Soft-tissue sarcoma and non-Hodgkin's lymphoma among a cohort of sawmill workers exposed to chlorophenate wood preservatives

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1. Background

At the time this cohort study began in 1987, there were conflicting results from case control studies relating cancer outcome to exposure to chlorophenates in the literature. Significantly positive associations were found for soft tissue sarcoma (STS)[1, 2], and non-Hodgkin's lymphoma (NHL)[3] in some studies but no significant associations were seen in others for STS[4-6].

These inconsistent results raised the prospect of bias of retrospective exposure ascertainment in case-control studies. Also, several of the studies involved populations exposed to both chlorophenates and chlorophenoxy herbicides. Unlike chlorophenoxy herbicides, the dioxin contamination of chlorophenates has been shown to consist entirely of the hexa-, hepta- and octachlorinated dioxins[7]. The results of these studies left open the question of which agent or agents, if any, might be the proximate human carcinogen. As a result we designed a cohort study of sawmill workers in British Columbia, Canada who were exposed to only one class of dioxin-contaminated substances and in whom we could avoid the problem of retrospective exposure assessment by relying on employment histories abstracted from routinely collected records

Overview of Study Design

We recruited 23,829 workers from 11 sawmills which began using chlorophenates between the 1940s and early 1970s and 2658 workers in non-chlorophenate mills. Personnel records were used to identify suitable subjects who had worked at least one year between 1 Jan 1950 and 31 Dec 1985, and to extract personal identifiers and a full job history.

An industrial history was reconstructed for each of the chlorophenate mills using old records and key informant interviews. These were used to create time lines which showed the history of the introduction of chlorophenates, the various changes in formulation, application technology, and locations in the milling process where chlorophenates were applied. From these time lines, the study team identified "exposure constant time periods" (ECTP) for each mill. These were defined as time periods during which the chlorophenate application process and formulation used by the mill were constant. It was inferred that, during a given exposure constant time period, exposures to chlorophenates would be reasonably stable for a given job in the mill. Usually, three or four such periods were defined for each mill.

Next, all recorded job titles from a given ECTP were collated and jobs which differed only by seniority, or were the same in terms of opportunities for exposure, were combined, so that no more than 100 job titles were left for any ECTP. Finally, at least 10 expert workers were

identified and asked to independently rate the chlorophenate exposure for each job title in each ECTP. A separate study had determined the reliability and validity of this method of retrospectively assessing chlorophenate exposure using experienced worker raters to be 0.91 and 0.65 respectively when the results were compared to actual urinary chlorophenate levels[7, 8]

The experienced workers rated the job title by frequency and duration of exposure, route of entry, and site of skin contact (if any). Since the process of sawmilling is relatively simple and the different mills used similar formulations over time we combined data from different mills to create a common measure of exposure. Each worker's job history was translated into estimates of exposure to chlorophenates. Using the rater information the frequency and duration of exposure for each job title are multiplied to obtain a score between 0 and 2000. These scores combined the average of worker raters' estimates of duration and frequency of exposure to chlorophenates and can be roughly interpreted as the number of 'exposure hours per year'. The score for each of the workers' job titles was multiplied by the period of time in that job and summed across all job titles to get a cumulative exposure score. It was adapted for use as a transient dose variable in the analysis.

The personal identifier file was linked, using probabilistic methods, to the BC Death File (1950-1989) and the B.C. Cancer Incidence File (1969-1989) and the Canadian Mortality Data Base. To improve follow-up we checked pension and B.C. motor vehicle records, and inquiries were made at local union halls in order to ascertain the vital status and update records of the last known date alive of all those who had left a sawmill but were not found to be dead after linkage. While this dramatically reduced the number of person years, the overall number of unknown person years was still large enough to affect results. Therefore, we arranged for Statistics Canada to link those sawmill workers, for whom we had Social Insurance Numbers, to the Canadian income tax file.

Standardized mortality and incidence ratio (SIR) analyses were carried out using the Person-Years program for cohort study analysis created by Coleman, Hermon and Douglas for IARC (IARC Internal Report #89/006, Lyon, 1989). The BC male population served as the external comparison group. Causes of death were resolved to the ICD 8 classification and cancer incidence was resolved to ICD 9. Person years at risk began after one year of exposure. In the overall analyses of mortality and cancer incidence, chlorophenate and non-chlorophenate mills were analysed separately. In analyses of exposure gradients, person years and outcomes from non-chlorophenate mills were included in the lowest exposure category. For certain cancers of interest, lagged analyses were carried out to take special account of the latent period between first exposure and disease outcome. Similarly the Standardized Rate Ratio was used in another set of analyses in order to remove the healthy worker effect and its conservative bias on the results.

Results

Intraclass correlation coefficients were calculated for each group of worker exposure raters in each time period at each mill and the levels of reliability were similar to those found in the feasibility studies. The range of exposure scores in each mill was similar, and comparable work areas in different mills ended up with similar exposure scores. These findings supported the original expectation that mills could be combined for analysis.

The cohort provided a total of 583,190 person years (PY) of follow-up in chlorophenate mills and 41,280 in non-chlorophenate mills, assuming that any cohort member not found in the mortality follow-up was alive in 1990. The 70,119 PY lost to follow-up could have had unpredictable consequences for analysis, so each analysis was done twice, including and excluding these person years.

The all cause Standardized Mortality Ratio (SMR) for workers in chlorophenate mills is 0.96

if PY are counted until the last known year alive and 0.81 if unknowns are assumed to alive at the end of 1990; whereas for the non-chlorophenate mills, it is 0.89 and 0.86, respectively. For the cancers of interest and cause specific mortality there was no association between chlorophenol exposure in BC sawmills and soft tissue sarcoma (STS). For NHL the SMR was 1.08 if PY are counted until the last known year alive. When this is divided between lymphosarcoma and other NHLs, the SMRs are 1.46 (95% C.I. - 1.00 - 2.07) and 0.75, respectively. If PY are calculated until the end of 1990 the SMR for lymphosarcoma drops to 1.26 (95% C.I. 0.86 - 1.79). SMRs for respiratory, lung, male genital, and kidney cancer are all greater than 1.0, with a lower confidence limit which is also greater than 1.0 when PY are counted until the last known year alive but not when they are calculated to the end of 1990. When the mortality gradients by level of cumulative exposure to chlorophenates are calculated there are no statistically significant positive dose-response gradients seen for either of the causes by either method of PY accrual.

Standardized Incidence Ratio (SIR) for incident cancers were calculated for the period 1969–1989. Cancers which were identified solely on death records (a circumstance primarily confined to deaths outside of BC) were included as incident cancers as of their date of death. SIRs for NHL and STS were not elevated in either analysis.

Lagging the exposures 5, 15, or 20 years had no meaningful effect on the results; the gradient for NHL persists at approximately the same level of strength across all analyses. Nor did we find the risk was concentrated in any particular mills nor in those mills associated with pulp mills. The only major product change occurred around 1964 when there was a switch to predominantly tetrachlorophenate products as opposed to pentachlorophenate products and no effect on the results was found.

Because of the positive trend for NHL with chlorophenate exposure, several additional analyses were done to further examine this relationship. The Standardized Rate Ratio analysis in Table 1 was done to control for the healthy worker effect by using the cohort itself as a set of internal controls. We also examined the effect of years of work in chlorophenate mills and the pattern of increasing risk with increasing work experience is similar, in terms of the strength of association, to previous analyses based on cumulative hours of chlorophenate exposure. This raises the prospect that the association may not be related to chlorophenate exposure, but rather to other aspects of work in a sawmill, such as exposure to wood dust.

Table 1 Relative risk of developing non-Hodgkin's Lymphoma with increasing levels of chlorophenate exposure:

Cum Hrs Exp	SIR (to 1989)	SRR (to 1989)
<120	0.68 (0.23, 1.56)	1
120-1999	0.59 (0.31, 1.03)	0.87 (0.27, 2.80)
2000-3999	1.04 (0.59, 1.74)	1.57 (0.50, 4.90)
4000-9999	1.02 (0.63, 1.57)	1.38 (0.45, 4.17)
≥10,000	1.30 (0.91, 1.80)	1.62 (0.55, 4.80)
	χ^2 trend = 4.43 p=0.04	χ^2 trend = 3.61 p=0.06

To gain further insight into this issue, the patterns of incidence of NHL were disaggregated by years of work and cumulative exposure (Table 2). The table shows that all of the excess risk is concentrated in the cell with the highest exposure and longest work history. Poisson regression analysis of table 5 revealed that cumulative exposure did not add any explanatory power after years of work were added to the model. When the variables were entered in reverse order, years of work did not add explanantory power to cumulative exposure.

Table 2
Observed (expected) Cases of Non-Hodgkin's Lymphoma by Years of Work and Cumulative Exposure, Exposed Mills Only, (to 1989)

Cumulative Exposure	Years of Work <5	5 - 9	10 - 14	15 - 19	20+
<120	1 (1.36)	0 (0.44)	0 (0.19)	0 (0.11)	1 (0.18)
120-1999	7 (11.82)	0 (1.74)	0 (0.58)	1 (0.34)	1 (0.65)
2000-3999	6 (6.33)	3 (2.24)	1 (0.71)	1 (0.46)	0 (0.80)
4000-9999	0 (2.16)	5 (4.93)	3 (2.27)	4 (2.17)	3 (3.18)
≥10,000	0 (0.0)	2 (0.99)	1 (2.39)	3 (3.62)	20* (12.99)

*SIR=1.54; p=0.04

Discussion

This study was designed to detect a minimum SMR/SIR of 150 for NHL and 250 for STS. As the number of cases was greater than predicted the effective power was better than predicted power of 90%.

In this study we found no association between STS and exposure to chlorophenates in BC sawmills. In general, analyses of mortality from NHL were negative. However, there were only 37 deaths from NHL in the full 40 years of mortality follow-up while there were 65 incident cases over 20 years of cancer follow-up. Because the case-fatality rate was lower than expected, the analyses of NHL incidence were judged separately from the mortality analysis.

The analyses of NHL incidence tend to be weakly positive. Although the overall SIR for NHL is only 1.0 - 1.2 (depending upon the accounting of PY), the gradient analysis is "positive" when person-years lost to follow up are included. When the prospect of a healthy worker effect is removed through the SRR analysis, the exposure-group specific rate ratios are higher than their respective incidence ratios on SIR analysis, but no exposure subgroup, individually, has a statistically significant RR. However, Table2 shows that the risk gradient with cumulative exposure cannot be separated from years of work. This raises the prospect that wood dust or other undefined sawmill exposures may be the proximate risk factor.

The case for chlorophenate exposure as a risk factor rather than some other factor is based upon three observations. First, it is possible that random errors entered the estimates of exposure by job title, which would reduce the strength of association between cumulative exposure and risk of NHL. Potential sources of error include the exposure estimation process, the definition of exposure constant time periods, the grouping and collating of job titles, and the care with which job title changes were recorded in sawmill personnel records. In contrast, there is almost no room for random error in the recording of work time *per se*. Thus, years of exposure may be as good a surrogate measure of exposure as cumulative exposure was. Second, the risk was concentrated in the subgroup with more than 20 years of exposure, who were also in the greatest cumulative exposure category. This is consistent with the pattern of induction and latency usually found in relation to occupational cancer. Finally, if wood dust or other unknown sawmill exposures were the proximate risk factor, they might be expected to elevate the risk in the control mills, and they did not.

There are also several reasons to reject the notion that there is another, unidentified risk factor in the sawmills. First, analysis did not reveal increased risk in any one work area within each mill. Three other studies of wood working occupations failed to find an association with NHL[9-11] and this is consistent with our lack of significant findings in our control mills. Lastly, although NHL has been associated with metal working and solvent exposures[11] the prevalence of these exposures is low in sawmills and occurs in both chlorophenate using and non-using mills.

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