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Reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry

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Objectives The purpose of the study was to determine whether paternal occupational exposure to dioxin-contaminated chlorophenols is associated with an increased risk of congenital anomalies or other adverse reproductive outcomes in offspring.

Methods As a result of a multistep linkage, 19,675 births between 1952 and 1988 were identified as children of a cohort of 9,512 fathers who had worked at least one year in British Columbia sawmills where chlorophenate wood preservatives had been used. A nested case-referent analysis was applied, using conditional logistic regression, with five referents matched per case according to year of birth and gender. Chlorophenate exposure was based on expert raters’ estimations of hours of exposure applied to specific time windows prior to birth.

Results The offspring of male sawmill workers were at increased risk for developing congenital anomalies of the eye, particularly congenital cataracts; elevated risks for developing anencephaly or spina bifida and congenital anomalies of genital organs were shown according to specific windows of exposure. No associations were found for low birthweight, prematurity, stillbirths, or neonatal deaths.

Conclusions The study adds further support to the hypothesis of male-mediated developmental toxicity. Paternal exposure to chlorophenates was associated with the development of certain congenital anomalies in offspring.

Key terms abnormalities, dioxins, epidemiology, occupational exposure, reproduction.

Chlorophenates have been widely used as antisapstain fungicides during wood storage and transport. These dioxin-contaminated commercial solutions contained mixtures of sodium tetrachlorophenates and pentachlorophenates and were used in the sawmills of British Columbia (BC), Canada, from the 1940s until 1989. Workplace exposure to these dioxin-contaminated substances occurred through skin contact with the liquid solution at dip tanks and spray booths, with the chlorophenate-soaked lumber, and with equipment during maintenance, as well as through the breathing of chlorophenol vapor, aerosols, or contaminated sawdust (1—3). Concerns regarding the potential health effects of chlorophenols and dioxins and restriction by foreign markets provided the impetus to stop their use in sawmills.

Both tetrachlorophenol and pentachlorophenol are mutagenic according to in-vitro testing (4). Animal studies of pentachlorophenol and dioxins have demonstrated fetotoxicity, with soft-tissue and skeletal anomalies developing after maternal exposure (5—6). Epidemiologic studies of reproductive effects have focused on a broad class of substances contaminated by chlorinated dioxins. The most studied occurrence of dioxin contamination is the result of war-time activities in Vietnam, when Agent Orange and other defoliants were widely used. An increase in the incidence of stillbirths and malformations such as spina bifida and cleft palate were found among the progeny of those living in the areas of heaviest defoliation (7).

The potential for paternal exposures affecting reproductive outcomes among offspring has been documented for a variety of toxicants. In this regard, the laboratory (8) and epidemiologic studies of dioxin-like substances have been inconclusive. A survey of wives of employees

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exposed to chlorinated dioxins found no associations between adverse pregnancy outcomes and paternal dioxin exposure (9). A report concerning exposure of American male veterans to the herbicide Agent Orange found elevated risks of spina bifida and cleft lip with or without cleft palate in their offspring (10). A subsequent study showed an elevated risk of offspring having one or more major malformations (11). Others have found no elevated risks in offspring related to paternal exposure to dioxin-containing herbicides during the Vietnam war (12, 13).

A recent case-referent study used the BC population-based register of birth outcomes to identify which paternal occupations were associated with birth defects in offspring (14). The fathers' usual occupation at the time of birth, available for the period 1952 to 1973, was obtained from the birth certificates. An analysis of 20 categories of birth defects showed that sawmill workers specifically had an elevated odds ratio (OR ≥ 1.5) of fathering children who were affected with patent ductus arteriosus, "other heart defects," congenital dislocation of the hip, cleft lip, or obstructive renal defect.

Because of these findings, the following question was posed in relation to a cohort of BC sawmill workers: Are paternal occupational exposures to chlorophenolic wood preservatives associated with an increased risk of congenital anomalies, stillbirths, prematurity, low birthweight, or perinatal mortality among their offspring?

**Subjects and methods**

**The British Columbia sawmill cohort**

The cohort consisted of 23,829 sawmill production and maintenance workers from 11 chlorophenate-using mills in British Columbia (15). All the workers had been employed for at least one year in a study mill between 1 January 1950 and 31 December 1985. Personnel records were accessed to obtain job history and personal identifying information.

As historical chlorophenate measurements were not available for this cohort, 10 or more experienced workers independently rated the exposure of each job title for a specific "exposure-constant" time period during which the same chlorophenate application process and formulation were used (16, 17). On the average, 92 job titles were rated for each period in each mill. The average frequency (f = days per year) and duration (d = hours per day) of exposure to chlorophenate were multiplied to give an index of exposure for each job title, "exposure hours per year" (I = fd). The index was then multiplied by the number of years spent in a particular job (t). When summed over all of the individual worker's job titles over a specific window of time, the index yielded a cumulative value of total hours of exposure to chlorophenates (E = Σ Ij·tj).

Continuous estimates of cumulative hours of exposure to chlorophenates were calculated for the following three time windows: (i) exposures up to three months prior to conception (CUM1), (ii) exposures in the three months prior to conception (CUM2), and (iii) exposures through the entire period of pregnancy (CUM3). Maximal indices of exposure (hours of chlorophenate exposure per year) were determined for the most-exposed job in each period. Because of high correlations between the shorter periods (r = 0.91 and 0.96 for the correlation of CUM2 and CUM3 with MAX2 and MAX3, respectively), the effects of maximal exposures were analyzed for the first period (MAX1) only.

**Data file linkages**

We performed a probabilistic linkage (18) of sawmill cohort records with the live and stillbirth records maintained by the BC Division of Vital Statistics, for the period 1952 through 1988 inclusive. In an attempt to improve upon the fathers' personal identifiers, an intermediate step was to link the cohort records with the marriage register. The personal identifiers used for the linkages were father's full name and birthdate, and, when available, the wife's first name and birthdate. All birth registrations include information from the "Physician's Notice of Birth" which included birthdate, gender, gestational age, and birthweight of the offspring. Information on such characteristics as parity and ethnic group were not consistently recorded in the notice and were therefore not included in the analyses.

The BC Health Surveillance Registry was established in 1952 with a mandate to "ascertain, record, and classify handicapping conditions, congenital anomalies, and genetic defects in the population" (19). Over 60 registering sources, including government agencies concerned with health and human resources, hospitals, treatment and rehabilitation centers, voluntary agencies, physicians and the vital registration system, all forward pertinent information to the registry. The disease conditions are coded according to the ninth edition of the International Classification of Disease (ICD-9) (20). The registry's records up to 1988 were directly matched to the birth registration records, using unique birth registration numbers. A total of 18 linkages were excluded due to discrepancies between the physician's notice of birth and the records of the Health Surveillance Registry for both the birthdate and the gender of the child; 45 with inconsistent matches for parents' ages were retained in the analyses.

**Statistical analyses**

In order to make the analysis of the data more manageable, in view of the large number of outcomes being examined, a nested case-referent strategy was adopted.
For the analysis of congenital anomalies, the calendar year of birth and the gender of the newborn were used as matching variables. Five referents were matched to each case and were selected from all the offspring at risk when the case occurred. Only children born after their father had started work at the sawmill were included in the analyses. Conditional logistic regression using matched sets was applied (21), using the statistical package EGRET (22). The exposure variable of interest (treated as continuous) was forced into the model, while the covariates “mother’s age” and “father’s age” were subsequently entered together. The dependant variables were all congenital anomalies to the third digit of the ICD-9 classification, where there was a minimum of 20 cases among the cohort.

For the birth outcomes of prematurity, low birthweight, small for gestational age, stillbirth, and neonatal morality, for which there was a greater number of occurrences, matching was based on birth year of the newborn only, gender being treated as an additional covariate in the regression model. For low birthweight, further adjustment was made according to gestational age groupings, while, for neonatal deaths, further adjustment was made for gestational age and birthweight groupings. Small for gestational age was defined as less than the 10th percentile based on the distribution for BC newborns (23); because of the large number of cases, two referents were matched to each case. Prematurity was defined as having been born at less than 37 weeks’ gestation, low birthweight was defined as less than 2500 g, and neonatal death was defined as death of a liveborn infant before the age of one year. Stillbirths were of at least 28 weeks’ gestation and were not included in the analysis of any other outcomes.

Children in the same family born subsequent to an affected child were not used either as a case or as a referent. Thus siblings could not be chosen as referents of a case. Twins with the same outcome were counted as a single birth event, such that one case of the pair would be selected randomly and treated as a case. If twins were selected as a referent, one twin was randomly chosen. For the analysis of prematurity, low birthweight, small for gestational age, twins, and triplets were excluded from the study base, a total of 19 675 newborns fathered by 9512 cohort members were eligible for further study (table 1). Multiple births were recorded; a total of 203 pairs of twins and 3 triplet groups were born. For 48.3% of the fathers, only one child was born in the study period since they had begun work at the sawmill.

A description of the four measures of chlorophenate exposure is given in table 2. During the three-month period prior to conception (CUM2), 54.7% of the fathers had no exposure. In table 3 the adjusted relative risk estimates, based on differences in estimated chlorophenate exposure of 100 h, are presented for stillbirths, small for gestational age, prematurity, and neonatal deaths. None of the exposure variables were positively related to any of these major reproductive health indicators.

### Table 1. Characteristics of the 19 675 infants (48.6% boys, 51.4% girls) born to the cohort of sawmill workers since the start of employment.

| Characteristic          | Mean      | Median | SD   | Range     |
|------------------------|-----------|--------|------|-----------|
| Birth year             | 1970      | 1970   |      | 1952–1988 |
| Gestational age (weeks)| 39.6      | 40     | 1.9  | 16–46     |
| Birthweight (g)        | 3389      | 3400   | 575  | 180–5700  |
| Maternal age (years)   | 26.5      | 26     | 5.5  | 13–45     |
| Paternal age (years)   | 30.0      | 29     | 8.2  | 17–66     |

### Table 2. Estimated cumulative hours of exposure to chlorophenates (CUM1 to CUM3) and the maximal index of exposure (MAX1) variables. (CUM1 = estimated cumulative hours of exposure up to three months prior to conception, CUM2 = estimated cumulative hours of exposure in the three months prior to conception, CUM3 = estimated cumulative hours of exposure through the entire period of pregnancy, MAX1 = maximal index of exposure (hours per year) for any sawmill job held up to three months prior to conception)

| Mean  | Median | Interquartile range | Range  |
|-------|--------|---------------------|--------|
| CUM1  | 3130.8 | 1915                | 794–4081| 0–44977 |
| CUM2  | 65.2   | 0                   | 0–151  | 0–582  |
| CUM3  | 288.0  | 6                   | 0–503  | 0–5152 |
| MAX1  | 1101.7 | 1186                | 706–1533| 0–2000 |
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Table 3. Relative risks for major reproductive health indicators associated with each 100 h of estimated exposure to chlorophenates. (CUM1 = estimated cumulative hours of exposure up to three months prior to conception, CUM2 = estimated cumulative hours of exposure in the three months prior to conception, CUM3 = estimated cumulative hours of exposure through the entire period of pregnancy, MAX1 = maximal index of exposure (hours per year) for any sawmill job held up to three months prior to conception, OR = odds ratio, 95% CI = 95% confidence interval)

| Health indicator | Number of cases analyzed | CUM1 OR (95% CI) | CUM2 OR (95% CI) | CUM3 OR (95% CI) | MAX1 OR (95% CI) |
|------------------|-------------------------|-----------------|-----------------|-----------------|-----------------|
| Prematurity      | 857                     | 1.00 (0.99-1.001) | 0.99 (0.93-1.005) | 0.96 (0.94-0.98) | 0.99 (0.98-1.003) |
| Small for gestational age | 2128             | 1.00 (0.99-1.001) | 1.00 (0.96-1.004) | 1.01 (0.99-1.02) | 1.00 (0.92-1.01) |
| Low birthweightsa | 848                  | 1.00 (0.99-1.000) | 1.01 (0.97-1.00)  | 0.99 (0.97-1.01) | 0.99 (0.97-1.01) |
| Stillborn         | 159                   | 1.00 (0.97-1.06)  | 1.08 (0.94-1.15)  | 1.00 (0.96-1.04) | 1.01 (0.95-1.08) |
| Neonatal deathsa  | 300                   | 1.00 (0.99-1.001) | 1.02 (0.89-1.17)  | 1.02 (0.98-1.06) | 1.00 (0.96-1.02) |

a Adjustment was made for the gender of the infant, maternal and paternal age; matching was based on birth year.

b Gestational age was used as an additional covariate.

c The gestational age and birthweight groupings were used as additional covariates.

Table 4. Relative risks for congenital anomalies for each 100 h of estimated exposure to chlorophenates. (CUM1 = estimated cumulative hours of exposure up to three months prior to conception, CUM2 = estimated cumulative hours of exposure in the three months prior to conception, CUM3 = estimated cumulative hours of exposure through the entire period of pregnancy, MAX1 = maximal index of exposure (hours per year) for any sawmill job held up to three months prior to conception)

| Congenital anomalies | Number of cases analyzed | Odds ratio |
|----------------------|--------------------------|------------|
|                      | CUM1                     | CUM2 | CUM3 | MAX1 |
| Anencephaly or spina bifida (740, 741) | 22 | 1.01 | 1.17 | 1.04 | 1.11** |
| Other nervous system (742) | 33 | 1.01 | 1.22 | 1.08 | 0.99 |
| Eye (743) | 22 | 1.01* | 2.01** | 1.21** | 1.04 |
| Ear, face and neck (744) | 26 | 1.01 | 1.07 | 0.98 | 1.02 |
| Bulbus cordis (745) | 38 | 1.00 | 0.94 | 0.99 | 0.95 |
| Other heart (746) | 38 | 1.00 | 1.00 | 0.99 | 0.99 |
| Other circulatory system (747) | 57 | 1.00 | 1.00 | 1.01 | 0.98 |
| Respiratory system (748) | 20 | 1.00 | 0.58 | 0.94 | 0.98 |
| Cleft palate or cleft lip or both (749) | 29 | 1.00 | 1.12 | 1.06 | 0.98 |
| Upper alimentary tract (750) | 39 | 1.00 | 1.00 | 0.98 | 0.98 |
| Digestive system (751) | 19 | 1.00 | 0.67 | 0.93 | 0.98 |
| Genital organs (752) | 105 | 1.00 | 1.11 | 1.05* | 1.00 |
| Urinary system (753) | 39 | 1.00 | 0.94 | 1.01 | 0.95 |
| Musculoskeletal deformities (754) | 214 | 1.00 | 1.01 | 1.01 | 1.01 |
| Other limb (755) | 43 | 1.00 | 1.07 | 1.04 | 0.93* |
| Other musculoskeletal (756) | 51 | 1.00 | 1.21 | 1.02 | 0.98 |
| Other integumental (757) | 34 | 1.00 | 0.87 | 0.98 | 0.99 |
| Chromosome anomalies or syndromes (758) | 38 | 1.00 | 0.91 | 0.95 | 1.01 |

a Code of the International Classification of Diseases (ninth revision) in parentheses.

b P < 0.05.
c P < 0.005, based on conditional logistic regression analyses, matching for gender and year of birth and adjusting for maternal and paternal age.

tween high paternal exposures to chlorophenates during preconception and pregnancy and congenital cataracts was observed. The fathers with higher cumulative exposure in the three-month period before conception had 5.7 times the risk of having infants with congenital cataracts. The risk of having children with cataracts was greater than that for eye congenital anomalies in general; this finding suggests that congenital cataracts are the specific outcome of concern. By comparison, the relative risks found for spina bifida and undescended testicle did not differ very much from that found for their three-digit categories. Elevated risks for developing these congenital anomalies were seen for one window of exposure only. The categorical analysis showed a dose-response gradient of risk for the associations found to be signifi-
The seminal fluid transfer of chemicals or have been demonstrated for a variety of agents (27). Direct genetic effects on offspring are either direct germ-cell effects or indirect transmission of agents (25). Direct genetic effects on male germ cells are primarily intragenic mutations, while effects on the eye and genital organs (data not shown). When total days of employment was tried as an exposure variable, other than a positive but weaker association with congenital anomalies of the eye, none of the selected congenital anomalies were related.

**Discussion**

Exposure to chlorophenates was positively related to congenital anomalies of the eye and genital organs, and to anencephaly and spina bifida in the progeny of the exposed male sawmill workers. The large size of our sawmill cohort gave sufficient power to analyze many adverse reproductive outcomes with low prevalence, including some congenital anomalies coded according to the four-digit ICD classification. The highest relative risk for the offspring of the sawmill cohort was an OR of 5.68 when the exposed sawmill workers (28). Another indirect route of exposure may be by household contamination with substances brought home by the father, although this mechanism is less well documented (29).

Pentachlorophenol has been detected in the semen of exposed sawmill workers (28). Another indirect route of exposure related to time windows or critical periods (30) related to time of conception and birth. An embryo or fetus exhibits different susceptibilities and responses to chemical exposure depending on its developmental state at the time of exposure. In a study on Wilms’ tumor (31), separate analyses were conducted for employment at any time prior to pregnancy (preconception), and one year prior to and including birth (pregnancy). We further refined the analysis by dividing the exposure period according to the three months prior to estimated conception (spermatogenesis) and the period of pregnancy. We were unable to distinguish exposures occurring during the first three months of pregnancy from the rest of the pregnancy because of the high correlations between the exposure measures. The positive findings for anencephaly or spina bifida and for congenital anomalies of the genital organs were specific to particular periods of exposure (the maximal index of exposure in the preconception period and cumulative estimate exposure during the pregnancy period, respectively). Elevated risks were found for congenital anomalies of the eye for each of the cumulative exposure periods (up to 3 months prior to conception, spermatogenesis and pregnancy). This increased risk may be explained in part by the correlation between measures, particularly for the short periods (r = 0.86).

The use of a standardized health surveillance register allowed us to ascertain adverse reproductive outcomes without introducing selection bias. The BC Health Surveillance Registry has nearly 100% reporting through multiple sources and emphasizes the quality control of diagnoses. Matching infants by year of birth in the case-referent analysis further ensured the consistency of follow-up of the cases with matched referents.

| Congenital anomalies | Number of cases | CUM1 OR95%CI | CUM2 OR95%CI | CUM3 OR95%CI | MAX1 OR95%CI |
|----------------------|----------------|-------------|-------------|-------------|-------------|
| Spina bifida or anencephaly (740, 741) | 22 | 1.20 0.9–1.5 | 1.27 0.8–2.0 | 1.24 0.8–2.0 | 2.38 1.1–5.3 |
| Spina bifida (741) | 18 | 1.18 0.8–1.8 | 1.32 0.8–2.1 | 1.31 0.8–2.2 | 1.8 0.8–4.1 |
| Eye (743) | 22 | 1.47 1.1–2.9 | 2.97 1.5–5.6 | 2.29 1.4–4.8 | 1.4 0.7–2.8 |
| Cataracts (743.3) | 11 | 1.48 0.9–2.4 | 5.68 1.4–22.6 | 4.34 1.4–13.8 | 2.32 0.7–2.9 |
| Genital organs (752) | 106 | 1.08 0.9–1.3 | 1.29 0.9–1.5 | 1.3 1.0–1.7 | 1.03 0.8–1.4 |
| Undescended Testicle (752.5) | 57 | 1.19 0.9–1.5 | 1.16 0.8–1.6 | 1.4 1.0–1.9 | 1.25 0.8–1.9 |

a Based on conditional logistic regression analyses, matching for gender and year of birth and adjusting for maternal and paternal age.

b Code of the International Classification of Diseases (ninth revision) in parentheses.
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There remains the distinct possibility of exposure misclassification. Such nondifferential misclassification would be expected to bias the risk estimates towards the null. Studies of adverse reproductive outcomes in the offspring of dioxin-exposed male cohorts have usually relied on broad categories of exposure, with workers in a specific industry grouped together. We were able to estimate chlorophenate exposures within the sawmill cohort using a validated system of expert worker raters (16, 17).

Other potential exposures at the sawmill, such as diesel exhaust, asbestos, or sawdust, were not considered in this study. Duration of work at the mill during the preconception period, which may have some relationship to consistent mill exposures such as sawdust, was not found to be related to any of the adverse reproductive outcomes that were positively related to chlorophenol exposure. Therefore it seems likely that chlorophenates, rather than other exposures, had the more proximate relationship with these outcomes. The large number of comparisons may lead to statistically significant associations that are due to chance alone. We have chosen to report all the associations tested for. Information on potential confounders such as parental smoking, drinking, drug intake, medical history, or maternal occupation were not available for adjustment in the analysis. However, personal habits would likely not differ according to the level of cumulative exposure to chlorophenates.

In summary, we have found that offspring of sawmill workers were at increased risk for developing congenital anomalies of the eye with increased cumulative hours of estimated exposure to chlorophenates both during preconception and pregnancy. Congenital cutaneomata showed the highest relative risks at all stages. An increased risk of developing congenital anomalies of the genital organs was related to the father’s cumulative exposures during pregnancy. The maximal index of exposure to chlorophenols during the preconception period was positively related to the prevalence of anencephaly or spina bifida in the exposed fathers’ progeny.

These findings add further support to the hypothesis of male-mediated developmental toxicity. Additional studies are needed to elucidate the mechanisms by which paternal exposure to chlorophenates affects the reproductive outcomes of offspring, as well as to determine whether it is the dioxin contaminant that is the etiologic agent.

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