

Childhood Cancer in the Offspring of Male Sawmill Workers Occupationally Exposed to Chlorophenolate Fungicides

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The objective of this study was to determine whether paternal occupational exposure to chlorophenol fungicides and their dioxin contaminants is associated with childhood cancer in the offspring of sawmill workers. We used data from 23,829 British Columbian sawmill workers employed for at least 1 continuous year between 1950 and 1985 in 11 sawmills that used chlorophenolates. Probabilistic linkage of the sawmill worker cohort to the provincial marriage and birth files produced an offspring cohort of 19,674 children born at least 1 year after the initiation of employment in the period 1952–1988. We then linked the offspring cohort to the British Columbia Cancer Registry. We included all malignancies in cases younger than 20 years of age that appeared on the cancer registry between 1969 and 1993. We calculated standardized incidence ratios (SIRs) using the British Columbia population as a reference. A nested case-control analysis assessed the effects of paternal cumulative exposure and windows of exposure on the risk of developing cancer in the offspring. We identified 40 cases of cancer during 259,919 person-years of follow-up. The all-cancer SIR was 1.0 [95% confidence interval (CI), 0.7–1.4]; the SIR for leukemia was 1.0 (CI, 0.5–1.8); and the SIR for brain cancer was 1.3 (CI, 0.6–2.5). The nested case-control analysis showed slightly increased risks in the highest categories of chlorophenol exposure, although none was statistically significant. Our analyses provide little evidence to support a relationship between the risk of childhood cancer and paternal occupational exposure to chlorophenolate fungicides in British Columbian sawmills. *Key words:* cancer, children, chlorophenols, occupational exposure, paternal exposure, pesticides, reproductive toxicology. *Environ Health Perspect* 108:499–503 (2000). [Online 13 April 2000] <http://ehpnet1.niehs.nih.gov/docs/2000/108p499-503heacock/abstract.html>

The past decade has seen increasing interest in male reproductive health, particularly the effects of environmental endocrine disruptors such as dioxins and certain pesticides. In both animals and humans, studies have reported deteriorating spermatogenesis, altered sex ratios at birth, progressive increases in testicular carcinoma, and birth defects of the male genitalia (1–9). Studies of male-mediated reproductive carcinogenicity are also gaining widespread attention. The first published report identified an association between fathers' employment in a job involving exposure to polycyclic aromatic hydrocarbons and childhood malignancy (10). Since that report, a number of epidemiologic investigations have examined paternal occupational exposures in relation to childhood cancers. Although causal relationships have not been established, certain exposures and occupations are consistently reported. Exposures suspected of increasing the risk of childhood cancer include ionizing radiation, paints, dyes, pigments, solvents, petroleum products, wood dust, and pesticides (11–14). Occupations potentially at risk include painting; mechanical and motor-vehicle-related occupations; electrical/electronics assembling, installing, and repairing; agriculture; and pulp and paper work (15–18).

Chlorophenols are pesticides that command considerable attention. They have been classified by the International Agency for Research on Cancer (IARC) as possibly carcinogenic to humans (19). A number of studies that examined the human carcinogenicity of chlorophenols have reported increased risks for cancer, particularly soft-tissue sarcoma and non-Hodgkin lymphoma (19). The IARC evaluation suggests that bias and chance are unlikely but confounding by dioxins may play a role in the elevated risks. Few studies have been published on the reproductive effects of chlorophenols. Studies of laboratory animals reviewed in the IARC report (19) are inconclusive (20,21). Very little information exists regarding the human reproductive effects of chlorophenol exposure. Analytic studies of reproductive outcomes of chlorophenol-exposed sawmill workers and their offspring have demonstrated no effect on male fertility (22) and no increases in low-birth weight, premature, or stillborn births (23). However, an increased prevalence of certain birth defects was reported (23). A cross-sectional survey of day-care workers exposed to chlorophenol-treated wood paneling suggested reductions in birth weight and birth length among offspring (24), and a case report described two women

who experienced miscarriages after home exposure to pentachlorophenol (25).

Chlorophenols were widely used in the British Columbia (BC) sawmill industry between the 1950s and the late 1980s to prevent sapstain fungi from growing on lumber. The most common method of treating sawed wood was dipping and spraying. Workplace exposures occurred primarily through direct skin contact and, to a lesser extent, through inhaling chlorophenol vapors, aerosols, and contaminated sawdust. Polychlorinated dioxins and furans are formed during the production of chlorophenols, and chlorophenolate formulations are contaminated with these compounds (26,27).

The purpose of this study was to examine the effects of paternal chlorophenol exposure, including cumulative exposure and timing of exposure, on the risk of cancer in the offspring of British Columbian sawmill workers employed between 1950 and 1985.

Subjects and Methods

Retrospective exposure assessment of the sawmill worker cohort. All males employed for at least 1 year between 1 January 1950 and 31 December 1985 in 1 of 11 large softwood lumber mills that used the sodium salts of penta- and tetrachlorophenol, hereafter referred to as chlorophenates, were included in the cohort ($n = 23,829$). Initially, we reviewed mill records and interviewed experienced workers, managers, engineers, and chlorophenolate distributors to extract information about technology and formulation changes and locations in the milling process where chlorophenates were used, thereby reconstructing each mill's history of chlorophenolate application. Thus we established discrete time periods within which exposure conditions remained constant [exposure-constant time periods (ECTPs)]. Each mill

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experienced approximately four ECTPs throughout the study period. Job titles that existed for each time period in every mill were rated by 10–15 experienced workers (who had worked in the mill during the ECTP in question) for frequency and duration of exposure to chlorophenates. The estimates of chlorophenate exposure for each job in individual ECTPs were pooled to obtain an estimate of exposure for each job title. An index of cumulative duration of chlorophenate exposure for each worker was created based on his job history. We validated this method using measurements of urinary metabolites (28,29).

Identifying the offspring cohort. We identified the offspring cohort via probabilistic linkage using the computer program Automatch (Data Star Inc., Burtonsville, MD). The process involved three linkages: sawmill cohort to provincial marriage files, provincial marriage to birth files, and sawmill cohort directly to provincial birth files. Birth records contained information from the Physicians Notice of Birth form, which includes child's date and place of birth, gestational age, sex, birth weight, mother's and (if available) father's full name, and address of parents. The sawmill cohort file was first linked to the marriage file to obtain information on the mother's full name, which appears on all birth certificates (the father's name is sometimes incomplete). We then linked the cohort file with any additional information from the marriage file to the birth files. The matching criteria used for the probabilistic linkage was the fathers' full name and date of birth, and, when available, the wife's first name and date of birth. This produced an offspring cohort containing all cohort-linked children born in BC between 1952 (the first year for which birth data were available) and 1988 (the last year that chlorophenates were used in the BC sawmill industry) who were registered with the provincial Vital Statistics Agency, which is operated under the BC Ministry of Health (Victoria, BC, Canada).

Offspring cohort–cancer registry linkage. We used the Automatch program (Data Star, Inc.) for probabilistic linkage between the offspring cohort and the BC Cancer Registry maintained at the BC Cancer Agency (Vancouver, BC, Canada). The BC Cancer Registry is thought to be complete from 1969 onward because all children in BC with cancer are treated in institutions affiliated with the BC Cancer Agency, and the agency sends its reports to the registry. All children born in BC between 1 January 1952 and 31 December 1988, who were younger than 20 years of age at diagnosis and who were diagnosed with cancer between 1969 and 1993, were included in the linkage. The linkage fields used included full name (first, middle,

and last) and date of birth (day/month/year). We manually verified all links using supplementary cohort information to resolve uncertainties. Once true matches were finalized, we reviewed registry data to identify site and histology of cancer.

Statistical Analyses

Cohort analysis. We tabulated person-year contributions for each child from 1969 (when cancer registry data became available) or their birth year subsequent to 1969 until cancer diagnosis, termination of the follow-up period (19 years of age), or study end (31 December 1993). Once a child was diagnosed with cancer, he or she was censored and no further person-years were contributed by that child.

We assessed childhood cancer risk using the standardized incidence ratio (SIR), adjusted for age and calendar year, and its 95% confidence interval (CI) (30). Expected cases of cancer were based on person-years at risk for the offspring cohort using sex-, age-, and calendar-year-specific provincial childhood cancer rates. SIRs for all histologies and sites of cancer identified in the linkage were computed in Excel version 4.0 (31).

Nested case–control analysis. To examine the effects of both cumulative exposure and timing of exposure to the father, we adopted a nested case–control approach. We calculated the estimated odds ratios (ORs) using logistic regression. The analysis was run on Stata release 5.0 (32).

We included all cases of childhood cancer (0–19 years of age inclusive) appearing in the BC Cancer Registry between 1969 and 1993 and identified as true matches in the offspring cohort to BC Cancer Registry linkage. We randomly selected five controls per case, matched on sex and year of birth, from the balance of the offspring cohort. Very little has been published regarding appropriate inclusion and exclusion criteria for control selection in occupational nested case–control studies using workers' offspring as the sampling frame. Marion and Ward (33) described a survival analysis approach to the selection of controls in a study of reproductive outcomes at birth among workers' offspring. The authors suggested that critical events occur only once in survival analysis; thus, when a birth-related abnormality occurred, the subsequent experience of the parent should not be used. Marion and Ward (33) suggested the following criteria for the selection of controls: *a*) once a case has occurred, subsequent births to the same parent were excluded as either cases or controls; however, earlier births to the parents of a case could be controls; *b*) siblings of controls could serve as controls unless another sibling had become a case; and *c*) each multiple birth was considered a single event.

Determining the baseline model for regression analysis. Controls were frequency-matched to cases on the basis of sex and birth year; therefore, these variables were included in all models. Covariates of interest were mother's age, father's age, birth weight, gestational age, total births in the family, and child's age (in four 5-year categories). Age is a covariate that is often controlled for in statistical analyses because of its role as a confounder. Parental age increases risk for certain peri- and postnatal birth outcomes but little has been published on its association with childhood cancer. A review of the literature (34) concluded that there was insufficient evidence to implicate increasing maternal age with risk for childhood cancer; however, a recently published study (35) reported an effect of maternal and paternal age on risk for both leukemia and brain cancer. In this study, the importance of mother's age, father's age, birth weight, gestational age, and total births was unknown, so we conducted a stepwise logistic regression analysis and sequentially dropped variables with *p*-values > 0.10 from the model. We chose the *p* > 0.10 criterion to allow the inclusion of potentially important effects in the model but exclude variables with spurious significance. The covariates subsequently dropped from the model were child's age, mother's age, father's age, birth weight, gestational age, and total births. Hence, the baseline model included only sex and birth year. Therefore, for each exposure category being examined, the model included the baseline model as well as the exposure category. We created five exposure variables based on different windows of exposure to chlorophenols (Figure 1). Window 1 shows paternal occupational exposure to chlorophenates during the period from commencement of employment until 90 days before conception. Window 2 shows paternal occupational exposure to chlorophenates during the 90 days before conception. Window 3 shows paternal occupational exposure to chlorophenates during pregnancy. Window 4 shows paternal occupational exposure to chlorophenates from the birth of offspring until cancer diagnosis of the offspring. Cumulative exposure = paternal occupational exposure from commencement of employment until cancer diagnosis of the offspring.

We created three categories of exposure (low, medium, and high) for each of the exposure variables to estimate risk associated with increasing exposure. Exposure hour cut-off points were determined by ordering chlorophenate exposure and selecting logical cut-off points. Considerations included at least five cases in each cell; paternal chlorophenate exposure in each cell (i.e., the lowest category not only containing offspring whose

fathers had 0 exposure hr); and cells that would reasonably represent low, medium, and high exposure categories. The high category contains fewer children than the low and medium categories in an attempt to aggregate only the highest paternal exposures (Table 1). The low-exposure categories often contained more children than the medium and high categories because they contained all of the children whose fathers had no exposure.

We tested trends by assigning a value to each of the three categories equal to the mid point of the values in the exposure category, i.e., for the cumulative exposure analysis, the category 0–1,250 exposure hr was assigned the value 625.

Results

Among the 23,829 men employed at the 11 mills that used chlorophenates during the period 1952–1988, 19,674 births occurred after 1 full year of employment. There were 10,104 boys (51.4%) and 9,570 girls (48.6%) for a birth ratio of 1.06:1, which approximates the provincial norm (1.05:1). Based on 259,919 person-years of follow-up, 40 cases of childhood cancer were diagnosed in the offspring 0–19 years of age. Among the girls, we identified 22 cases of cancer: five leukemias, of which three were acute lymphoblastic leukemia; six brain cancers, of which four were astrocytoma; two lymphomas; three reproductive (including two ovarian and one cervical) cancers; two bone cancers; two eye cancers; one liver cancer; and one skin cancer. Among the boys, we identified 18 cases of cancer: six cases of leukemia, of which three were acute lymphoblastic leukemia; three brain cancers; three bone and connective-tissue cancers; two lymphomas; and one cancer each of liver, thyroid, kidney, and nonmelanoma skin cancer.

Cohort analysis. Table 2 presents results of the cohort (SIR) analysis for all cancers combined, all leukemias, and all brain cancers. The overall risk, based on 40 cases, was 1.0 (CI, 0.7–1.4); the risk for leukemia, based on 11 cases, was 1.0 (CI, 0.5–1.8); and the risk for brain cancer, based on 9 cases, was 1.3 (CI, 0.6–2.5). We also performed analyses by sex, and SIRs were consistently higher for girls than boys. For all sites combined, the risk was slightly elevated for the girls (SIR 1.2; CI, 0.8–1.8), and the risk was somewhat decreased for the boys (SIR 0.9; CI, 0.5–1.4). Risk for leukemia

among both sexes approximated unity. The six brain cancer cases among the girls indicated a 2-fold increase in risk (SIR 2.0; CI, 0.7–4.4), including a 2.5-fold increased risk for astrocytoma (SIR 2.5; CI, 0.7–6.3), whereas the three cases of brain cancer among the boys indicated an SIR of 0.8 (CI, 0.2–2.3). Among the girls, other sites with at least two cases and an SIR ≥ 2.0 were eye and ovary (however, the confidence intervals always included unity). Among the boys, no sites with two or more cases had elevated risks.

Nested case-control analysis. Table 3 shows the results of the nested case-control analysis by increasing levels of paternal cumulative exposure to chlorophenates. For all sites combined and for brain cancer, the results indicate a nonsignificant increased OR with exposure to high levels of chlorophenates. A nonsignificant decreased risk for leukemia occurred with increasing exposure.

To assess whether a relationship existed by timing of exposure, the data were analyzed by four windows of exposure, each reflecting a distinct period whereby reproductive damage could occur. Not surprisingly, children's exposure levels in these windows were often similar. In particular, a child's exposure level in the second and third window had a correlation, $r = 0.87$, the second and fourth window had $r = 0.64$, and the third and fourth window had $r = 0.75$. The correlation between the first and subsequent windows was always < 0.2 . Results of the analysis by windows of exposure (Table 1) showed an elevated but nonsignificant OR in the high categories of the correlated second, third, and fourth time windows. Again, however, all confidence intervals included unity and tests for trend were nonsignificant. Because we

identified elevated SIRs for brain cancer in the cohort analysis, we performed subanalyses for brain cancer. Exposure was divided into only two levels (low and high) because of the small number of cases (nine); therefore, trend testing was not possible. We performed analyses for cumulative exposure and windows of exposure. We observed nonsignificant increased risks in each high category of exposure: cumulative exposure OR = 1.5 (CI, 0.4–6.9); window 1 OR = 2.1 (CI, 0.5–9.7); window 2 OR = 2.1 (CI, 0.4–9.9); window 3 OR = 2.0 (CI, 0.4–9.3); and window 4 OR = 1.4 (CI, 0.3–6.2).

Discussion

No statistically significant associations were found between paternal occupational exposure to chlorophenate fungicides in British Columbian sawmills between 1950 and 1988 and the risk of childhood cancer. In the cohort analysis, overall risks were not elevated; however, when the cohort was disaggregated by sex, risks among girls, particularly for brain cancer ($n = 6$), ovarian cancer ($n = 2$), and eye cancer ($n = 2$), were elevated, although CIs always included unity. In the nested case-control analyses, risk of all cancers combined and the risk for brain cancers was increased for the highest level of exposure, but this was not true for leukemias. However, small numbers in each of the exposure categories contributed to unstable parameter estimates and nonsignificant test results. For the analysis addressing the timing of exposure, we saw similar results for exposure windows 2, 3, and 4. This is not surprising given the correlation among exposure levels in these windows.

Previous studies of parental pesticide exposure and risk of childhood cancer have

Table 1. Risk for developing childhood cancer (all sites) associated with windows of paternal chlorophenate exposure.

Category	Exposure (hr)	Cases	Controls	OR ^a	CI
Window 1 ^b					
Low	< 1,000	14	59	1.0	–
Medium	1,000–4,999	19	106	0.8	0.4–1.6
High	$\geq 5,000$	7	35	0.8	0.3–2.3
<i>p</i> for trend = 0.88					
Window 2 ^c					
Low	< 10	21	114	1.0	–
Medium	10–249	11	60	1.0	0.5–2.5
High	≥ 250	8	26	1.7	0.7–4.7
<i>p</i> for trend = 0.30					
Window 3 ^d					
Low	< 10	19	106	1.0	–
Medium	10–699	13	60	1.2	0.6–3.1
High	≥ 700	8	34	1.3	0.6–3.9
<i>p</i> for trend = 0.55					
Window 4 ^e					
Low	< 1	18	96	1.0	–
Medium	1–8,999	15	80	1.0	0.5–2.6
High	$\geq 9,000$	7	24	1.7	0.5–4.8
<i>p</i> for trend = 0.42					

^aAdjusted for sex and year of birth. ^bFather's employment until 90 days before conception: stem-cell effects. ^cDuring the 90 days before conception: spermatogenesis/germ-cell effects. ^dDuring pregnancy: transplacental effects. ^eFrom birth until cancer diagnosis: postnatal effects.

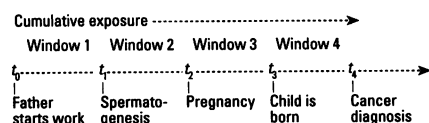


Figure 1. Time line describing cumulative exposure to chlorophenates and windows of exposure.

Table 2. Childhood cancer diagnosed 1969–1993 among offspring of sawmill workers employed in mills that used chlorophenates.

Age ^a and type	Cases		SIR	CI
	Observed	Expected		
All cancers				
0–4	11	11.6	1.0	0.5–1.7
5–9	12	7.6	1.6	0.8–2.8
10–14	7	7.9	0.9	0.4–1.8
15–19	10	11.3	0.9	0.4–1.6
Combined ^b	40	38.4	1.0	0.7–1.4
Leukemia				
0–4	4	5.0	0.8	0.2–2.1
5–9	3	2.8	1.1	0.2–3.2
10–14	3	1.7	1.8	0.4–5.2
15–19	1	1.8	0.6	0.0–3.1
Combined ^b	11	11.3	1.0	0.5–1.8
Brain cancer				
0–4	4	2.2	1.8	0.5–4.6
5–9	2	1.8	1.1	0.1–4.0
10–14	1	1.7	0.6	0.0–3.2
15–19	2	1.1	1.9	0.2–6.7
Combined ^b	9	6.8	1.3	0.6–2.5

^aIn years. ^bAll age groups (0–19 years of age).

been equivocal. Recently published review papers have reported only a limited number of positive associations with parental pesticide exposure (36,37). The authors concluded that improved methods to assess exposure, large study populations, and investigating the timing of exposure are necessary to accurately estimate the effects of parental pesticide exposure on the risk of developing childhood cancer.

Study strengths. In this study, the offspring cohort was ascertained using the best methods available at the time; therefore, the cohort should be reasonably complete. To our knowledge, this study contains the most extensive exposure assessment of any study published on the risk of childhood cancer in relation to paternal occupational exposure. The exposure assessment and large study population permitted a limited evaluation of dose–response relationships as well as the timing of exposure to be investigated. The correlation of exposure levels in all but window 1 suggest that the results may be representative of risks associated with the period from spermatogenesis onward. The difference between risks associated with the first and remaining windows confirms the suggestions by previous researchers (36,37) that timing of exposure may be an important aspect of its assessment.

Because of the rare occurrence of childhood cancer, most of the published studies used population-based case–control designs. Although such designs are efficient for studying childhood cancer, they have been criticized because of crude exposure assessment methods, small study populations, and the potential for selection and recall bias (36–41). An historical cohort study is

Table 3. Risk for developing childhood cancer, 1969–1993, associated with cumulative paternal chlorophenate exposure.

Category	Exposure	Cases/ controls	OR ^a	CI
All sites ^b				
Low	< 1,250	6/33	1.0	–
Medium	1,250–9,999	23/127	1.0	0.4–2.7
High	≥ 10,000	11/40	1.6	0.5–4.8
Brain cancer				
Low	< 3,560	4/19	1.0	–
High	≥ 3,560	5/16	1.5	0.4–6.9
Leukemia				
Low	< 3,000	6/26	1.0	–
High	≥ 3,560	5/19	0.8	0.2–3.6

^aAdjusted for sex and year of birth. ^b*p* for trend = 0.28.

potentially less prone to these biases and therefore is more likely to correctly identify causal relationships.

Study limitations. There are a number of limitations in the study design. The large size of the offspring cohort provided sufficient power to detect true differences at a relative risk of 1.44 for all cancers combined, 1.84 for leukemia, and 2.17 for brain cancers. For exposures causing only slightly elevated risks, very large populations with long follow-up times are needed. In this study, 83% of the offspring cohort reached 19 years of age before 1994. Complete follow-up of the offspring cohort would occur in 2007, thus providing 14 further years of follow-up (42,913 person-years). It is unlikely that a sufficient number of new cases of childhood cancer will develop in this time to greatly improve study power; most of the children would be teenagers and beyond the age (younger than 10 years of age) when leukemia and brain cancer are most likely to occur. The years 1952–1968 represent the early life of many children in the offspring cohort, and several leukemias and brain cancers might have been diagnosed in the cohort during this period. A potential way of including this period would be to link the offspring cohort to a general mortality database. Most childhood cancer cases diagnosed before 1969 died and often, with childhood cancer before 1970, incidence and mortality occurred in close proximity to one another. A mortality follow-up of the offspring cohort from 1 January 1952 (when the births of the offspring cohort were first counted) until 31 December 1968 (just before the commencement of the BC cancer registry) would add a total of 80,648 person-years to the database; 33,966 person-years would be among children younger than 10 years of age. A linkage with mortality data is being considered to capture events that occurred before 1969. The analysis presented here covers 66% of the person-years that occurred before 10 years of age for the period from 1952 until 1993.

Another study limitation is exposure misclassification. The original study was designed to reduce errors in exposure quantification (28,29,42,43). Quantitative estimates of chlorophenate exposure for job titles held by each worker were not possible because no exposure data had been routinely collected during the study period, i.e., 1950–1985. Retrospective exposure classifications for each job title were based on estimations made by expert raters. Preliminary feasibility studies on the reliability of methods showed that the mean estimates of all raters were relatively stable (group intraclass correlation coefficients ranged from 0.69 to 0.94). We assessed validity by examining urinary chlorophenate levels in a sample mill and comparing the levels with raters' exposure estimates: correlation coefficients ranged from 0.49 to 0.69. Exposure misclassification that did occur should have been nondifferential and would normally be expected to bias findings toward the null. Given that the regression analyses were based on categorized exposure groups, the Berkson error model should apply, at least in part, suggesting that bias toward the null would be minimized (44).

Incomplete offspring ascertainment is a potential limitation of our study. We captured the offspring cohort using probabilistic linkage augmented with manual resolution of uncertain links. Hence, the methodology used to obtain the offspring cohort provided links between the sawmill worker cohort and all matching births registered at the provincial Division of Vital Statistics. It is possible that a small proportion of the births to the sawmill worker cohort was not registered or that data entry errors resulted in true matches not being picked up in the probabilistic linkage. However, there is no indication that any missed offspring would be at either higher or lower risk of cancer than those included in the study. Thus, although power may be reduced, bias is unlikely.

Migration is another factor that could bias the results. Because provincial birth records were used in the linkage, children born outside the province were excluded from the study. This exclusion has the potential to create a migration bias. However, our cohort mortality data (based on linkage to the Canadian Mortality Data Base, which is maintained by the Health Statistics Division of Statistics Canada, and contains all deaths recorded in Canada since 1950) indicated that 96% of the deaths occurred in BC; therefore, we could assume that most of the workers resided in BC throughout their working lives and their children were born in the same province. The rate of migration into BC exceeded the rate of migration out of the province during the four decades of this study. Children born

in BC but who move out will cause a conservative bias because they will be retained in the denominator. There is no reason to believe that there would be a change in cancer risk for those who moved out of the province. There is reciprocal reporting among Canadian cancer registries for children treated outside the province; therefore, cancer cases who live in BC but are treated elsewhere in Canada should be included.

Lastly, confounding may be an issue in our study. We did not collect data on paternal home pesticide use (i.e., nonoccupational) or data on maternal exposure (either occupational or lifestyle). However, smoking data were collected on 328 men in three mills where urinary chlorophenolate measurements were taken in the 1980s. Results showed a correlation of 0.024 (i.e., no correlation) between pack-years of smoking and total chlorophenolate levels in urine; therefore, confounding by smoking should not have occurred. Other potentially confounding variables may be systematically different between geographic locations of sawmills but it is unlikely that these factors would be correlated with chlorophenolate exposure within the mills.

In conclusion, this large retrospective cohort study of cancer incidence in the offspring of British Columbian sawmill workers failed to find a clear relationship between paternal occupational exposure to chlorophenolate fungicides and the risk of childhood cancer. Although the study included > 18,000 children, childhood cancer is rare and therefore only 40 cases were observed. This small number and the potential misclassification of exposure limited our ability to detect small risks.

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