pentachlorphenol workers as well as the workers exposed to lower chlorinated phenols and chlorphenoxyacid esters. Thank you for your longstanding commitment to this research project and the invaluable help which you have provided to date.

Sincerely,

Warren H. Wallace, M.D.
Department of Medicine
Northwestern University Medical School

Daniel O. Hryhorczuk, M.D., M.P.H.
School of Public Health
University of Illinois-Chicago

WHW/DOH:sk

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# A MORBIDITY STUDY OF CHEMICAL WORKERS WHO HAD BEEN ENGAGED IN THE PRODUCTION OF PENTACHLOROPHENOL

Daniel O. Hryhorczuk, M.D., M.P.H.[1,3], Warren H. Wallace, M.D.[2], Victoria Persky, M.D.[1,2,3], Sylvia Furner, Ph.D.[3], James R. Webster, Jr., M.D.[2], Denise Oleske, Ph.D.[4], Barbara Hazlehorst, R.N., Richard Letz, Ph.D.[5], Philip B. Gorelick, M.D., M.P.H.[6], Thomas G. Cole, Ph.D.[7], Ralph Ellefson, Ph.D.[8], Charles Zugerman, M.D.[9]

[1] Department of Preventive Medicine, Northwestern University Medical School, Chicago

[2] Department of Medicine, Northwestern University Medical School, Chicago

[3] Epidemiology and Environmental and Occupational Health Programs, University of Illinois School of Public Health, Chicago

[4] Department of Health Systems Management, Rush University, Chicago

[5] Division of Environmental and Occupational Health, Emory University School of Public Health, Atlanta

[6] Department of Neurology, Rush University, Chicago

[7] Lipid Research Center, Department of Medicine, Washington University, St. Louis

[8] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester

[9] Department of Dermatology, Northwestern University Medical School, Chicago

## ABSTRACT

**Objective** To examine the effects of occupational exposure to pentachlorophenol (PCP) and its chlorinated dioxin and dibenzofuran contaminants on the skin, liver, porphyrin metabolism, lipid metabolism, central nervous system, and peripheral nervous system.

**Design** Medical survey

**Participants** The exposed participants were employed at a chemical plant where they were engaged in the production of PCP between 1938 and 1978. The referent group consisted of workers from the same plant who were not exposed to these or related compounds. A total of 366 PCP exposed workers and 303 unexposed workers participated in the medical survey.

**Measurements** Exposure was determined from computerized personnel records. The medical survey included an administered questionnaire; medical record review; physical examination by dermatologists, internists, and neurologists; computerized neurobehavioral testing; quantitative sensory testing; analyses of blood for liver function tests, lipids, and apolipoproteins; and analysis of 24-hour urine for quantitative porphyrins.

**Main Results** 17.8% of PCP exposed workers had evidence of current or past chloracne. PCP workers with chloracne had a significantly higher *prevalence of elevated gamma glutamyl transpeptidase (GGT > 65 u/l; 22.6 vs 7.6%)* and mean urinary excretion of coproporphyrins (117.0 vs 90.6 mcg/24 hours) than unexposed workers *after controlling for potential confounders*. Exposed workers had poorer performance than unexposed on specific subtests of memory and psychomotor function and PCP exposed workers with chloracne had a higher prevalence of positional tremor. This study did not detect consistent differences between PCP exposed workers and unexposed workers with respect to general health, *other* liver functions, lipid *or apolipoprotein* levels, or peripheral neuropathy.

**Conclusion** Occupational exposure to PCP is associated with chloracne and biochemical abnormalities which may persist years after exposure.

## INTRODUCTION

Pentachlorophenol (PCP) is a pesticide which is widely used for wood preservation. Major uses include commercial wood treatment in the lumber industry and slime control in the pulp and paper industry. The sodium salt of PCP (NaPCP) is also used in wood preservation as a sapstain control agent. Minor uses have included various non-industrial applications as a herbicide, antimicrobial, and disinfectant.

From 1984 to 1988, the United States Environmental Protection Agency issued a series of strict regulatory controls over the manufacture, use, and disposal of PCP[USEPA]. 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[NTP].

Acute poisoning with PCP in workers produces a characteristic syndrome of hyperpyrexia caused by uncoupling of oxidative phosphorylation[Wood]. The chronic effects of exposure to PCP have been studied in PCP production workers[Beader, Triebig, Zober, Bauchinger, Baxter, OMalley], PCP formulators[Jones], wood treatment workers[Begley, Klemmer], sprayers[Jones], and sawmill workers[Embree, Enarson, Kleinman]. Several studies have demonstrated that exposure to commercial PCP can produce chloracne[Beader, Baxter, OMalley, Sehgal, Cole]. Some studies have observed irritant effects on the eyes and upper respiratory tract[Beader, Kleinman]; peripheral sensory neuropathy[Treibig]; reversible renal impairment[Begley]; decreased bilirubin[Baxter, Jones], increased serum glutamatdehydrogenase (GLDH) [Zober]; decreased hematocrit and white blood cell count[Enarson], and increased frequency of chromosome alterations in lymphocytes[Bauchinger].

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 (the subject of this paper) as well as lower chlorinated phenols, and esters of chlorphenoxy acids. The purpose of this study was to determine if these workers 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 these primary hypotheses 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 chlorphenoxy 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 secondary hypotheses will be presented in subsequent papers.

## METHODS AND MATERIALS

### 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 chlorinated benzenes, nitrochlorobenzene, orthonitrophenol, nitroaniline, $PCL_3$, $P_2S_5$, chlorine bleaches, and detergent materials. The plant had produced lower chlorinated phenols from 1931 to 1983, had produced polychlorinated biphenyls from 1929 to 1977, and had esterified 2,4,5-trichlorophenoxyacetic acid (brought in from another facility) from 1960-1971.

Pentachlorophenol was produced by direct chlorination of phenol, orthochlorophenol, parachlorophenol, 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 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) all hourly production workers who had been engaged in the production of PCP for 3 or more days between 1938 and 1978; 2) all hourly production workers who had been engaged in the production of mono- and

dichlorophenols between 1931 and 1983; 3) all 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 called the Medical and Environmental Health Inventory (MEHI) maintained by the company. An internal audit of this 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, prior to 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 which were 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.

Several sources of exposure misclassification were detected and corrected between November 7, 1985 (the date of initial sample selection) and September 1, 1987 (the start of data analysis) by reconciling the MEHI classification of vital status and exposure with other data sources. Ten workers were added to the exposure group after correcting MEHI errors. Thirty five exposed and 91 unexposed workers presumed to be alive at the time of sample selection were deleted when they were discovered to be deceased. Seven high school students who had been employed as part-time coop workers were deleted from the unexposed group because of their age. Four salaried workers with potential exposure and 1 worker hired after the stopping date of 10/1/84 were also deleted from the unexposed group. The largest source of detected misclassification error was a misidentification of historical maintenance departments in the MEHI database. One hundred and twelve workers were deleted from the unexposed sample when a review of company records indicated that they had worked as maintenance workers and did not meet the definition of no exposure. Twelve workers originally classified as exposed were moved to unexposed due to a correction of departmental classification. Three originally classified as unexposed were moved to the exposed group due to a correction of departmental classification. One worker was moved from the unexposed group to the exposed group after he was noted to have chloracne on plant medical records and reported working in the pentachlorophenol unit on his occupational history questionnaire.

Six hundred and forty seven of the 763 eligible exposed workers were located (85%) and 473 of those located participated in the medical examination (73%). Four hundred and forty five of the 559 eligible unexposed were located (80%) and 303 of those located participated in the medical examination (68%).

This paper presents the results of the analyses of the primary hypotheses for the group of workers who had been engaged in the production of pentachlorophenol. Three hundred and sixty six (77%) of the

473 exposed workers in this study 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 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 114 (31.2%) of the PCP workers and 40 (13.2%) of the unexposed 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 prior to 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 which had been archived and lost. All available

records were reviewed and coded by trained record review technicians. All onsite 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 was 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 face to face by trained interviewers. Portions of the questionnaire were adapted from previously used survey instruments including the National Center for Health Statistic's Health Interview Survey[NHIS], the NIOSH Dioxin Morbidity Study Questionnaire[Calvert], British Medical Research Council's Respiratory Questionnaire[MRC], the Multiple Risk Factor Intervention Trial Questionnaire[MRFIT], and the Swedish Questionnaire 16[Hogstead]. 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 by internal medicine 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[OMalley] 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 5 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 liver disease was determined by participant's self-reporting of a doctor's diagnosis of hepatitis or cirrhosis and by self-reporting of the symptom of jaundice on the medical history questionnaire. These medical events were considered to be potentially work-related only if they appeared after first employment at the plant. The prevalence of physical findings consistent with liver disease was determined by internists' examination which included palpation of the liver, measurement of liver span, and examination of sclera, venous pattern, ascites, and right upper quadrant tenderness.

The history of porphyria was determined by asking participants the question "Have you ever been told by a doctor that you had porphyria?" The history of symptoms suggestive of porphyria was determined by asking participants the question "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 5 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. The history of

central nervous system dysfunction was determined by participants' self-reporting of neuropsychiatric symptoms on the medical history questionnaire. The history of elevated blood lipids was determined by asking the question "Has a doctor ever told you that you had high fat or cholesterol in your blood?" The history of peripheral neuropathy was determined by asking the question "Have you ever been told by a doctor that you had neuritis, or other problems with the nerves in your hands or feet that were not caused by an injury?" Participants were also asked to report if they had ever experienced numbness or tingling in the fingers or toes that lasted for a day or more, loss of muscle strength in the arms or hands, or difficulty moving fingers or grasping things that were not due to an accident or injury. The prevalence of physical findings consistent with peripheral neuropathy was determined by neurologists' examination which included tests of pinprick discrimination, vibration sensitivity, stocking glove neuropathy as measured by distal to proximal marching pinprick; reflexes, tremor; and muscle atrophy, strength, and tone.

Neurobehavioral outcomes were measured using the Neurobehavioral Examination System (NES) Baker. The NES battery included vocabulary, pattern memory, serial digit learning, symbol digit substitution, finger tapping, hand-eye coordination, continuous performance test, and mood scales. Test data were scored and summarized using NES software. Technicians administering the test battery kept a logbook in which they recorded any factors or circumstances that might interfere with a participant's performance. Saliva alcohol concentration was measured prior to beginning neurobehavioral testing using Chem-Elec Abusa-Sticks. Vibratory and thermal sensory thresholds for the dominant index finger and big toe were measured using the Sensortek Vibration and Thermal Sensitivity Tester Sosenko. The testing algorithm was a two-alternative forced-choice paradigm with computer-assisted parameter estimation by sequential testing Lieberman.

Fasting blood samples were obtained from each participant on the morning of the medical examination. Liver function tests, cholesterol, and triglycerides were analyzed by Smith-Kline-Bioscience using a Technicon SMAC Analyzer. HDL-cholesterol was measured by heparin-manganese technique. LDL-cholesterol was calculated from the Friedewald formula[Friedewald]. Prothrombin time was measured using photooptical technique on a MLA-700. For apolipoproteins, blood specimens were drawn into evacuated tubes containing EDTA. Plasma was separated by centrifugation within 4 hours of specimen collection and was frozen at -70° until analyzed. Concentrations of apolipoproteins A-I, A-II, B, and E were determined by radioimmunoassay at the Lipid Research Center of Washington University [Schonfeld a,b,c, Falko]. Reference ranges for abnormal test results were those of the analyzing laboratory.

Each participant was asked to begin a 24-hour 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. Quantitative porphyrins were analyzed using high performance liquid chromatography.

Data were analyzed for completeness and accuracy at several stages in the data collection and analysis. Onsite quality control clerks, as well as Survey Research Laboratory supervisors, provided continuous monitoring of the completeness and consistency of the data collection. Participants were re-interviewed 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 pre-established 0.1% error threshold was exceeded, all data entered during that week were re-entered and re-checked for accuracy.

For all laboratory tests except apolipoproteins, a subgroup of samples was split into two

specimens, and both specimens submitted blind to the laboratory for subsequent analysis. The coefficients of variation of the technical errors of the liver function tests, with the exception of bilirubin, were all well below 10%, with most below 5%. The coefficient of variation for bilirubin, which is sensitive to fluorescent light, was 10.77%. Coefficients of variation for the lipids were all below 5%. Coefficients of variation for urinary porphyrins, however, 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).

In addition to the split samples, quality control was ascertained for the liver function tests and lipids analyzed by Smith-Kline-Bioscience using external standards provided by the American College of Pathologists. Each of the tests was within 1.6 standard deviations of the pooled specimens from all laboratories to which our laboratory was compared, with most of the tests well within one standard deviation. Interassay variations were also monitored for all liver function and lipid tests. With the exception of SGPT (15.7% against the low standard and 3.4% against the high standard), interassay coefficients of variation for the liver function and lipid tests were all lower than 10%, with most lower than 5%. Coefficients of variation for apolipoproteins were higher, with values ranging from 6.4% to 19.8%.

**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

Comparisons of mean urinary uroporphyrin, coproporphyrin, and porphobilinogen were performed using the Student t test and linear regression using non-transformed 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-hour urine porphyrins (using Mayo Clinic normal values) were adjusted for age, gender, race, current alcohol consumption, past mercury exposure, and serum ferritin. Comparisons of mean values of blood lipids and apolipoproteins were adjusted for age, gender, race, body mass index, use of antihypertensive medications, current smoking, current alcohol, and diabetes, after excluding participants who were on thyroid, lipid-lowering, or estrogen drugs.

Participants were excluded from the neurobehavioral analysis if they had a history of stroke, head injury with loss of consciousness, were on antiseizure or psychotropic medication, had used marijuana or recreational drugs in the past 12 months, had severe visual problems, illiteracy, or if they had a positive saliva alcohol at the time of exam. Comparisons of neurobehavioral test scores were adjusted for age, gender, race, vocabulary, schooling (for vocabulary regression), current alcohol consumption, and past mercury exposure. Comparisons of abnormal neurologic findings, except tremor, were adjusted for age, height, and alcohol, after excluding participants with diabetes, renal failure, and those taking potentially neurotoxic medications (chloramphenicol, nitrofurantoin, vincristine, and hydralazine). Comparisons of positional tremor in the upper extremities were adjusted for age, current alcohol, current smoking, and mercury exposure after excluding participants taking theophylline or epinephrine. Vibration thresholds of the dominant index finger and great toe (V) were transformed to Ln $V^2/2$ which is a direct measure of the displacement of the vibratory post in microns[Bovet]. The temperature thresholds (T) of the dominant index finger and great toe were transformed to the square root of T.[Bovet] Comparisons of these transformed variables were adjusted for age and height after excluding participants with diabetes, renal failure, those

taking neurotoxic medications, and participants unable to use their preferred extremity.

## 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 than the distribution of the unexposed workers with the unexposed group having 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. There were no significant differences between any of the exposure groups and unexposed workers with regard to race or current alcohol consumption.

### 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 ill over the past 12 months (adjusted OR=1.47, p=.042), but there was no significant difference in the mean number of days stayed home ill (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 adjusting for age, gender, race, years of schooling, and employment status. After adjusting for these same variables, there were no significant differences between the 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; $p < .001$). The prevalences of additional pertinent physical findings are presented in Table 3. 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.

**Liver**

There were no significant differences between the unexposed group and the Ever PCP group or

Only PCP group with respect to past medical history of hepatitis, jaundice, or cirrhosis. Four workers in the Ever PCP chloracne group gave a history of past hepatitis compared to 4 workers in the unexposed group (6.2% vs 1.7%; p=0.045 after adjusting for age and alcohol), but the difference was not significant after excluding workers whose hepatitis occurred before employment at the plant. When the Only PCP chloracne group was compared to unexposed workers, there was again a significant difference in a history of ever having had hepatitis (9.7% vs 1.7%, adjusted p=.0165), but no significant difference in hepatitis after employment at the Krummrich plant. Two of the workers in the Only PCP chloracne group had abnormal liver consistency compared to one worker in the unexposed group (6.5% vs 0.3%; adjusted p=.0195). *One of these workers had metastatic cancer with probable liver involvement at the time of examinaion.*

Mean values of serum liver function tests are presented in Table 4. There were no significant differences between unexposed workers and any of the PCP exposure groups with regard to mean serum values of total protein, albumin, LDH, SGOT, SGPT, alkaline phosphatase, and prothrombin time in the adjusted analyses using dichotomous exposure or days of exposure. There were also no significant differences between the unexposed workers and any of the PCP exposure subgroups in the percentages of abnormal results for these same liver function tests in the adjusted analyses using dichotomous exposure. Workers in the Ever PCP group had a significantly higher percentage of abnormal LDH (1.9 vs 1.0%) and a significantly lower prothrombin time (5.9 vs 8.5 seconds) in the adjusted analysis using days of exposure. The mean serum bilirubin in the Ever PCP group was significantly lower than in the unexposed workers in the unadjusted, but not in the adjusted analyses (0.55 vs 0.60 mg/dl; p=0.023).

There were no significant differences in mean serum GGT between the unexposed group and the Ever or Only PCP groups. Workers in the Ever PCP Chloracne group had a higher mean serum GGT than

unexposed workers (52.6 vs 35.8 U/l) but this difference was not significant in the unadjusted or adjusted analyses. The mean serum GGT was significantly higher in the Only PCP Chloracne group than in the unexposed workers (74.0 vs 35.8 U/l) after adjusting for age and current alcohol consumption. This difference remained significant after adjusting for age, sex, body mass index and current alcohol consumption and excluding workers who were taking oral contraceptives, phenobarbitol, dilantin, or coumarin (p=.001). 22.6% of the Only PCP Chloracne group had GGT values above 65 U/l compared to 7.6% of the unexposed group, and this difference was significant in both unadjusted (p=0.006) and adjusted (p=0.001) analyses. We did not find a significant interaction between PCP exposure and current alcohol consumption on GGT in workers with chloracne.

*Two workers in the Only PCP chloracne group had GGT levels greater than 3 times the upper limit of normal (greater than 195 u/l). One of these workers (GGT = 640 u/l) had metastatic cancer at the time of examination. When this worker was removed from the GGT analysis, both the mean (55.1 u/l) and % abnormal GGT (20.0%) among the Only PCP chloracne group remained significantly higher than unexposed. While the second worker did not have a medical reason for exclusion, regression diagnostic methods revealed that his GGT value (GGT = 570 u/l) exerted strong influence on parameter estimation. When this second outlier was removed from the multivariable regression analysis, the % abnormal GGT (17.9 vs 7.6%), but not the mean GGT, remained statistically significant (p=0.014).*

**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=.019; Table 3). Two workers in the Only PCP Chloracne group were found to have hypertrichosis on dermatologic examination (6.5 vs 0.3%; p=.024). These two workers were more likely than the unexposed group to report a history of excess hair growth (6.5% vs 0.7%; p=.045).

A comparison of 24-hour urine porphyrins by exposure subgroups is presented in Table 5. After excluding workers on estrogens and after adjusting for age, gender, race, current alcohol consumption, past mercury exposure, and 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 mcg vs 90.6 mcg; p=.0002) and a higher percentage of abnormal coproporphyrin excretion (67.7% vs 44.0%; p=.001) compared to unexposed in the unadjusted analyses. These differences remained statistically significant in the adjusted analyses. Workers in the Only PCP Chloracne group also had a significantly higher urinary excretion of coproporphyrin compared to unexposed (117.0 mcg vs 90.6 mcg in both the unadjusted (p=.029) and adjusted (p=.002) analyses. The two workers in this group who also had hypertrichosis had mild coproporphyrinuria (149 mcg and 136 mcg/24 hours) with normal urinary excretion of uroporphyrins. The percentage of abnormal urinary coproporphyrin excretion in the Only PCP Chlorance group was also higher than unexposed (61.3% vs 44.0%) but this difference was not statistically significant in either the unadjusted or adjusted analyses. The mean urinary excretion of pentaporphyrin was also significantly higher among workers in the Ever PCP Chloracne (3.3 mcg; p=0.032) and Only PCP Chloracne groups (4.2mcg; p=0.037) compared to unexposed (2.3 mcg) in the adjusted analyses. The percentage abnormal

pentaporphyrin excretion in these groups was higher than unexposed, but these differences were not statistically significant in the adjusted analyses.

**Lipids**

Workers in the Ever PCP Chloracne group were more likely to report a history of elevated blood lipids than unexposed workers (23.1% vs 12.0%; unadjusted p=.019). There were no significant differences in the percentages of workers reporting a history of elevated blood lipids between the unexposed and any of the other exposure subgroups. Table 6 presents the mean values of serum lipids by exposure subgroups. Serum lipids were strongly associated with several confounders, and the tests of significance are only presented for adjusted values. There were no significant differences between the unexposed and any of the PCP exposure subgroups with respect to mean serum concentrations of cholesterol, triglycerides, HDL-C, or LDL-C in the adjusted analyses. There were also no significant differences between the unexposed and these exposure subgroups with respect to apolipoprotein AI, AII, and E in the adjusted analyses. Mean serum apolipoprotein B was significantly higher in the Only PCP group compared to unexposed (135.2 vs 130.9 mg/dl) for days of exposure but not for dichotomous exposure.

**Neurobehavioral**

There were no significant differences in the percentage of participants who reported symptoms of tiredness, weekly headaches, lightheadedness, loss of coordination, difficulty concentrating, confusion, irritability, depression, difficulty falling asleep, unusual sleepiness, or decreased sex interest between the

unexposed and any of the PCP exposure subgroups. A significantly higher percentage of workers in the Ever PCP Group (24.2%) and Only PCP group (26.1%) reported difficulty remembering compared to the unexposed (17.5%), but these differences were not significant after adjusting for age.

Mean values of neurobehavioral test results are presented in Table 7. Neurobehavioral test results were strongly associated with several confounders, and the tests of significance are presented only as adjusted p values. There were no significant differences in vocabulary between the unexposed and any of the PCP exposure subgroups. Tests of memory included Pattern Memory (number correct and latency) and Serial Digit Learning. Workers in the Ever PCP, Only PCP, and Only PCP Chloracne groups had a lower mean number correct on the pattern memory test than unexposed, and these differences were statistically significant for dichotomous exposure but not days of exposure. Pattern memory latency was significantly higher in the Only PCP Chloracne group for dichotomous exposure but not days of exposure. Mean serial digit learning error score was significantly higher for the Ever PCP group compared to unexposed for days of exposure but not dichotomous exposure.

Tests of psychomotor function included Symbol Digit Time, Finger Tapping (right hand, left hand, and alternating), Hand Eye Coordination, and the Continuous Performance Test (CPT latency, false positives, and non-responses). Workers in the Only PCP group had a significantly higher symbol digit time (seconds/digit) than unexposed for days of exposure but not dichotomous exposure. There were no significant differences between unexposed and any of the PCP exposure subgroups with respect to finger tapping with the right or left hand. Workers in the Ever PCP Chloracne group had a significantly lower alternating finger tapping for dichotomous exposure but not days of exposure. CPT latency was significantly longer in the Ever PCP group and Only PCP group compared to unexposed for days of exposure but not dichotomous exposure. Workers in the Only PCP group had a significantly higher mean

number of CPT false positives than the unexposed for both dichotomous exposure and days of exposure. There were no significant differences between the unexposed and any of the exposure subgroups in the mean number of CPT non-response errors. There were also no significant differences between the unexposed and any of the exposure subgroups with respect to visual perceptual ability as measured by pattern recognition latency and number correct.

The Neurobehavioral Evaluation System also included a profile of current (over the past week) mood states. There were no significant differences between the unexposed and any of the exposure subgroups with respect to tension, depression, anger, or fatigue. Workers in the Ever PCP and Only PCP groups had significantly lower (i.e. better) mean scores for confusion than the unexposed for dichotomous exposure but not days of exposure.

**Peripheral Neuropathy**

After adjusting for the effects of age, height, and current alcohol consumption, there were no significant differences between the unexposed and any of the exposure subgroups with respect to symptoms of numbness or tingling in the fingers or toes, or loss of muscle strength in the arms or hands. Difficulty moving fingers or grasping things was significantly associated with days of exposure, but not dichotomous exposure, in the ever PCP group in the adjusted analysis. This symptom was not associated with dichotomous exposure or days of exposure in any of the other exposure subgroups in the adjusted analyses. Pertinent findings from the neurologic examination are presented in Table 3. There were no significant differences between the unexposed and any of the exposure subgroups in the prevalence of absent ankle reflexes or abnormal vibration sensation (tuning fork) in the adjusted analyses. A higher percentage of workers in the Only PCP group had stocking loss of pinprick sensation compared to

unexposed (13.5% vs 7.6%); this difference was statistically significant for dichotomous exposure but not days of exposure. A higher percentage of workers in the Only PCP Chloracne group had a positional tremor compared to unexposed (30.0 vs 8.2%). This difference was statistically significant after excluding workers taking theophylline or epinephrine and after adjusting for age, alcohol, current cigarette smoking, and mercury exposure. Mean values of transformed quantitative sensory thresholds by exposure subgroups are compared in Table 8. Workers in the Only PCP Chloracne group had significantly lower (better) vibration thresholds of the index finger than unexposed in the adjusted analysis when exposure was coded as a dichotomous variable. There were no other significant differences in vibration or thermal thresholds of the dominant index finger and great toe between the unexposed and any of the exposure subgroups in the adjusted analyses.

## 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 over 30 years. Since PCP has an elimination half-life of 30.2 hours[Braun], 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[Pirkle]. The primary hypotheses in this study focused on those health effects which some investigators have reported in dioxin-exposed individuals many years after exposure, specifically chloracne[Butler MG, Stingily, Moses, Suskind, May,Goldman, Pazderova, Poland, Bleiberg, Dugois, Baader, Baxter, OMalley], liver dysfunction[Zober, May, Moses, Mocarelli, Calvert, Pazderova], disorders of porphyrin metabolism[Bleiberg, Pazderova, Doss, Conten], neurobehavioral disturbances[Baur, Poland, Oliver, Pazderova, Lathrop, Hoffman], disorders of lipid metabolism[Oliver, Walker, Martin,

Pazderova, Suskind, and peripheral neuropathy[Treibig, Beader, Bauer, Moses, Pazderova, Pocchiari, Fillipini, Barbieri, Singer]. The design of this study is intended to measure the prevalence of persistent effects years after exposure, and not the incidence of reversible health effects during or shortly after exposure.

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 reviewed the plant medical records of workers who had been engaged in t%w production of PCP between 1951 and 1978[OMalley] 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 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 $\geq$ 365 days. O'Malley selected time intervals ranging from < 0.5 to $\geq$ 10 years.

Chloracne has also been observed in PCP production workers at other plants[Beader, Baxter] and in a worker with prolonged exposure to PCP-treated wood[Cole]. Technical PCP has been shown to produce chloracne in a rabbit ear model while pure PCP does not[Johnson].

*Our Only PCP Chloracne workers had a significantly higher prevalence of elevated gamma*

*glutamyl transpeptidase (GGT > 65 u/l) than the unexposed workers. This difference remained significant after exclusion of outliers and control for potential confounders. While the Only PCP Chloracne workers also had a significantly higher mean GGT than unexposed workers, the difference in means was influenced by two outliers, one of whom had metastatic liver cancer. The difference in means remained significant after exclusion of the worker with metastatic liver cancer, but not after exclusion of both outliers.* Other than GGT, we did not find any significant elevations in liver enzymes or other liver function tests between our exposed groups and unexposed in the adjusted analyses. We did not find any significant differences between our exposure subgroups and unexposed with regards to medical history of hepatitis after employment, jaundice, or cirrhosis. Two workers in our Only PCP chloracne group had abnormal liver consistency on physical exam which was significantly higher than the unexposed.

Previous studies of PCP-exposed workers have not reported increased GGT. Zober did not find elevated GGT among workers producing PCP or applying PCP[Zober]. Jones did not find differences in serum GGT between workers occupationally exposed to PCP and unexposed workers[Jones]. Baxter did not find elevated GGT among workers engaged in the production of PCP and unexposed workers[Baxter]. None of these studies of PCP-exposed workers, however, compared serum GGT of PCP-exposed workers with chloracne to unexposed workers.

Previous studies of TCDD-exposed individuals have observed elevated GGT compared to referent groups. May found elevated GGT levels in TCDD exposed workers with chloracne 10 years after their last exposure to TCDD[May]. Moses et al found significantly higher GGT among TCDD-exposed workers with chloracne compared to those without chloracne[Moses]. Mocarelli et al found mild elevations in GGT in children exposed to the highest concentration of TCDD in the Seveso accident[Mocarelli]. Calvert et al found a significant interaction between TCDD exposure and alcohol with out of range GGT in workers

more than 15 years after last exposure[Calvert]. The mechanism by which TCDD elevates GGT is unknown. Some investigators have suggested that GGT may be a marker of microsomal enzyme induction[Whitfield].

An interesting observation in our study was that the mean serum bilirubin of our Ever PCP workers was significantly lower than in unexposed workers in the unadjusted analysis. This difference did not remain significant after adjusting for age and current alcohol consumption, and we therefore do not consider it to be a statistically significant finding. Two previous studies have noted a decreased bilirubin in PCDD exposed workers. Baxter found a significantly lower total bilirubin among PCP production workers in the United Kingdom compared to unexposed workers[Baxter]. May found a lower serum bilirubin in TCDD exposed workers with chloracne 10 years after last exposure[May]. The mechanism by which PCDDs may lower serum bilirubin is also unknown, though some investigators have suggested that PCDDs may induce bilirubin glucuronyl transferase[May].

Our PCP workers with chloracne had significantly elevated mean urinary excretions of coproporphyrin and pentaporphyrin compared to the unexposed 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 a low grade coproporphyrinuria or a transition constellation to the initial phase of Type A hepatic porphyria. These are the earliest, subclinical stages in Doss's classification of chemically induced chronic hepatic porphyria[Doss].

Studies of porphyrin metabolism in TCDD exposed individuals have yielded conflicting results. In the two plants where workers were found to have clinical porphyria[Bleiberg, Pazderova], hexachlorobenzene may have been a confounding exposure[Jones]. Residents of Seveso have been found to have subclinical

coproporphyrinuria compared to controls[Cantoni]. The only documented cases of porphyria cutanea tarda among Seveso residents occurred in a family with congenital uroporphorinogen decarboxlylase (UROD) deficiency[Doss]. Studies of PCP exposed workers have also yielded conflicting results. Baxter found no abnormalities in the urinary excretion of coproporphyrin, uroporphyrin, and alpha levulonic acid (ALA) among workers engaged in the production of PCP at a plant in the United Kingdom. Pines et al found higher mean urinary excretion of coproporphyrin and ALA in workers employed in wood processing and furniture manufacture compared to controls[Pines]. 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[Maroni].

Animal studies are consistent with the induction of porphyrinuria by exposure to contaminants present in technical PCP. Goldstein et al compared the porphyrinogenic effect of technical (contaminanted with CDDs and CDFs) vs pure PCP in female rats[Goldstein]. Rats fed 500 ppm of technical PCP for 8 months had significant elevations in urinary excretion of coproporphyrin, uroporphyrin, and ALA compared to controls, while 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[Doss] . *The contaminants present in the technical PCP produced at the study plant are listed in Table 1. 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 man*[NTP].

Mean porphyrin levels in our unexposed group were higher than those of many, but not all, previous studies[Nowsir]. This may be due to laboratory procedures, a possibility supported by the high

coefficients of variation of our porphyrin assays. An alternate explanation would be exposure to other porphorinogens, such as alcohol or other chemicals at the plant. Both of these factors would tend to bias the results towards the null hypothesis.

Workers with chloracne who were exposed to PCP in our study had higher levels of serum cholesterol, triglycerides, LDL-cholesterol, apolipoprotein B and apolipoprotein E than persons who were not exposed. These differences, however, were not significant after control for age, gender, use of antihypertensive medication, smoking, diabetes, and alcohol intake. Other studies have yielded conflicting results concerning the effects of PCP exposure on lipid levels. A previous survey at the study plant found a significantly higher percentage of workers with abnormal levels of VLDL and a lower percentage of workers with high levels of HDL, with no differences in triglycerides, cholesterol, or LDL among those with chloracne compared to those without chloracne. Baxter et al noted higher levels of triglycerides and lower levels of HDL-cholesterol, with no significant differences in cholesterol levels, in persons exposed to PCP[Baxter]. The effects were more marked in those with chloracne. In contrast, Jones et al[Jones] found no differences in cholesterol or HDL cholesterol levels and Klemmer et al[Klemmer] found no differences in cholesterol after control for age and ethnicity between persons with and without PCP exposure. Studies of TCDD exposure have also yielded conflicting results with several but not all of the studies noting higher serum cholesterol or triglycerides or lower HDL-cholesterol levels in persons exposed to TCDD [Oliver, Walker, Martin, Pazderova, May, Suskind, Moses]. Suggested mechanisms include decreased binding of LDL to its receptors[Bombick] and decreased lipoprotein lipase activity[Brewster]. We are the first, to our knowledge, to examine the effect of PCP exposure on apolipoproteins.

We did not detect significant differences between PCP-exposed workers and unexposed workers with respect to symptoms of central nervous dysfunction after adjusting for age. Neurobehavioral testing

did not detect any global differences in central nervous system function between PCP-exposed and unexposed workers after adjusting for confounders. We did observe some significant differences in performance on individual tests. Work in the PCP department was associated with slightly slower reaction times on the continuous performance test which is a test of sustained visual attention. PCP exposed workers with chloracne had a lower mean alternating finger tapping than unexposed. PCP-exposed workers had fewer mean number correct on the pattern memory test which is a test of visual spatial memory and significantly poorer scores on the serial digit learning test. On the other hand, PCP exposed workers had significantly lower (better) scores on the mood scale for confusion.

Previous studies of workers exposed to PCP have provided very little data on the central nervous system toxicity of this compound and its contaminants. Bauer described lingering tiredness, depression, apathy, nervousness, mild headaches, sleep disturbances, and a decrease in libido and potency in 7 of 17 workers who were engaged in the production of PCP in West Germany[Bauer]. Klemmer found no significant differences in the age-adjusted prevalence of neuroses in 47 wood treatment workers exposed to PCP compared to unexposed workers[Klemmer]. Interpretation of our neurobehavioral test results is complicated by the large number of tests used to examine the single hypothesis of CNS dysfunction as well as the multiple comparisons among groups. We did not find a consistent pattern of differences with dichotomous exposure, days of exposure, and chloracne. These neurobehavioral findings should therefore be regarded as exploratory and must await confirmation in future studies.

We did not detect significant differences between PCP-exposed workers and unexposed workers with regard to symptoms of peripheral neuropathy. A higher percentage of PCP workers were found to have had a stocking loss of pinprick discrimination on neurologic examination, but this difference was statistically significant only for workers in the Only PCP subgroup for dichotomous exposure and was not

significant for days of exposure. Differences in the percentages of workers with absent ankle reflexes or abnormal vibration sensation on neurologic exam were not statistically significant. There were also no significant differences in adjusted vibratory and thermal thresholds between the exposure subgroups on quantitative sensory testing.

Previous studies have observed an association between occupational exposure to PCP and peripheral neuropathy. Baader and Bauer examined 10 of 17 workers who had been engaged in the production of PCP, all but one of whom had chloracne[Baader]. Eight of these 10 workers gave a history of neuralgic pain in the lower extremities. These investigators did not detect any definite signs of neuritis on physical examination and suggested that neuralgia may be a more appropriate term to describe this condition. The authors cited animal studies which showed slight chromatolysis of nerve cells and diffuse areas of lymphocytic and mononuclear infiltration following chronic poisoning with PCP. In a later review of these same 17 workers, Bauer noted that 9 had symptomatic neuritis and 7 more complained of severe pain in the lower extremities. Four exhibited sensitivity disturbances, 2 had mild pain without atrophy, and 2 had impairment of the Achilles reflex[Bauer]. Triebig measured motor and sensory nerve conduction velocity in 18 workers exposed to PCP[Triebig]. He found a significant decrease of sensory nerve conduction velocities but could not demonstrate a dose response relationship.

Our sole positive finding of stocking decrease in pinprick sensation must be weighed against the lack of significant differences in symptoms and the lack of significant differences on neurologic examination of ankle reflexes and vibration sensation in the lower extremities. It must also be weighed against the lack of significant differences in sensory thresholds for vibration and temperature in the lower extremities, although it is possible that the dissociation of pain and temperature findings may reflect a small fiber neuropathy that is specific for pain conducting fibers. We cannot conclude, on the basis of

this single abnormality, that PCP exposure was causally related to peripheral neuropathy in our group of workers.

An unexpected observation in our study was the significant difference in the prevalence of positional tremor between the Only PCP chloracne group and unexposed workers. This finding remained significant after controlling for confounders. Kleinman described a case of a PCP-exposed worker who complained of trembling hands, temperature intolerance, and chloracne[Kleinman]. *Klawans observed a postural and terminal intention tremor in 35 out of 45 railroad workers involved in the clean-up of a chlorinated phenol spill*[Klawans]. Since this finding was not one of our a priori hypotheses, causal inferences must await data from other studies.

*The major limitations of this study are our reliance on computerized personnel records rather than serum levels of PCDDs and PCDFs as measures of exposure; incomplete follow-up and recruitment of the study cohorts; and low power in the subgroup analyses. Our measures of exposure included ever worked in PCP (Ever PCP), worked in PCP but not in lower chlorinated phenols or agricultural esters (Only PCP), numbers of days in these departments, and use of chloracne as a marker of exposure (Ever PCP chloracne and Only PCP chloracne). While our audit of the computerized personnel database revealed a low error rate on occupational exposure variables (2.3%), other potential sources of misclassification were inherent in our reliance on these work records. 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 departmental classifications. Finally, prior to 1982 the departmental assignments of maintenance workers were not recorded by the company, and the*

*exposures of workers rotating through maintenance jobs were unknown.*

In the absence of serum levels of PCDDs and PCDFs, we have used chloracne as a marker of heavy exposure. Chloracne has been found to be correlated with serum PCDD levels in other studies [Neuberger]. The use of chloracne as a marker of exposure is further supported by previous literature, by the dose response relationship observed with chloracne and duration of exposure in our study, and by the fact that our most consistent findings, the elevation in serum GGT and urinary coproporphyrins, were observed among the subset of PCP workers with chloracne.

*We were able to locate 85% of our exposed cohort and 80% of our unexposed cohort. Seventy three percent of the exposed and 68% of the unexposed who were located participated in the health survey. While these locatability and participation rates are reasonable for a morbidity study with eligibility for inclusion dating back to 1938, the incompleteness of data on all eligible members of the study populations is an important limitation of this study. Also, 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. Negative results should be interpreted with a consideration of the potential for beta error.*

Another limitation of this study is potential confounding from other chemical exposures. The plant under study was also the major producer of polychlorinated biphenyls (PCBs) in the United States. While PCB workers were excluded from our unexposed group, 15.6% of our PCP workers had also been engaged in the production of PCBs, and heavy exposure to PCBs has been associated with coproporphyrinuria[x]. Separation of exposures was attempted in the analysis by stratifying on PCB exposure when positive associations were observed, specifically the elevated GGT and coproporphyrins in the subgroup of PCP

workers with chloracne. Four workers in the Only PCP chloracne group had worked in the production of PCBs. When these 4 workers were excluded from the GGT analysis, there were still significant differences between the Only PCP chloracne and unexposed groups in the mean GGT levels (p=.040) and percent abnormal GGT (p=.008) in the adjusted analyses. These 4 workers had a mean urinary coproporphyrin of 215.2 mcg and a mean urinary pentaporphyrin of 13.3 mcg. When they were excluded from the porphyrin analysis, the differences in mean urinary porphyrins between the Only PCP Chloracne and the unexposed groups, while still higher, were no longer statistically significant. We are therefore unable to determine whether the coproporphyrinuria in our Only PCP chloracne subgroup was due to exposure to PCP alone or a combined effect of PCP and PCBs.

A further 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 towards the null hypothesis. The long lag times between last exposure and time of medical examination limit our ability to study past incident events.

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 which we observed in PCP exposed workers was chloracne. The other findings which we believe are most consistent with current knowledge on the effects of exposure to CDDs and CDFs were the observed elevations in serum GGT and urinary excretion of porphyrins in persons with chloracne. We did not find evidence of a persistent effect of PCP exposure on lipid metabolism or convincing evidence of an association between PCP exposure and

peripheral neuropathy. Other findings, such as subclinical differences in performance on neurobevavioral tests or the presence of positional tremor should be regarded as exploratory observations and must await confirmation in future studies.

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Table 1 Impurities in Technical Pentachlorophenol

| Component | NTP[a] | Goldstein | O'Malley | |
|---|---|---|---|---|
| Phenols | | | | |
| Trichloro | 0.01% | ns | ns | |
| Tetrachloro | 3.8% | 3.0% | ns | |
| Dibenzo-p-Dioxins | | | Mean (n=25) | Range |
| Tetrachloro | – | <0.1 ppm | ns | |
| Pentachloro | ns[b] | <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 | 1380 ppm | 721 ppm | 15-1880 ppm |
| Dibenzofurans | | | Mean (n=8) | Range |
| 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 |

[a] NTP sample: industry composite of technical-grade pentachlorophenol prepared from material supplied by three U.S. manufacturers

[b] ns: not specified

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Table 2 Demographic Characteristics by Exposure Subgroups

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

* $.01 < p \leq .05$
** $.001 < p \leq .01$
*** $p \leq .001$

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Table 3 Pertinent Physical Findings by Exposure Subgroup

| Characteristic | Unexposed | | Ever PCP | | Only PCP | | Ever PCP Chloracne | | Only PCP Chloracne | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) | No. | (%) |
| Hyperpigmentation | 27 | ( 8.9) | 28 | ( 7.7) | 22 | ( 8.5) | 7 | (10.8) | 5 | (16.1) |
| Hypertrichosis[1] | 1 | ( 0.3) | 4 | ( 1.1) | 2 | (0.8) | 3 | ( 4.6)* | 2 | ( 6.5)* |
| Abnormal liver consistency[2] | 1 | ( 0.3) | 4 | ( 1.1) | 4 | (1.5) | 2 | ( 3.1) | 2 | ( 6.5)* |
| Absent right ankle reflex[2,3] | 25 | (8.3) | 48 | (13.1) | 39 | (15.0) | 6 | ( 9.2) | 3 | (9.7) |
| Absent left ankle reflex[2,3] | 23 | (7.6) | 50 | (13.7) | 39 | (15.0) | 8 | (12.3) | 3 | (9.7) |
| Abnormal vibration [2,3] | 125 | (41.4) | 194 | (53.0) | 140 | (53.9) | 30 | (46.2) | 16 | (51.6) |
| Stocking loss of pinprick[2,3] | 23 | ( 7.6) | 50 | (13.7) | 35 | (13.5)* | 12 | (18.5) | 7 | (22.6) |
| Tremor, positional, upper[4] extremity | 23 | ( 8.2) | 44 | (13.2) | 35 | (14.7) | 13 | (21.3) | 9 | (30.0)*** |

[1] Unadjusted p
Dichotomous exposure
* $.01 < p \leq .05$

[2] P value adjusted for age and alcohol
Dichotomous exposure
* $.01 < p \leq .05$
** $.001 < p \leq .01$
*** $p \leq .001$

[3] P value adjusted for age, height, and alcohol and excluding participants with diabetes, renal failure, and neurotoxic medications (chloramphenicol, nitrofurantoin, vincristine, and hydralazine)

[4] P value adjusted for age, alcohol, mercury exposure, and current smoking and excluding participants on theophylline and epinephrine

Table 4 Liver Function Tests by Exposure Subgroups[1]

| Test | Unexposed | Ever PCP | Only PCP | Ever PCP Chloracne | Only PCP Chloracne |
|---|---|---|---|---|---|
| Total Protein (g/dl) | | | | | |
| Mean | 7.14 | 7.12 | 7.12 | 7.12 | 7.18 |
| % < 6.0 | 0.3 | 0.6 | 0.8 | 1.5 | 3.2 |
| Albumin (g/dl) | | | | | |
| Mean | 4.37 | 4.34 | 4.35 | 4.39 | 4.42 |
| % < 3.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Total Bilirubin (mg/dl) | | | | | |
| Mean | 0.60 | 0.55 | 0.56 | 0.58 | 0.59 |
| % > 1.2 | 5.3 | 1.9 | 1.6 | 4.6 | 6.5 |
| GGT (u/l)[2] | | | | | |
| Mean | 35.8 | 36.9 | 36.5 | 52.6 | 74.0** |
| % > 65 | 7.6 | 8.5 | 8.9 | 13.9 | 22.6** |
| LDH (u/l) | | | | | |
| Mean | 161.0 | 165.6 | 164.6 | 167.0 | 167.0 |
| % > 250 | 1.0 | 1.9* | 1.6 | 3.1 | 6.5 |
| SGOT (u/l) | | | | | |
| Mean | 23.0 | 21.7 | 20.9 | 21.5 | 22.1 |
| % > 50 | 3.0 | 1.7 | 0.8 | 1.5 | 3.2 |
| SGPT (u/l) | | | | | |
| Mean | 28.5 | 27.2 | 26.6 | 26.4 | 29.5 |
| % > 55 | 6.0 | 5.8 | 5.4 | 3.1 | 6.5 |
| Alkaline Phosphatase (u/l) | | | | | |
| Mean | 78.0 | 81.8 | 81.8 | 83.5 | 90.5 |
| % > 140 | 2.3 | 3.6 | 3.5 | 3.1 | 6.5 |
| Prothrombin Time (seconds) | | | | | |
| Mean | 12.1 | 12.1 | 12.1 | 12.0 | 12.0 |
| % > 12.7 | 8.5 | 5.9* | 4.3 | 6.4 | 3.3 |

[1] All p values adjusted for age and current alcohol consumption
Dichotomous exposure
** $p \leq .01$
Days of exposure
* $0.01 < p \leq 0.05$

[2] P values for GGT adjusted for age, sex, current alcohol consumption, and body mass index after excluding workers who were taking oral contraceptives, phenobarbitol, dilantin, or coumarin.

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Table 5 Comparison of 24-hour Urine Porphyrins by Exposure Subgroup[1,2]

| Urinary Porphyrin (mcgs) | Unexposed | Ever PCP | Only PCP | Ever PCP Chloracne | Only PCP Chloracne |
|---|---|---|---|---|---|
| Uroporphyrin | | | | | |
| Mean | 24.9 | 25.0 | 23.6 | 27.9 | 22.9 |
| % Abnormal[1] | 8.8 | 9.0 | 7.5 | 10.9 | 3.3 |
| Hepta | | | | | |
| Mean | 3.2 | 3.9 | 3.5 | 4.0 | 3.0 |
| % Abnormal | 1.0 | 2.5 | 1.6 | 3.1 | 0.0 |
| Hexa | | | | | |
| Mean | 1.2 | 1.3 | 1.3 | 1.3 | 1.6 |
| % Abnormal | 1.7 | 1.1 | 1.6 | 1.6 | 3.3 |
| Penta | | | | | |
| Mean | 2.3 | 2.3 | 2.3 | 3.3* | 4.2* |
| % Abnormal | 12.8 | 10.2 | 8.9 | 18.5 | 22.6 |
| Copro | | | | | |
| Mean | 90.6 | 91.9 | 90.9 | 113.2** | 117.0** |
| % Abnormal | 44.0 | 40.1 | 36.8 | 67.7** | 61.3 |
| Porphobilinogen | | | | | |
| Mean | 1.09 | 1.07 | 1.04 | 1.15 | 1.06 |
| % Abnormal | 6.0 | 4.4 | 3.1 | 4.6 | 0.0 |

[1] Abnormal 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

[2] All 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
* $.01 < p \leq .05$
** $p \leq .01$

Table 6 Serum Lipids and Apolipoproteins by Exposure Subgroups[1]

| Test Mg/dl | Unexposed | Ever PCP | Only PCP | Ever PCP Chloracne | Only PCP Chloracne |
|---|---|---|---|---|---|
| Cholesterol | | | | | |
| Mean | 232.2 | 237.0 | 237.7 | 241.6 | 242.9 |
| Triglycerides | | | | | |
| Mean | 176.4 | 179.4 | 175.3 | 204.3 | 224.8 |
| HDL-C | | | | | |
| Mean | 43.9 | 42.6 | 43.0 | 42.3 | 41.3 |
| LDL-C | | | | | |
| Mean | 157.2 | 160.8 | 163.1 | 159.2 | 162.5 |
| Apolipoprotein AI | | | | | |
| Mean | 130.4 | 134.3 | 133.2 | 131.8 | 131.6 |
| Apolipoprotein AII | | | | | |
| Mean | 39.5 | 37.1 | 37.0 | 39.5 | 40.7 |
| Apolipoprotein B | | | | | |
| Mean | 130.9 | 136.6 | 135.2* | 139.5 | 144.2 |
| Apolipoprotein E | | | | | |
| Mean | 5.6 | 5.6 | 5.6 | 6.0 | 6.1 |

[1] P values adjusted for age, gender, BMI, race, HBP drugs, smoking, diabetes, and current alcohol after excluding participants on thyroid, lipid-lowering, and estrogen drugs

Days of exposure

* $p \leq .05$

Table 7 Neurobehavioral Test Scores by Exposure Subgroups[1,2]

| Test | Unexposed | Ever PCP | Only PCP | Ever PCP Chloracne | Only PCP Chloracne |
|---|---|---|---|---|---|
| VERBAL ABILITY | | | | | |
| Vocabulary[3] (# Correct) Mean | 18.5 | 17.8 | 17.3 | 18.5 | 16.7 |
| MEMORY | | | | | |
| Pattern Memory (# Correct) Mean | 12.2 | 11.4* | 11.3* | 11.4* | 11.1 |
| Latency (Seconds) Mean | 6.9 | 7.5 | 7.7 | 7.5 | 8.6* |
| Serial Digit Learning (Score) Mean | 6.2 | 7.4* | 7.5 | 6.5 | 6.9 |
| PSYCHOMOTOR FUNCTION | | | | | |
| Symbol Digit Time (Seconds/Digit) Mean | 3.1 | 3.5 | 3.6* | 3.3 | 3.6 |
| Finger Tapping (Right Hand) Mean | 58.1 | 55.4 | 54.7 | 55.7 | 53.9 |
| Finger Tapping (Left Hand) Mean | 50.8 | 48.1 | 47.2 | 49.1 | 44.7 |
| Finger Tapping (Alternating) Mean | 44.6 | 41.8 | 41.1 | 40.4* | 38.2 |
| Hand-Eye Coordination (Mean Error) Mean | 4.9 | 5.1 | 5.2 | 4.7 | 5.2 |
| CPT[3] (Latency, msec) Mean | 409.2 | 425.7* | 428.6*** | 427.0 | 430.5 |
| CPT (False Positives) Mean | 0.54 | 1.08 | 1.28*,** | 0.70 | 0.95 |
| CPT (Non-Response) Mean | 1.1 | 1.5 | 1.5 | 1.0 | 1.2 |

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Table 7, continued Neurobehavioral Test Scores by Exposure Subgroups[1,2]

| Test | Unexposed | Ever PCP | Only PCP | Ever PCP Chloracne | Only PCP Chloracne |
|---|---|---|---|---|---|
| VISUAL PERCEPTUAL ABILITY | | | | | |
| Pattern Recognition (Latency, msec) Mean | 5.0 | 5.5 | 5.6 | 5.2 | 5.5 |
| Pattern Recognition (Number Correct) Mean | 14.7 | 14.7 | 14.6 | 14.8 | 14.7 |
| MOODS | | | | | |
| Tension (Score) Mean | 2.3 | 2.2 | 2.1 | 2.2 | 2.3 |
| Depression (Score) Mean | 1.6 | 1.6 | 1.6 | 1.7 | 1.7 |
| Anger (Score) Mean | 1.6 | 1.4 | 1.5 | 1.5 | 1.5 |
| Fatigue (Score) Mean | 2.5 | 2.6 | 2.6 | 2.7 | 2.8 |
| Confusion (Score) Mean | 1.9 | 1.8* | 1.8* | 1.8 | 1.9 |

[1] Excluding participants with a history of stroke, head injury with loss of consciousness; those taking antiseizure or psychotropic medications; those who used marijuana or recreational drugs in the past 12 months; those with severe visual problems, illiteracy, or positive saliva alcohol at the time of exam.

[2] All p values, except for vocabulary, adjusted for age, gender, race, schooling, current alcohol, and mercury exposure

Exposed yes/no
* $.01 < p \leq .05$
** $.001 < p \leq .01$
*** $p \leq .001$
Days of exposure
+ $.01 < p \leq .05$
++ $.001 < p \leq .01$
+++ $p \leq .001$

[3] Vocabulary comparisons, were adjusted for age, gender, race, schooling, current alcohol, and mercury exposure

[4] Continuous Performance Test

Table 8 Transformed Quantitative Sensory Tests by Exposure Subgroups[1,2]

| Test | Unexposed | Ever PCP | Only PCP | Ever PCP Chloracne | Only PCP Chloracne |
|---|---|---|---|---|---|
| Vibration Index Finger Mean | -0.12 | 0.13 | 0.15 | -0.09 | -0.24** |
| Vibration Toe Mean | 1.83 | 2.39 | 2.49 | 2.44 | 2.77 |
| Thermal Index Finger Mean | 1.06 | 1.09 | 1.11 | 1.13 | 1.11 |
| Thermal Toe Mean | 1.07 | 1.13 | 1.14 | 1.18 | 1.25 |

[1] Vibratory threshold transormed to $LnV^2/2$; temperature threshold transformed to square root of C°

[2] All p values adjusted for age and height after excluding participants with diabetes, uremia, on neurotoxic medications, and those unable to use their preferred extremity

Dichotomous exposure

** $p \leq .01$