

Occupational exposure to chlorophenates

Renal, hepatic and other health effects

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ENARSON DA, CHAN-YEUNG M, EMBREE V, WANG R, SCHULZER M. Occupational exposure to chlorophenates: Renal, hepatic and other health effects. *Scand J Work Environ Health* 12 (1986) 144–148. A group of 71 chlorophenate-exposed sawmill workers were identified as part of a group undergoing an extensive health and environmental evaluation in a pulp mill. This group was compared with a group (N = 351) with no physical proximity to the area in which chlorophenates were used. Exposure was higher for those directly handling the wood and lower for those working in the area but not handling the wood. Those with chlorophenate exposure were not significantly more likely to report a history of jaundice or liver, kidney or heart disease. Moreover, the serum creatinine, bilirubin, glutamic oxaloacetic transaminase (GOT), and alkaline phosphatase values did not differ from those of the reference group. The hemoglobin level was similar in the three groups. But the peripheral blood leukocyte count was marginally lower in the exposed groups and their hematocrit was reduced, significantly so for the heavily exposed group. Urinalysis showed an increased prevalence of microscopic hematuria, especially with lower cell counts. No unequivocal explanation is available for the reduced hematocrit or the low level of hematuria.

Key terms: hematology, sawmill, serum chemistry, urinalysis.

Chlorophenate compounds have been used increasingly since the 1930s in the coastal lumber industry in our province for antifungal and antisap-stain purposes. Concern over potential health effects of these compounds and the contaminant dioxins contained in them have become sharply focused in recent years. The scientific data addressing these concerns are somewhat incomplete. Prior to these concerns becoming a major issue in labor-management negotiations, a comprehensive health and industrial hygiene survey was conducted by the Occupational Diseases Research Unit, Respiratory Division, Vancouver General Hospital and the Industrial Hygiene Department, Workers' Compensation Board of British Columbia at a pulp, paper, and sawmill in Powell River, British Columbia (BC), between October 1978 and April 1979. One of a number of specific research questions included the health effects of exposure to chlorophenates used in the sawmill division.

Subjects and methods

Study population

The total available workforce (2 090 persons) in a large pulp, paper, and sawmill was invited to participate in

the study, of whom 1 932 (92 %) participated. Only the results of white males are presented in this report.

The sawmill uses an in-line high-pressure spray box for chlorophenate application to control sap stain. Treatment occurs immediately before the grading, pulling, and stacking of lumber. The mill has a horse-shoe-shaped line, resulting in proximity to the spray box for some positions not immediately pre- or post-treatment in work organization.

The workers were grouped according to levels and routes of exposure to chlorophenates as follows:

1. Control or reference group consisting of those working in areas where there were no identifiable air contaminants (mostly the log pond and office). Only those who had not changed jobs since first being employed were included. This group totaled 351.
2. Airborne exposure group consisting of those working in close proximity to recently treated lumber but not in manual contact with it. The group included slasher helpers, slasher trim helpers, trimmer spotters, and some day cleaners. This group totaled 31.
3. Dermal exposure group consisting of those manually handling recently treated lumber. This group included pullers, grade deck sorters, graders, and stencilmens; it totaled 40.

Health survey

Individuals enrolled in the study were asked for informed consent. They then underwent the following procedures.

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Questionnaire. Trained interviewers administered a standardized questionnaire including sections on present and lifetime health problems (8), personal and life-style characteristics, and occupational history.

Life-style information included smoking history, frequency of alcohol intake during the past 12 months, and daily alcohol intake during the 7 d preceding the interview. The average number of drinks per day was calculated. One bottle of beer (12 oz or 0.36 l), one glass of wine (4 oz or 0.12 l), or one measure of hard liquor was regarded as one drink. As the alcohol consumption over the previous year was highly correlated with alcohol consumption over the week prior to the study (correlation coefficient 0.9), we have used the latter measure in our calculations.

Physical examination. A limited physical examination was carried out including measurement of height, weight, and blood pressure.

Table 1 indicates the characteristics of the various groups. The exposed groups were younger and had less seniority than the reference group. Blood pressure levels matched the differences in age. A higher proportion of the exposed groups comprised current smokers. There was no difference in alcohol use.

The participants reported a history of a number of conditions: jaundice 6.7 %, liver disease 3.0 %, kidney disease 5.2 %, heart disease 3.9 %, and skin rash 7.3 %. Several (15.2 %) were currently on medication of one sort or another: antihypertensives 4 %; sedatives 2 %; antibiotics 2 %; antihistamine 1.7 %; anti-asthma medications 1.9 %. The distribution of these was similar among the three exposure groups.

Laboratory tests

Fifteen milliliters of blood was obtained from each worker for the measurement of hemoglobin, hematocrit, white blood cell count (WBC), serum protein, blood urea nitrogen (BUN), creatinine, total bilirubin, serum glutamic oxaloacetic transaminase (SGOT), and alkaline phosphatase. The hemoglobin, hematocrit, and leukocyte counts were performed on a Coulter-S® analyzer. Total bilirubin was measured by a manual Jendrassik-Groff method. SGOT, alkaline phosphatase, creatinine, and BUN were measured with an Abbott® ABA-100 with Spin-Chem® reagents from

Smith-Klein Laboratories. Total protein was measured by the Biuret method.

Urine specimens were obtained from the subjects during the survey. They were examined by the same technician in the routine laboratory of the local hospital within 2 h of collection. Chemical urinalysis was by "Multistix", Ames Co. (Division of Miles Laboratories) Elkhart, Indiana. For microscopy, 10 ml of well-mixed urine was centrifuged at 3 000 r/min for 10 min, the sediment was examined, and cells were enumerated per high-power field (HPF × 400), while casts were counted per low-power field (LPF × 100).

Exposure assessment

The airborne levels of chlorophenates were assessed by personal monitors carried by individual workers over the period of one workshift. Individuals were selected to represent the variety of occupational exposures to chlorophenates throughout the mill.

Urine samples were collected from a small number of individuals working in the areas where the wood treatment was carried out. Chemical analysis for unbound pentachlorophenate and tetrachlorophenate (PCP/TCP) in urine was conducted in a standard manner (3, 9, 10) by the Industrial Hygiene Laboratory of the Workers' Compensation Board of British Columbia.

A minimum of 100 ml of urine was collected from each worker before the beginning of the workshift. Samples were collected in disposable sterilized wide-mouthed plastic bottles individually packaged in clean plastic bags.

Sample preparation consisted of acidification of 2 ml of urine and extraction with 2 ml of toluene. Two microliters of the toluene extract was then injected into a gas chromatograph equipped with an electron capture detector. Each chlorinated phenol was identified and quantified by comparison with calibration graphs. Urine samples with a specific gravity greater than 1.012 were converted to a standard specific gravity of 1.024 during the final calculation of the corrected PCP/TCP values.

The levels of chlorophenates in serum were determined at the BC Research Laboratory for five individuals in each of the three groups. The serum sam-

Table 1. Personal, employment, and life-style characteristics of the exposure groups.

Group	Total number	Smokers		Alcohol users		Age (years)		Duration of employment (years)		Diastolic blood pressure	
		Never	Current	Never	Heavy					mmHg	kPa
		N %	N %	N %	N %	Mean	SD	Mean	SD	Mean	SD
Airborne exposure	31	5 16	17 55	8 26	6 19	36	10	9	4	80	11
Dermal exposure	40	9 23	27 68	8 20	6 15	28	8	5	3	72	9
Reference	351	100 28	151 43	66 19	44 13	39	14	10	10	79	12
										10.5	1.6

Table 2. Levels of total chlorophenates ($\mu\text{mol/l}$) measured in the environmental and biological samples of the subjects.

Group	Source sample								
	Air			Urine			Serum		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Airborne exposure	12	0.156	0.086	3	0.512	0.241	5	1.394	1.449
Dermal exposure	10	0.149	0.110	3	0.932	0.029	5	3.580	1.821
Reference	..	..	..	..	..	..	5	0.331	0.055

Table 3. Hematologic values of the workers according to exposure to chlorophenates.

Variable	Total exposed population		Airborne exposure		Dermal exposure	
	Mean	SD	Difference from the mean	95 % confidence interval	Difference from the mean	95 % confidence interval
Hemoglobin (g/dl)	15.31	0.89	0.08	-0.25— +0.41	-0.12	-0.42— +0.18
Hematocrit ^a (%)	44.07	2.61	-0.47	-1.43— +0.47	-1.08	-1.96— -0.20
Leukocytes ^b (N)	7 533	1 919	-198	-459— +856	-1 480	-1 085— +125

^a Adjusted for age, smoking, and alcohol consumption.^b Adjusted for age and smoking.**Table 4.** Values of variables measured in the serum of the exposed workers.

Variable	Total exposed population		Airborne exposure		Dermal exposure	
	Mean	SD	Difference from the mean	95 % confidence interval	Difference from the mean	95 % confidence interval
Total protein ^a ($\mu\text{mol/l}$)	1 025.9	521.6	14.5	-4.4— +34.8	-2.9	-21.7— +14.5
Creatinine ^b ($\mu\text{mol/l}$)	97.2	15.0	4.4	-0.9— +10.6	25.6	-2.7— +8.0
Blood urea nitrogen ^b ($\mu\text{mol/l}$)	5.6	1.4	0.3	-0.2— +0.9	0.1	-0.4— +0.6
Total bilirubin ^c ($\mu\text{mol/l}$)	10.4	4.8	-0.5	-2.2— +1.4	0.5	-1.2— +2.1
Glutamic oxaloacetic transaminase ^{d, e} (kat/l)	42.1	19.7	-5.5	-12.7— +1.7	-1.8	-8.5— +4.8
Alkaline phosphatase ^{a, e} (kat/l)	103.5	28.6	-5.2	-15.7— +5.3	-3.0	-12.7— +6.7

^a Adjusted for age and smoking.^b Adjusted for age, smoking, alcohol consumption, and diastolic blood pressure.^c Adjusted for alcohol consumption and smoking.^d Adjusted for age, smoking, and alcohol consumption.^e Values are 10^{-8} .

ples, frozen and stored at -70°C , were randomly selected within each category and submitted for analysis in a blinded manner. Acidified samples were extracted with toluene, the extract was dried with anhydrous sodium sulfate (Na_2SO_4), and the solvent was removed in a stream of nitrogen. The extracts were then methylated with diazomethane and analyzed for pentachloro- and tetrachlorophenates with a Hewlett Packard model 5710A gas chromatograph equipped with an electron capture detector. The column specifications were: 15 m of fused silica (wall-coated, open tubular, 0.20-mm inner diameter, silicon compound SE52); temperature 175°C ; inlet pressure 20 psi (139 kPa) 95:5 argon:methane. Aldrin and/or dieldrin was added as an internal standard. There was

insufficient serum to check recoveries, but this analytical procedure routinely gives better than 90 % recovery on a wide range of aqueous samples.

The levels of chlorophenates in biological samples are reported in table 2. The dermal exposure group had the highest measured levels; their values in serum were about ten times higher than those of the referents and three times higher than those of the airborne exposure group. In urine, the dermal exposure group had values almost twice as high as those of the airborne exposure group. It should be noted however that these findings were based on only three urine samples and five blood samples from each exposure group and that the standard deviation about the mean was large, particularly for the serum results.

Statistical analysis

Statistical analysis was carried out with the analysis of variance chi-square and regression analysis, as appropriate. Previous publications (4, 6) have shown that the serum and urine tests may have been influenced by factors other than those under study. For determining the effect of exposure to chlorophenates, we compared the exposed groups with the reference group after adjustment using direct standardization for potential confounding variables.

Results

The hematology measurements in the studied population are summarized in table 3. The hemoglobin and the leukocyte counts were adjusted for age and tobacco smoking habit; hematocrit was additionally adjusted for alcohol habit with the use of multiple regression. The table indicates the mean value for the studied population and the residual value for each of the exposed groups after adjustment for the mentioned variables. The hemoglobin level shows no consistent pattern in relation to exposure and is not significantly different among the groups. Both the hematocrit and the leukocyte count, however, were lower in the exposed groups and showed a dose-response relationship with exposure. The difference was statistically significant only for hematocrit in the dermal exposure group.

Table 4 displays, in a similar fashion, the results of serum chemistry measures. There were no consistent dose-response relationships, and none of the differences were statistically significant. Table 5 gives the results of the multiple logistic regression analysis of the urinalysis measurements in the study population. Erythrocytes were more common in the urine of the exposed workers, and this excess showed a dose-response relationship, most marked for fewer numbers of erythrocytes per high-power field and statistically significant only for the heavily exposed group.

Discussion

Studies investigating chlorophenolate exposure have been reported for pesticide and wood treatment workers in a variety of regions. Health concerns have recently been raised by the case-referent studies arising out of the observation of a number of soft-tissue sarcomas clustered among workers exposed to the chemical in Sweden (7).

Intensity of exposure appears to vary substantially across regions and workplaces. Bevenue et al (2) reported on pesticide-exposed subjects in Hawaii with biological levels of pentachlorophenol about 10 times those reported in the present study. The referents in the Bevenue study had levels comparable to the airborne group in the present report. Cranmer & Freal (5) reported on pesticide handlers in Florida with levels similar to those of the present study. Wood et al (13) reported on five cases of pentachlorophenol poisoning,

Table 5. Urinalysis measurements according to exposure to chlorophenates. (HPF = high-power field)

	Prevalence (%)	Odds ratio	
		Airborne exposure group	Dermal exposure group
Protein > trace ^a	7.2	0.11	0.89
Leucocytes			
> occasional/HPF ^b	46.0	1.88	1.10
> 5/HPF ^b	8.7	0.38	0.10
Erythrocytes			
> occasional/HPF ^c	18.9	6.36	7.45*
> 3/HPF ^c	7.7	2.53	2.95

^a Adjusted for smoking and diastolic blood pressure.

^b Adjusted for age and alcohol consumption.

^c Adjusted for age and smoking.

* $p < 0.05$.

including two fatalities, occurring in two small wood preservative plants in the United States.

Sterling et al (11) found self-reported ill-health effects (dermatologic, respiratory, and neurological) among British Columbia sawmill workers, and more ill health was reported at higher levels of exposure. Takahashi et al (12) reported a significantly increased prevalence of C-reactive protein in 14 chlorophenolate-exposed pesticide workers in Hawaii in comparison to that of a group of 34 referents. Begley et al (1) found lower than expected levels of creatinine clearance prior to vacation in a group of 18 wood treatment workers, with significant improvement after 20 d of vacation. Tubular reabsorption of phosphorus, a measure of renal tubular function, was also lower than expected prior to vacation but showed no improvement. Wylie et al (14), studying, over a period of months, a group of six workers involved in the production of chlorophenates in Idaho, reported the occurrence of chromosome aberrations in this group more frequently than in four unexposed subjects.

For the majority of the parameters we studied, workers exposed to chlorophenates appear quite similar to their colleagues working in the same plant but not exposed to chlorophenates. The exceptions are certain hematology and urinalysis measurements. The observation of lower hematocrit in the presence of no differences in hemoglobin levels would suggest a difference in hemoconcentration. There is no obvious explanation for this difference however. The degree of physical activity and the temperature of the work area are not obvious explanations. The lower leukocyte counts in exposed workers might suggest bone marrow suppression, but these differences were not statistically significant. In addition the association of a low level of hematuria with the more heavily exposed group is not easily explained.

Acknowledgments

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