

FOCUS ON TOMORROW

RESEARCH FUNDED BY WORKSAFEBC

Cancer and Occupational Exposure to Pentachlorophenol and Tetrachlorophenol

August 2005

Principal Investigator/Applicant
Dr. Paul Demers

RS2001/02-020

WORK SAFE BC

WORKING TO MAKE A DIFFERENCE

**Cancer and Occupational Exposure to
Pentachlorophenol and Tetrachlorophenol**

Final Report to the Workers' Compensation Board of BC

Paul A. Demers^{1,2}

Hugh W. Davies¹

Melissa Friesen¹

Clyde Hertzman²

Aleck Ostry²

Kay Teschke^{1,2}

- 1. School of Occupational and Environmental Hygiene**
- 2. Department of Health Care and Epidemiology**

University of British Columbia

August 2nd, 2005

Table of Contents

	Page
Table of contents.....	i
Executive Summary	ii
Introduction.....	1
Methods.....	2
Results.....	6
Tables	10
Discussion.....	22
Conclusions.....	26
References.....	27

Executive Summary

Introduction

In a previous analysis of the British Columbia Sawmill Cohort an association between non-Hodgkin's Lymphoma (NHL) and chlorophenol exposure was observed. Several other studies have found chlorophenol-exposed workers to have an increased risk of non-Hodgkin's lymphoma as well as other cancers, but the evidence has not been consistent. Animals studies seem to indicate that pentachlorophenol is a more potent carcinogen than other chlorophenols. This study is a six-year extended follow-up of the BC Sawmill Cohort, examining the effects of pentachlorophenol and tetrachlorophenol independently.

Methods

The cohort consisted of men employed for one year or more by 14 BC sawmills between 1950 and 1995. Fatal (1950-95) and incident (1969-95) cancers were identified using record linkage with national registries. Senior workers and managers in each mill estimated the proportion of time worked with dermal exposure to chlorophenols for each job. Specific fungicide formulations used during different time periods were identified using mill records and interviews to differentiate between exposure to pentachlorophenol and tetrachlorophenol. Comparisons were made using cancer rates in the general BC population and dose-response relationships were assessed using Poisson regression. The analyses focused on cancer sites of *a priori* interest (non-Hodgkin's lymphoma, soft tissue sarcoma, multiple myeloma, lung, kidney, sinonasal, and nasopharyngeal), because they had been observed to be in excess in earlier studies of workers exposed to chlorophenols or related phenoxy herbicides.

Results

The updated cohort consisted of 27,464 men. Overall there were 5,850 (21% of all cohort members) deaths and 977 (4%) people were lost to follow-up and had their person-years truncated at date of last employment. For the cancer incidence analyses, cohort members who died or were lost to follow-up prior to 1969 (the first year of cancer registration in BC and most other provinces) were excluded leaving 25,685 men. Overall there were 2,571 cancers diagnosed, excluding non-melanoma skin cancers, which are poorly identified.

Rate of death for major causes were similar to, or lower than, those predicted based on the rates in the general population of British Columbia. There were statistically significant lower risks for some causes that were consistent with the pattern that would be expected due to the “healthy worker effect.” Overall cancer incidence and mortality were similar to that of the general population and there were no striking overall excesses of any of the specific cancers, including those of *a priori* interest.

Associations between the risks of non-Hodgkin’s lymphoma, multiple myeloma, and kidney cancer and dermal exposure to chlorophenol fungicides in sawmills were observed. This relationship was strongest for all three cancers when exposure was restricted to pentachlorophenol. While the relative risks among the most highly exposed were only slightly or moderately elevated compared to the general population, strong dose-response relationships were observed compared to the least exposed workers.

This study did not find any evidence of an increased risk of other cancers of *a priori* interest, including soft tissue sarcoma or connective tissue cancers alone as well as lung, sinonasal, or nasopharyngeal cancer.

Conclusions

This extended follow-up of the BC sawmill workers cohort found associations between the risks of non-Hodgkin's lymphoma, multiple myeloma, and kidney cancer and level of dermal exposure to chlorophenol fungicides, particularly with pentachlorophenol. No evidence of an association between chlorophenols and other sites of *a priori* interest were observed.

This study had insufficient power to examine dose-response relationships for rare cancers such as soft tissue sarcoma, sinonasal, or nasopharyngeal cancers. In addition, the ability of this study to adjust for the effects of potential non-occupational confounding factors was limited and non-differential misclassification of exposure may have contributed to obscuring potential associations. However, this is one of the largest studies ever conducted to examine the risk of cancer amongst workers exposed to chlorophenols and phenoxy herbicides and the largest to examine the risk specifically associated with pentachlorophenol and tetrachlorophenol. It is also the first cohort study of workers exposed to this family of chemicals to focus on dermal exposure and to attempt to quantify exposure through this route.

Introduction

Sodium salts of pentachlorophenol (PCP) and tetrachlorophenol (TeCP) were used extensively as fungicides in the lumber industry between 1950 and 1990 [Teschke et al, 1994]. Concerns regarding the potential carcinogenic effects of chlorophenols were first raised in the 1970's when it was discovered that they might be contaminated with polychlorinated dioxins. By the early 1990's their widespread use on lumber was discontinued in most countries. However, tens of thousands of people from Canada and many other countries continue to be exposed to PCP through its use as a wood preservative for telephone poles, pilings, and fence posts, and as a pesticide in leather tanneries and some other industries [IARC, 1999].

The relationship between cancer and exposure to chlorophenols and related chlorophenoxy herbicides has been examined in a number of epidemiologic studies. The most consistently observed findings have been excesses of non-Hodgkin's lymphoma [Hardell et al, 1994; Garabedian et al, 1999; Kogevinas et al, 1995] and soft tissue sarcoma [Erikson et al, 1981, 1990; Hardell et al, 1995; Hardell L, Sändstrom, 1979; Hoppin et al, 1998], although excesses of multiple myeloma [t Mannetje et al, 2005; Mikoczy et al, 1994], lung [Hooiveld et al, 1998; Kogevinas et al, 1997], kidney [Hooiveld et al, 1998; Ramlow et al, 1996], nasopharynx and sinonasal [Mirabelli et al, 2000] have also been observed. However, the results of studies have not always been consistent [IARC, 1999]. In addition, few studies have provided results specifically for pentachlorophenol or tetrachlorophenol and those that have had relatively small numbers of exposed people [Jappinen et al, 1989; Kogevinas et al, 1995; Ramlow et al, 1996]. The evidence regarding the human carcinogenicity of polychlorophenols and their salts was most recently classified as "limited" by the International Agency for Research on Cancer (IARC) [1999]. While the committee concluded that there was sufficient evidence for

carcinogenicity of pentachlorophenol in animals, the evidence for humans was inadequate to draw conclusions. For tetrachlorophenol there was too little data for animals or humans from which to draw conclusions.

In the late 1980's, a cohort study of sawmill workers in British Columbia, Canada was started to determine if workers exposed to sodium pentachlorophenol and tetrachlorophenol fungicides were at an increased risk of cancer [Hertzman et al, 1997; Teschke et al, 1998]. As part of the study extensive efforts were made to retrospectively estimate dermal exposure to chlorophenols [Hertzman et al, 1988; Teschke et al, 1989]. Small excesses in overall cancer and lung cancer incidence were observed, but the most significant result was a trend of increasing risk of non-Hodgkin's lymphoma associated with increasing exposure. The objective of this study is to assess the human carcinogenicity of pentachlorophenol and tetrachlorophenol independently using data from the BC sawmill workers cohort study with the extended follow-up data now available.

Methods

Cohort Enumeration and Follow-Up

The sawmill cohort consists of 26,487 male¹ workers employed for at least one year between 1950 and 1995 at one of 14 sawmills in British Columbia, the Western-most province of Canada. Personal identifying information (including name, birth date, and social insurance number if available) was abstracted from the personnel records at each mill. Job history (including start and end dates, job title, and department for every sawmill job, leave periods, termination date and reason for termination), was also abstracted from mill records.

1. Although the full sawmill cohort includes several hundred women, they were added when the cohort was updated and no deaths had occurred as of 1995. Thus, they were excluded from mortality and cancer incidence analyses.

Using probabilistic linkage techniques [Howe and Lindsay, 1981] personal identifying information on members of the cohort was linked to the BC Death File (1950-1989), the Canadian Mortality Data Base (1950-1995), the BC Cancer Incidence File (1969-1989), and the Canadian Cancer Incidence Data Base (1969-1995). The national mortality and cancer incidence linkages extended follow-up six years beyond those conducted for the original chlorophenol mortality and cancer incidence analyses and expanded cancer incidence follow-up to include national coverage. Follow-up included use of pension records, BC motor vehicle license records, union records, and, for those with social insurance numbers, linkage to Revenue Canada's income tax file.

Assessment of Exposure

Exposure assessment was based on the detailed work history of each cohort member and mill-specific assessments using historical records and key informants. Historical information was collected for each mill detailing times when sawmill facilities were renovated, built, or demolished and when chlorophenols were introduced and discontinued. These were used to create *exposure-constant time periods* during which production processes remained relatively constant and exposures were expected to be stable for each job. All recorded job titles in these time periods were collated and those that differed little in terms of job tasks, but were the same in terms of chlorophenol exposure, were combined to create an abbreviated list of about 100 jobs in each period.

Occupational exposure to chlorophenols in sawmills may occur through either inhalation of mist or dermal absorption of the liquid solutions. A study of urinary chlorophenol levels in sawmill workers in the Northwest United States found that 95% of the estimated total exposure

was due to dermal absorption [Fenske et al, 1987]. No records of historical exposure levels were available in British Columbia sawmills. To assess exposure, interviews were conducted with senior workers with at least 5 years of experience in each *exposure-constant time period* in each mill. Between 9 and 20 workers were interviewed for each period. Both the validity and reliability of these methods have been assessed [Hertzman et al, 1988; Teschke et al, 1989]. Correlation coefficients of 0.76 and 0.72 were observed between workers' estimates and urinary chlorophenol levels were observed for exposure during the summer and fall respectively based on jobs held for eight weeks prior to sample collection [Hertzman et al, 1988]. The use of relatively large groups of senior workers, with a mean of 15 years experience, also produced relatively reliable estimates (group intraclass correlation coefficients of 0.91). A further analysis found that as good or better than estimates by industrial hygienists, a method commonly used in cohort studies when measurement data are not available [Teschke et al, 1989].

The workers' estimates of exposure were assigned to each job title and combined with job history information from the personnel records of each individual to calculate cumulative hours of dermal chlorophenol exposure for each subject. As part of a different study of the respiratory health effects of fungicides that were used in the BC sawmill industry after the chlorophenols were discontinued, the date that chlorophenols were discontinued in each mill was identified [Demers et al, 2000].

Mill records were reviewed to identify which fungicide formulations were used and the dates of their use to develop separate indices of exposure for pentachlorophenol and tetrachlorophenol. Technical grade chlorophenols and formulations are not pure substances and usually consist of either PCP or TCP or a combination as the active ingredients, as well as their manufacturing impurities and smaller amounts of the other chemicals. In general, formulations

containing predominantly pentachlorophenol were used from 1941 to 1965 and after 1965 formulations containing predominantly tetrachlorophenol were used, although most formulations contained both in varying quantities. Information regarding formulations was used in combination with “exposure hours per year” to calculate two new indices of dermal exposure: full-time equivalent years (2,000 hours) for PCP and TCP exposure. In cases where formulations containing both chlorophenols were used, the exposure index was weighted to reflect the proportion of active ingredient. The indices for exposure to PCP and TCP were not strongly correlated ($r=0.45$) based on cumulative exposure at end of follow-up.

Analysis

Standardized incidence ratio (SIR) and standardized mortality ratio (SMR) analyses were performed using British Columbia provincial rates as the external reference population. The Life Table Analysis System (PC-LTAS) developed by the US National Institute for Occupational Safety and Health [NIOSH, 2000] was used to perform the analyses. Ninety-five percent confidence intervals (CIs) for SMRs and SIRs were calculated assuming a Poisson distribution [Breslow and Day, 1987]. Analyses were performed counting time at risk until the date the person was last known to be alive based on linkage with motor vehicle, pension, and BC Linked Health Database files. For analyses of incident cancers follow-up was further discontinued at time of diagnosis of the cancer being analysed, to allow for the possibility of multiple primaries.

The analyses focused on cancer sites of *a priori* suspicion because they have been observed to be in excess in earlier studies (non-Hodgkin’s lymphoma, soft tissue sarcoma, multiple myeloma, lung, kidney, sinonasal, and nasopharyngeal). While most cancers were categorized using the standard International Classification of Disease, 9th revision (ICD9)

groups, soft tissues sarcoma was examined using both site (connective tissue) and histology [Hoppin et al, 1999].

The risk of cancer based on both incidence and mortality were examined in relation to the quantitative indices described in the exposure assessment section above. The indices were used in combination with detailed work history data to create cumulative exposure metrics for each chlorophenol. Internal comparisons, using workers in the lowest exposure category as the reference group, were also performed to examine dose-response relationships. Relative risks (RR) were calculated using maximum likelihood methods [Breslow and Day, 1987] after adjustment for age and time period effects using Poisson regression. Ninety-five percent confidence intervals were based on the standard error of the coefficients derived from the model. Poisson regression was performed using STATA/SE 8.2 analytical software (StataCorp, College Station, Texas, USA). Lagging of exposure by 10 and 20-year intervals were used to allow for a latency period.

Results

The updated cohort consisted of 27,464 men. Based on surname, 1,627 men were classified as South Asians (almost all Punjabi) and 447 were classified as East Asian (almost all Chinese). Overall there were 5,850 (21% of all cohort members) deaths and 977 (4%) were lost to follow-up and had their person years truncated at date of last employment. For the cancer incidence analyses cohort members who died or were lost to follow-up prior to 1969 (the first year of cancer registration in BC and most other provinces) were excluded leaving 25,685 men. There were 1,534 South Asians and 335 East Asians in the cancer incidence sub-cohort. Overall

there were 2,571 cancers diagnosed, excluding non-melanoma skin cancers, which are poorly identified. Only 11 (<1%) were lost to follow-up for the cancer incidence analysis.

Table 1 presents the overall mortality results for the full cohort. Observed deaths for major causes of deaths were similar to, or lower than, those predicted based on the rates in the general population of British Columbia. There were statistically significant lower risks for some causes that were consistent with the pattern that would be expected due to the “healthy worker effect.” Table 2 presents the overall cancer mortality and incidence results for major cancers and sites of *a priori* interest. There were no striking mortality or incidence excesses of any of the specific cancers and all confidence limits included one.

The relationship between these cancers and cumulative exposure to all chlorophenols, pentachlorophenol, and tetrachlorophenol was examined and the results for major sites of *a priori* interest and those suggestive of a dose-response are presented in Tables 3 to 8. There were too few sino-nasal (n=6) and nasopharyngeal (n=4) cancers to assess dose-response, but the few cases were not clustered in the higher exposure categories.

For non-Hodgkin’s lymphoma no evidence of a dose-response was observed in either the SMR or SIR analyses and the number of observed cancers in the highest exposed groups was similar to expected (Table 3). However, some evidence of a trend with pentachlorophenol exposure was apparent in the internal analyses of both the mortality and incidence data, although the relative risks did not increase monotonically. The relative risks in the mortality analysis were higher than the incidence analysis, although the trend was somewhat stronger in the later.

No association was observed between either soft tissue cancer incidence or mortality and any indicator of chlorophenol exposure in either the SMR or SIR analyses (Table 4). There were too few cases to perform internal analyses for this cancer site. However, there were more

incident cases of soft tissue sarcoma observed based solely on the histologic classification. This allowed for some internal analysis, although general population rates were not available for comparison. Again, there was no association observed with any indicator of chlorophenol exposure. In the incidence analyses for both connective tissue cancer and soft tissue sarcoma, risks appeared to decrease with level of exposure.

Multiple myeloma exhibited a pattern similar to non-Hodgkin's lymphoma (Table 5). Although there was clear evidence of a dose-response was observed in either the SMR or SIR analyses and the number of observed cancers in the highest exposed groups was somewhat higher than expected. However, some evidence of a trend was apparent in the internal analyses of both the mortality and incidence data, although the relative risks did not increase monotonically. This trend was much stronger for pentachlorophenol than tetrachlorophenol for both mortality and incidence and the relative risks in the mortality analysis were somewhat higher than the incidence analysis.

Some evidence for a dose-response was observed for kidney cancer mortality and both pentachlorophenol and tetrachlorophenol exposure (Table 6). Excesses were also observed in the highest exposed groups in the SMR analysis compared to the general population. The trend was somewhat stronger for pentachlorophenol exposure. The evidence for a dose-response was much weaker in the incidence analyses although a weak trend with pentachlorophenol was still apparent.

No association between level of exposure to pentachlorophenol, tetrachlorophenol, or all chlorophenols and lung cancer incidence or mortality were observed in any analysis (Table 7).

Although the numbers were small, there appeared to be evidence of a dose-response relationship with liver cancer and overall chlorophenol exposure and pentachlorophenol, but not

with tetrachlorophenol (Table 8). A suggestive trend was apparent for both mortality and incidence, although the relative risks dropped in the highest exposure categories and the trends were not statistically significant. Some elevated relative risks were observed in higher exposed strata in Poisson regression analyses of several other cancers that were not considered *a priori* to be associated with chlorophenols or related herbicides, but the relative risks did not appear to increase consistently with level of exposure and the trends were also not statistically significant.

Analyses were performed using lagging to allow for a latency period for incident non-Hodgkin's lymphoma, soft tissue sarcoma, multiple myeloma, kidney cancer, lung cancer and liver cancer and cumulative exposure to pentachlorophenol (Table 9). The associations between non-Hodgkin's lymphoma and kidney cancer and pentachlorophenol appeared to be strongest allowing for a 20-year latency period. While the statistical significance of the trend with multiple myeloma appeared to slightly weaken with the greater latency period, a monotonically increasing pattern was observed in the 20-year lag model. Lagging weakened the association with liver cancer incidence and had no effect on the relationship with lung cancer. Lagging exposure for soft tissue sarcoma further reduced the number of cases in the highest exposed categories. Analyses were repeated using lagging for cumulative exposure to tetrachlorophenol (Table 10). Associations between cancer risk and level of exposure did not improve.

Table 1: Major Causes of Death among Male BC Sawmill Workers: 1950-1995

Disease Category	Deaths	SMR (95% CI)*
All Deaths	5872	0.95 (0.93-0.98)
All Cancers	1495	1.00 (0.95-1.05)
Infective & Parastic Diseases	49	0.59 (0.44-0.78)
Endocrine/Nutritional/Metabolic	107	1.01 (0.83-1.23)
Blood Diseases	15	1.05 (0.59-1.73)
Mental Disorders	62	0.89 (0.68-1.13)
Nervous System/Sense Organ Disease	69	0.76 (0.59-0.96)
Circulatory Disease	2510	0.98 (0.94-1.02)
Respiratory Disease	384	0.83 (0.75-0.92)
Digestive Disease	217	0.81 (0.71-0.93)
Genitourinary Disease	71	0.95 (0.74-1.19)
Musculoskeletal Disease	13	0.95 (0.50-1.62)
Symptoms/Ill-Defined	71	1.16 (0.91-1.46)
Accidents/Poisoning/Violence	759	0.93 (0.86-1.00)
All Other Causes of Death	22	1.14 (0.71-1.73)

Table 3: Cancer Mortality among BC Sawmill Workers by Level of Exposure to Chlorophenols*

Disease Category	Mortality*		Incidence#	
	Deaths	SMR (95% CI)	Cancers	SIR (95% CI)
All Cancers	1495	1.00 (0.95-1.05)	2571	0.99 (0.95-1.04)
All Buccal Cavity/Pharynx	29	0.84 (0.57-1.21)	99	0.92 (0.75-1.12)
Naso-pharyngeal	4	0.71 (0.19-1.82)	4	0.42 (0.11-1.08)
All Digestive Cancers	441	0.97 (0.89-1.07)	600	0.98 (0.90-1.06)
Esophageal	41	1.01 (0.72-1.37)	31	0.84 (0.57-1.20)
Stomach	90	0.94 (0.75-1.15)	105	1.05 (0.86-1.28)
Colon	131	1.00 (0.83-1.18)	187	0.94 (0.81-1.09)
Rectum	54	1.10 (0.82-1.43)	158	1.08 (0.92-1.26)
Liver	22	0.98 (0.62-1.49)	21	0.79 (0.49-1.21)
Pancreas	83	1.00 (0.79-1.24)	76	1.05 (0.83-1.31)
All Respiratory Cancers	503	1.04 (0.95-1.13)	578	1.01 (0.94-1.09)
Sino-nasal	2	0.96 (0.12-3.47)	6	1.05 (0.39-2.29)
Larynx	14	0.86 (0.47-1.44)	40	0.87 (0.62-1.18)
Lung	482	1.04 (0.95-1.14)	519	1.02 (0.93-1.11)
Pleura	4	0.92 (0.25-2.35)	11	1.22 (0.61-2.18)
Prostate Cancer	153	1.04 (0.88-1.22)	580	0.96 (0.89-1.04)
Urinary Cancers	93	1.16 (0.93-1.42)	222	1.14 (0.99-1.31)
Kidney	30	1.31 (0.98-1.73)	79	1.10 (0.88-1.38)
Bladder & Other Urinary	43	1.01 (0.73-1.36)	143	1.16 (0.98-1.37)
Connective tissue cancer	7	1.10 (0.44-2.27)	13	0.84 (0.49-1.44)
Malignant melanoma	22	1.17 (0.73-1.77)	76	1.01 (0.81-1.26)
Brain Cancer	49	0.99 (0.73-1.31)	50	1.08 (0.80-1.43)
All Lymphatic/hematopoietic	122	0.88 (0.73-1.05)	202	0.94 (0.82-1.08)
Non-Hodgkin's Lymphoma	49	1.02 (0.75-1.34)	92	0.99 (0.81-1.21)
Hodgkin's Disease	8	0.74 (0.32-1.47)	18	0.94 (0.56-1.49)
Multiple Myeloma	23	0.94 (0.60-1.41)	25	0.80 (0.52-1.18)
Leukemia	42	0.78 (0.56-1.07)	67	1.03 (0.81-1.31)

* 1950-1995, relative to BC rates, adjusted for age & calendar period.

Table 4: Cancer Incidence among BC Sawmill Workers by Level of Exposure to Chlorophenols*

Disease Category	Mortality*		Incidence#	
	Deaths	SMR (95% CI)	Cancers	SIR (95% CI)
All Cancers	1495	1.00 (0.95-1.05)	2571	0.99 (0.95-1.04)
All Buccal Cavity/Pharynx	29	0.84 (0.57-1.21)	99	0.92 (0.75-1.12)
Naso-pharyngeal	4	0.71 (0.19-1.82)	4	0.42 (0.11-1.08)
All Digestive Cancers	441	0.97 (0.89-1.07)	600	0.98 (0.90-1.06)
Esophageal	41	1.01 (0.72-1.37)	31	0.84 (0.57-1.20)
Stomach	90	0.94 (0.75-1.15)	105	1.05 (0.86-1.28)
Colon	131	1.00 (0.83-1.18)	187	0.94 (0.81-1.09)
Rectum	54	1.10 (0.82-1.43)	158	1.08 (0.92-1.26)
Liver	22	0.98 (0.62-1.49)	21	0.79 (0.49-1.21)
Pancreas	83	1.00 (0.79-1.24)	76	1.05 (0.83-1.31)
All Respiratory Cancers	503	1.04 (0.95-1.13)	578	1.01 (0.94-1.09)
Sino-nasal	2	0.96 (0.12-3.47)	6	1.05 (0.39-2.29)
Larynx	14	0.86 (0.47-1.44)	40	0.87 (0.62-1.18)
Lung	482	1.04 (0.95-1.14)	519	1.02 (0.93-1.11)
Pleura	4	0.92 (0.25-2.35)	11	1.22 (0.61-2.18)
Prostate Cancer	153	1.04 (0.88-1.22)	580	0.96 (0.89-1.04)
Urinary Cancers	93	1.16 (0.93-1.42)	222	1.14 (0.99-1.31)
Kidney	30	1.31 (0.98-1.73)	79	1.10 (0.88-1.38)
Bladder & Other Urinary	43	1.01 (0.73-1.36)	143	1.16 (0.98-1.37)
Connective tissue cancer	7	1.10 (0.44-2.27)	13	0.84 (0.49-1.44)
Malignant melanoma	22	1.17 (0.73-1.77)	76	1.01 (0.81-1.26)
Brain Cancer	49	0.99 (0.73-1.31)	50	1.08 (0.80-1.43)
All Lymphatic/hematopoietic	122	0.88 (0.73-1.05)	202	0.94 (0.82-1.08)
Non-Hodgkin's Lymphoma	49	1.02 (0.75-1.34)	92	0.99 (0.81-1.21)
Hodgkin's Disease	8	0.74 (0.32-1.47)	18	0.94 (0.56-1.49)
Multiple Myeloma	23	0.94 (0.60-1.41)	25	0.80 (0.52-1.18)
Leukemia	42	0.78 (0.56-1.07)	67	1.03 (0.81-1.31)

* 1969-1995, relative to BC rates, adjusted for age & calendar period.

Table 2: Cancer Incidence and Mortality among BC Sawmill Workers

Disease Category	Mortality*		Incidence#	
	Deaths	SMR (95% CI)	Cancers	SIR (95% CI)
All Cancers	1495	1.00 (0.95-1.05)	2571	0.99 (0.95-1.04)
All Buccal Cavity/Pharynx	29	0.84 (0.57-1.21)	99	0.92 (0.75-1.12)
Naso-pharyngeal	4	0.71 (0.19-1.82)	4	0.42 (0.11-1.08)
All Digestive Cancers	441	0.97 (0.89-1.07)	600	0.98 (0.90-1.06)
Esophageal	41	1.01 (0.72-1.37)	31	0.84 (0.57-1.20)
Stomach	90	0.94 (0.75-1.15)	105	1.05 (0.86-1.28)
Colon	131	1.00 (0.83-1.18)	187	0.94 (0.81-1.09)
Rectum	54	1.10 (0.82-1.43)	158	1.08 (0.92-1.26)
Liver	22	0.98 (0.62-1.49)	21	0.79 (0.49-1.21)
Pancreas	83	1.00 (0.79-1.24)	76	1.05 (0.83-1.31)
All Respiratory Cancers	503	1.04 (0.95-1.13)	578	1.01 (0.94-1.09)
Sino-nasal	2	0.96 (0.12-3.47)	6	1.05 (0.39-2.29)
Larynx	14	0.86 (0.47-1.44)	40	0.87 (0.62-1.18)
Lung	482	1.04 (0.95-1.14)	519	1.02 (0.93-1.11)
Pleura	4	0.92 (0.25-2.35)	11	1.22 (0.61-2.18)
Prostate Cancer	153	1.04 (0.88-1.22)	580	0.96 (0.89-1.04)
Urinary Cancers	93	1.16 (0.93-1.42)	222	1.14 (0.99-1.31)
Kidney	30	1.31 (0.98-1.73)	79	1.10 (0.88-1.38)
Bladder & Other Urinary	43	1.01 (0.73-1.36)	143	1.16 (0.98-1.37)
Connective tissue cancer	7	1.10 (0.44-2.27)	13	0.84 (0.49-1.44)
Malignant melanoma	22	1.17 (0.73-1.77)	76	1.01 (0.81-1.26)
Brain Cancer	49	0.99 (0.73-1.31)	50	1.08 (0.80-1.43)
All Lymphatic/hematopoietic	122	0.88 (0.73-1.05)	202	0.94 (0.82-1.08)
Non-Hodgkin's Lymphoma	49	1.02 (0.75-1.34)	92	0.99 (0.81-1.21)
Hodgkin's Disease	8	0.74 (0.32-1.47)	18	0.94 (0.56-1.49)
Multiple Myeloma	23	0.94 (0.60-1.41)	25	0.80 (0.52-1.18)
Leukemia	42	0.78 (0.56-1.07)	67	1.03 (0.81-1.31)

* 1950-1995, relative to BC rates, adjusted for age & calendar period.

1969-1995, relative to BC rates, adjusted for age & calendar period.

Table 3 : Dose Response Analyses: Non-Hodgkin's Lymphoma

Analysis	All		PCP		TCP	
	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)
Mortality – SMR Analysis*						
<1	11	0.78 (0.39-1.39)	15	0.77 (0.43-1.27)	29	0.96 (0.64-1.38)
1-2	5	0.69 (0.22-1.61)	6	0.80 (0.29-1.74)	5	0.83 (0.27-1.93)
2-5	14	1.23 (0.67-2.07)	18	1.52 (0.90-2.40)	13	1.62 (0.86-2.77)
5+	19	1.21 (0.73-1.89)	10	1.07 (0.51-1.97)	2	0.51 (0.06-1.84)
Mortality – Poisson Regression						
<1	11	1.00 (reference)	15	1.00 (reference)	29	1.00 (reference)
1-2	5	0.90 (0.31-2.59)	6	1.21 (0.46-3.15)	5	0.93 (0.36-2.43)
2-5	14	1.81 (0.81-4.04)	18	2.44 (1.17-5.11)	13	1.96 (0.99-3.89)
5+	19	1.90 (0.87-4.17)	10	1.77 (0.75-4.21)	2	0.63 (0.15-2.69)
Trend		p=0.07		p=0.06		p=0.44
Incidence – SIR Analysis#						
<1	24	0.76 (0.49-1.12)	38	0.80 (0.57-1.10)	50	0.86 (0.64-1.13)
1-2	15	0.96 (0.54-1.58)	13	0.87 (0.46-1.49)	11	0.82 (0.41-1.47)
2-5	18	0.84 (0.50-1.33)	24	1.17 (0.75-1.73)	20	1.11 (0.68-1.71)
5+	25	1.16 (0.75-1.72)	17	1.06 (0.62-1.70)	11	1.20 (0.60-2.15)
Incidence – Poisson Regression						
<1	24	1.00 (reference)	38	1.00 (reference)	50	1.00 (reference)
1-2	15	1.26 (0.66-2.40)	13	1.33 (0.70-2.52)	11	0.91 (0.47-1.75)
2-5	18	1.10 (0.60-2.05)	24	1.88 (1.08-3.28)	20	1.34 (0.80-2.26)
5+	35	1.51 (0.87-2.60)	17	1.71 (0.91-3.24)	11	1.54 (0.79-2.99)
Trend		p=0.18		p=0.03		p=0.14

* 1950-1995, relative to BC rates, adjusted for age & calendar period.

1969-1995, relative to BC rates, adjusted for age & calendar period.

Table 4: Dose Response Analyses: Connective Tissues and Soft Tissue Sarcoma

Analysis	All		PCP		TCP	
	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)
Connective tissue mortality – SMR Analysis*						
<1	4	1.96 (0.53-5.02)	4	1.34 (0.36-3.43)	6	1.48
1-2	1	0.95 (0.02-5.29)	1	1.05 (0.03-5.85)	0	(exp=0.84)
2-5	1	0.68 (0.02-3.79)	1	0.73 (0.02-4.07)	0	(exp=1.01)
5+	1	0.55 (0.01-3.06)	1	0.96 (0.02-5.35)	1	2.14
Connective tissue incidence – SIR Analysis#						
<1	7	1.37 (0.55-2.82)	10	1.27 (0.61-2.34)	10	1.08 (0.52-1.99)
1-2	3	1.17 (0.24-3.42)	1	0.45 (0.01-2.51)	1	0.45 (0.01-2.51)
2-5	1	0.30 (0.01-1.68)	1	0.33 (0.01-1.84)	1	0.37 (0.01-2.06)
5+	2	0.46 (0.06-1.66)	1	0.42 (0.01-2.34)	1	0.81 (0.02-4.51)
Soft tissue sarcoma incidence – Poisson Regression						
<1	12	1.00 (reference)	18	1.00 (reference)	16	1.00 (reference)
1-2	5	0.85 (0.30-2.41)	3	0.64 (0.18-2.20)	3	0.77 (0.23-2.66)
2-5	4	0.58 (0.18-1.82)	2	0.18 (0.04-0.85)	4	0.66 (0.22-1.99)
5+	2	0.25 (0.05-1.16)				
Trend		0=0.06		p=0.11		p=0.43

* 1950-1995, relative to BC rates, adjusted for age & calendar period.

1969-1995, relative to BC rates, adjusted for age & calendar period.

Table 5: Dose Response Analyses: Multiple Myeloma

Analysis	All		PCP		TCP	
	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)
Mortality – SMR Analysis*						
<1	4	0.63 (0.17-1.61)	4	0.47 (0.13-1.20)	15	0.99 (0.55-1.63)
1-2	4	1.22 (0.33-3.12)	5	1.34 (0.43-3.12)	0	0.00 (exp=2.99)
2-5	5	0.86 (0.28-2.00)	4	0.60 (0.16-1.54)	4	0.96 (0.26-2.46)
5+	10	1.12 (0.54-2.06)	10	1.80 (0.86-3.31)	4	1.91 (0.52-4.89)
Mortality – Poisson Regression						
<1	4	1.00 (reference)	4	1.00 (reference)	15	1.00 (reference)
1-2	4	2.05 (0.51-8.22)	5	3.30 (0.87-12.51)	0	0.00
2-5	5	1.82 (0.48-6.90)	4	1.58 (0.38-6.63)	4	0.94 (0.31-2.91)
5+	10	2.83 (0.84-9.52)	10	4.80 (1.39-16.54)	4	1.84 (0.59-5.78)
Trend		p=0.11		p=0.03		p=0.55
Incidence – SIR Analysis#						
<1	5	0.58 (0.19-1.35)	6	0.50 (0.18-1.09)	15	0.82 (0.46-1.35)
1-2	3	0.70 (0.14-2.04)	4	0.84 (0.23-2.15)	1	0.24 (0.01-1.34)
2-5	6	0.85 (0.31-1.85)	4	0.50 (0.14-1.28)	5	0.84 (0.27-1.96)
5+	11	0.96 (0.48-1.72)	11	1.63 (0.81-2.92)	4	1.29 (0.35-3.30)
Incidence – Poisson Regression						
<1	5	1.00 (reference)	6	1.00 (reference)	15	1.00 (reference)
1-2	3	1.24 (0.30-5.19)	4	2.09 (0.57-7.61)	1	0.27 (0.04-2.04)
2-5	6	1.52 (0.46-5.07)	4	1.30 (0.34-4.98)	5	1.06 (0.38-2.94)
5+	11	1.80 (0.60-5.40)	11	4.18 (1.36-12.9)	4	1.80 (0.58-5.60)
Trend		p=0.28		p=0.02		p=0.48

* 1950-1995, relative to BC rates, adjusted for age & calendar period.

1969-1995, relative to BC rates, adjusted for age & calendar period.

Table 6: Dose Response Analyses: Kidney

Analysis	All		PCP		TCP	
	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)
Mortality – SMR Analysis*						
<1	13	1.23 (0.65-2.10)	15	1.05 (0.59-1.73)	25	1.04 (0.67-1.54)
1-2	4	0.73 (0.20-1.87)	6	1.01 (0.37-2.20)	5	1.10 (0.36-2.56)
2-5	11	1.21 (0.60-2.17)	17	1.72 (1.00-2.75)	14	2.24 (1.22-3.76)
5+	22	1.71 (1.07-2.58)	12	1.52 (0.79-2.66)	6	1.93 (0.71-4.20)
Mortality – Poisson Regression						
<1	13	1.00 (reference)	15	1.00 (reference)	25	1.00 (reference)
1-2	4	0.62 (0.20-1.89)	6	1.33 (0.51-3.47)	5	0.94 (0.36-2.46)
2-5	11	1.14 (0.51-2.58)	17	2.59 (1.22-5.49)	14	2.09 (1.07-4.08)
5+	22	1.64 (0.80-3.37)	12	2.30 (1.00-5.32)	6	1.87 (0.75-4.67)
Trend		p=0.12		p=0.02		p=0.04
Incidence – SIR Analysis#						
<1	25	1.16 (0.75-1.72)	32	1.03 (0.70-1.45)	47	1.12 (0.82-1.49)
1-2	12	1.12 (0.58-1.96)	9	0.80 (0.37-1.52)	6	0.65 (0.24-1.42)
2-5	15	0.95 (0.53-1.57)	22	1.34 (0.84-2.02)	14	1.06 (0.58-1.78)
5+	27	1.13 (0.74-1.65)	16	1.22 (0.70-1.98)	12	1.68 (0.87-2.94)
Incidence – Poisson Regression						
<1	25	1.00 (reference)	32	1.00 (reference)	47	1.00 (reference)
1-2	12	0.98 (0.49-1.96)	9	1.03 (0.49-2.18)	6	0.55 (0.23-1.28)
2-5	15	0.86 (0.45-1.64)	22	1.79 (0.99-3.24)	14	1.01 (0.56-1.84)
5+	27	1.04 (0.59-1.83)	16	1.66 (0.85-3.23)	12	1.80 (0.94-3.43)
Trend		p=0.97		p=0.07		p=0.31

* 1950-1995, relative to BC rates, adjusted for age & calendar period.

1969-1995, relative to BC rates, adjusted for age & calendar period.

Table 7: Dose Response Analyses: Lung Cancer

Analysis	All		PCP		TCP	
	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)
Mortality – SMR Analysis*						
<1	145	1.18 (1.00-1.39)	198	1.20 (1.04-1.38)	299	1.06 (0.94-1.19)
1-2	66	1.05 (0.82-1.35)	73	1.03 (0.78-1.35)	74	1.30 (1.00-1.68)
2-5	120	1.10 (0.92-1.32)	108	0.88 (0.69-1.13)	80	0.99 (0.77-1.27)
5+	151	0.90 (0.76-1.06)	103	1.00 (0.82-1.20)	29	0.71 (0.48-1.05)
Mortality – Poisson Regression						
<1	145	1.00 (reference)	198	1.00 (reference)	299	1.00 (reference)
1-2	66	0.90 (0.67-1.20)	73	1.05 (0.80-1.38)	74	1.18 (0.91-1.52)
2-5	120	1.10 (0.84-1.37)	108	0.96 (0.75-1.23)	80	0.97 (0.75-1.24)
5+	151	0.93 (0.73-1.17)	103	1.10 (0.85-1.42)	29	0.72 (0.49-1.06)
Trend		p=0.73		p=0.68		p=0.19
Incidence – SIR Analysis#						
<1	157	1.14 (0.97-1.34)	216	1.13 (0.98-1.27)	311	1.07 (0.96-1.12)
1-2	70	1.01 (0.79-1.28)	78	1.00 (0.79-1.25)	77	1.18 (0.94-1.48)
2-5	127	1.13 (0.95-1.35)	119	0.93 (0.77-1.12)	94	0.96 (0.78-1.18)
5+	165	0.89 (0.76-1.04)	106	0.97 (0.81-1.18)	37	0.72 (0.51-0.99)
Incidence – Poisson Regression						
<1	157	1.00 (reference)	216	1.00 (reference)	311	1.00 (reference)
1-2	70	0.89 (0.67-1.18)	78	1.11 (0.86-1.45)	77	1.06 (0.83-1.37)
2-5	127	1.02 (0.80-1.29)	119	1.07 (0.84-1.36)	94	0.97 (0.77-1.22)
5+	165	0.81 (0.65-1.02)	106	1.12 (0.87-1.44)	37	0.78 (0.55-1.10)
Trend		P=0.12		p=0.45		p=0.20

* 1950-1995, relative to BC rates, adjusted for age & calendar period.

1969-1995, relative to BC rates, adjusted for age & calendar period.

Table 8: Dose Response Analyses: Liver

Analysis	All		PCP		TCP	
	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)
Mortality – SMR Analysis*						
<1	3	0.47 (0.97-1.37)	4	0.45 (0.12-1.15)	14	1.00 (0.55-1.68)
1-2	2	0.61 (0.07-2.20)	5	1.44 (0.47-3.36)	7	2.58 (1.03-5.31)
2-5	8	1.52 (0.65-2.99)	8	1.43 (0.62-2.82)	1	0.27 (0.01-1.50)
5+	9	1.20 (0.55-2.28)	5	1.11 (0.36-2.59)	0	0.00 (exp=1.91)
Mortality – Poisson Regression						
<1	3	1.00 (reference)	4	1.00 (reference)	14	1.00 (reference)
1-2	2	1.13 (0.19-6.79)	5	3.46 (0.91-13.23)	8	0.95 (0.38-2.39)
2-5	8	1.97 (0.77-11.5)	8	3.72 (1.04-13.28)		
5+	9	2.44 (0.62-9.53)	5	2.53 (0.61-10.43)		
Trend		p=0.13		p=0.10		
Incidence – SIR Analysis#						
<1	2	0.26 (0.03-0.94)	3	0.27 (0.06-0.79)	11	0.71 (0.35-1.27)
1-2	2	0.52 (0.06-1.88)	4	0.98 (0.27-2.51)	7	2.02 (0.81-4.16)
2-5	9	1.53 (0.70-2.91)	12	1.95 (1.01-3.41)	3	0.60 (0.12-1.75)
5+	8	0.89 (0.38-1.75)	2	0.40 (0.05-1.44)	0	0.00 (exp=2.62)
Incidence – Poisson Regression						
<1	2	1.00 (reference)	3	1.00 (reference)	11	1.00 (reference)
1-2	2	1.81 (0.25-12.9)	4	4.09 (0.89-18.76)	7	2.65 (1.03-6.85)
2-5	9	5.54 (1.18-26.0)	12	8.47 (2.21-32.45)	3	0.52 (0.14-1.88)
5+	8	2.98 (0.61-14.7)	2	1.41 (0.21-9.22)		
Trend		P=0.133		p=0.18		p=0.58

* 1950-1995, relative to BC rates, adjusted for age & calendar period.

1969-1995, relative to BC rates, adjusted for age & calendar period.

Table 9: Cancer Incidence and Pentachlorophenol Exposure Allowing for a Latency Period

	No Lag		10-year Lag		20-year Lag	
	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)
Non-Hodgkin's Lymphoma						
<1	38	1.00 (reference)	39	1.00 (reference)	46	1.00 (reference)
1-2	13	1.33 (0.70-2.52)	12	1.53 (0.79-2.98)	13	1.83 (0.95-3.50)
2-5	24	1.88 (1.08-3.28)	26	2.34 (1.34-4.07)	21	2.05 (1.14-3.68)
5+	17	1.71 (0.91-3.24)	15	1.78 (0.92-3.47)	12	1.98 (0.97-4.06)
Trend		p=0.03		p=0.02		p=0.02
Soft Tissue Sarcoma						
<1	18	1.00 (reference)	18	1.00 (reference)	20	1.00 (reference)
1-2	3	0.64 (0.18-2.20)	3	0.80 (0.23-2.80)	1	0.34 (0.04-2.61)
2+	2	0.18 (0.04-0.85)	2	0.22 (0.05-1.03)	2	0.33 (0.07-1.59)
Trend		P=0.11		P=0.06		P=0.12
Multiple Myeloma						
<1	6	1.00 (reference)	6	1.00 (reference)	8	1.00 (reference)
1-2	4	2.09 (0.57-7.61)	5	3.10 (0.90-10.7)	3	1.72 (0.43-6.95)
2-5	4	1.30 (0.34-4.98)	5	1.80 (0.50-6.54)	6	2.05 (0.62-6.78)
5+	11	4.18 (1.36-12.9)	9	3.92 (1.21-12.7)	8	3.84 (1.20-12.3)
Trend		p=0.02		p=0.04		p=0.03
Kidney Cancer						
<1	32	1.00 (reference)	34	1.00 (reference)	39	1.00 (reference)
1-2	9	1.03 (0.49-2.18)	10	1.26 (0.61-2.60)	7	0.96 (0.42-2.21)
2-5	22	1.79 (0.99-3.24)	19	1.59 (0.85-2.94)	21	1.94 (1.06-3.53)
5+	16	1.66 (0.85-3.23)	16	1.75 (0.89-3.40)	12	1.80 (0.87-3.73)
Trend		p=0.07		p=0.08		p=0.03
Lung Cancer						
<1	216	1.00 (reference)	225	1.00 (reference)	268	1.00 (reference)
1-2	78	1.11 (0.86-1.45)	75	1.17 (0.89-1.53)	70	1.08 (0.82-1.42)
2-5	119	1.07 (0.84-1.36)	117	1.09 (0.85-1.38)	108	1.05 (0.83-1.34)
5+	106	1.12 (0.87-1.44)	102	1.16 (0.90-1.50)	73	1.13 (0.86-1.50)
Trend		p=0.45		p=0.30		p=0.40
Liver Cancer						
<1	3	1.00 (reference)	5	1.00 (reference)	8	1.00 (reference)
1-2	4	4.09 (0.89-18.76)	2	2.12 (0.48-9.29)	5	2.69 (0.82-8.81)
2-5	12	8.47 (2.21-32.45)	11	4.90 (1.53-15.71)	7	2.31 (0.76-7.05)
5+	2	1.41 (0.21-9.22)	2	0.91 (0.16-5.23)	1	0.50 (0.06-4.30)
Trend		p=0.18		p=0.33		p=0.77

Table 10: Cancer Incidence & Tetrachlorophenol Exposure Allowing for a Latency Period

	No Lag		10-year Lag		20-year Lag	
	n	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)
Non-Hodgkin's Lymphoma						
<1	50	1.00 (reference)	61	1.00 (reference)	78	1.00 (reference)
1-2	11	0.91 (0.47-1.75)	9	0.94 (0.46-1.90)	8	1.66 (0.78-3.54)
2-5	20	1.34 (0.80-2.26)	14	1.30 (0.71-2.37)	5	1.27 (0.49-3.26)
5+	11	1.54 (0.79-2.99)	8	1.95 (0.90-4.22)	1	1.48 (0.20-11.12)
Trend		p=0.14		p=0.11		p=0.32
Soft Tissue Sarcoma						
<1	16	1.00 (reference)	19	1.00 (reference)	23	1.00 (reference)
1-2	3	0.77 (0.23-2.66)	2	0.78 (0.18-3.40)		
2+	4	0.66 (0.22-1.99)	2	0.56 (0.12-2.50)		
Trend		P=0.43		P=0.42		P=1.00
Multiple Myeloma						
<1	15	1.00 (reference)	15	1.00 (reference)	19	1.00 (reference)
1-2	1	0.27 (0.04-2.04)	2	0.69 (0.15-3.04)	3	1.67 (0.48-5.89)
2-5	5	1.06 (0.38-2.94)	6	1.70 (0.64-4.53)	3	1.79 (0.48-6.65)
5+	4	1.80 (0.58-5.60)	2	1.46 (0.32-6.71)		
Trend		p=0.48		p=0.35		p=0.30
Kidney Cancer						
<1	47	1.00 (reference)	53	1.00 (reference)	66	1.00 (reference)
1-2	6	0.55 (0.23-1.28)	7	0.79 (0.36-1.75)	7	1.37 (0.61-3.06)
2-5	14	1.01 (0.56-1.84)	12	1.16 (0.61-2.21)	6	1.10 (0.45-2.67)
5+	12	1.80 (0.94-3.43)	7	1.71 (0.75-3.88)		
Trend		p=0.31		p=0.36		p=0.68
Lung Cancer						
<1	311	1.00 (reference)	358	1.00 (reference)	446	1.00 (reference)
1-2	77	1.06 (0.83-1.37)	66	1.08 (0.83-1.40)	41	1.13 (0.81-1.57)
2-5	94	0.97 (0.77-1.22)	71	0.95 (0.73-1.23)	26	0.77 (0.51-1.15)
5+	37	0.78 (0.55-1.10)	24	0.79 (0.52-1.20)	6	0.90 (0.40-2.05)
Trend		p=0.20		P=0.30		p=0.36
Liver Cancer						
<1	11	1.00 (reference)	14	1.00 (reference)	19	1.00 (reference)
1-2	7	2.65 (1.03-6.85)	5	2.05 (0.73-5.77)	1	0.61 (0.08-4.74)
2+	3	0.52 (0.14-1.88)	2	0.42 (0.09-1.91)	1	0.44 (0.05-3.47)
Trend		p=0.58		p=0.47		p=0.38

Discussion

This study observed associations between the risks of non-Hodgkin's lymphoma, multiple myeloma, and kidney cancer and dermal exposure to chlorophenol fungicides in sawmills. While the relative risks among the most highly exposed were only slightly or moderately elevated compared to the general population, strong dose-response relationships were observed compared to the least exposed workers. These relationships were strongest for all three cancers when analyses were restricted to pentachlorophenol exposure and were further strengthened by allowing for a 20-year latency period. An association between NHL and exposure to chlorophenols and phenoxy herbicides has been one of the most consistent findings of other studies [Hardell et al, 1994; Hooiveld et al, 1998; Garabedian et al, 1999; Kogevinas et al, 1995]. An excess of multiple myeloma has been observed in some [t Mannetje et al, 2005; Mikoczy et al, 1994], but not all studies of workers exposed to these substances [Hooiveld et al, 1998; Kogevinas et al, 1997]. Kidney cancer has also been observed in some [Hooiveld et al, 1998; Ramlow et al, 1996], but not all studies [Kogevinas et al, 1997].

This study did not find any evidence of an increased risk of soft tissue sarcoma or connective tissue cancers. While STS is one of the cancers most consistently observed among population exposed to phenoxy herbicides, the results from the few studies with sufficient power to examining the risk among workers exposed to chlorophenols alone have been somewhat mixed [Hoppin et al, 1998; Kogevinas et al, 1997; Woods et al, 1987]. Although this study had relatively low power to identify a dose-response relationship for rare cancers, that would not explain the suggested negative association for STS.

This study also did not find associations with lung, sinonasal, or nasopharyngeal cancer. Evidence of an excess of lung cancer has been observed in a few other studies of chlorophenol

and phenoxy herbicide exposed workers [Hooiveld et al, 1998; Kogevinas et al, 1997]. These workers may experience a mix of exposures that may differ from those experiences by sawmill workers. Despite the large size of this cohort, relatively few sinonasal or nasopharyngeal cancers were expected based on general population rates and the study had insufficient power to examine dose-response relationships for these rare cancers. In addition, previous studies have documented that almost all exposure to chlorophenols in sawmills is through dermal exposure and respiratory exposure may only play a very minimal role, although the impact of route of exposure on cancer risk is not clear.

There are a number of possible reasons for the inconsistency between some of the results of this study and the findings of previous studies. First, the health effects of various chlorophenols and phenoxy herbicides may differ. The results of animal studies have been found to differ by type of chlorophenol [IARC, 1999; Pepelco et al, 2005]. Most studies have reported results of workers exposed to a mix of these related chemicals and only one reported results for exposure to pentachlorophenol [Ramlow et al, 1996], while none have reported results for tetrachlorophenol alone. In addition, it is difficult to determine how the studies compare in regards to level or route of exposure.

The BC sawmill cohort was initiated because of concern that chlorophenol fungicides may potentially be contaminated with dioxins. Both technical grade TeCP and PCP and formulations have been found to be contaminated with hexachlorinated (range = below the limit of detection - 23 ppm), heptachlorinated (range = 0.05 - 180 ppm), and octachlorinated dibenzodioxins (range = below the limit of detection - 3,600 ppm) [Teschke et al, 1994]. Because of this, previous analyses of this cohort did not differentiate between the two fungicides. However, it is important to note that the only dioxin that has been classified as either a human or

animal carcinogen by IARC is 2,3,7,8-tetrachlorodibenzodioxin (TCDD) and this congener has not been detected in technical grade PCP or TeCP or the distributors' formulated products [Teschke et al, 1994]. A study by Kontsas and colleagues [1998] of Finnish sawmill workers exposed to tetrachlorophenol fungicides found that the plasma concentrations of polychlorinated dibenzodioxins among exposed workers were similar to unexposed workers and within the range of background levels found in the general population. Thus, sawmill workers are exposed to dioxins that may have lower carcinogenic potential than TCDD and the levels of exposure may be similar to background levels in the population. In contrast, measurements of urinary chlorophenol levels in sawmill workers have usually been one to three orders of magnitude greater than population background levels [Fenske et al, 1987; Hertzman et al, 1988; Teschke et al, 1989].

As with most retrospective cohort studies of occupational cancer, the ability of this study to adjust for the effects of potential non-occupational confounding factors was limited. This problem is most likely to have affected comparisons of the cancer rates in the study population to those in the general population of British Columbia, where the distributions of these lifestyle factors could more markedly differ. This was partially addressed in this study by performing analyses of dose-response within the cohort using Poisson regression. Thus, in order to distort a relationship, a potential confounder would have to be associated with level of exposure as well as disease. Smoking histories were obtained by personal interviews with 2,000 of the cohort members who were employed in 1979 or later. After adjusting for age the smoking rates in the sample of the study population were similar to those of the general population of BC and were not correlated with exposure.

Extensive efforts were directed towards assessing exposure in this study [Hertzman et al, 1988; Teschke et al, 1989]. Although efforts to assess the validity of the approach indicated a relatively high correlation with urinary chlorophenols, non-differential misclassification of exposure remained and may have obscured some associations. In addition, efforts to assess validity were limited to the most recent time period and, although processes in the sawmill industry are relatively simple and stable, it is possible that estimates for earlier time periods may be less valid [Teschke et al, 1996].

Another limitation of this study was its power to examine very rare cancers, in particular sino-nasal cancer, nasopharyngeal, and soft tissue sarcoma. While this study is much larger than previous cohort studies of workers exposed to either TeCP or PCP, it was difficult to examine the risk of these rare cancers in internal analyses. As with almost all retrospective cohort studies, non-differential misclassification of exposure may have contributed to obscuring potential associations. While this study did not find strong associations with exposure to tetrachlorophenol alone, it became the dominant chlorophenol during the later decades of the study and it may be possible that insufficient time has passed to fully assess its impact.

This study also has several strengths that deserve mention. It is one of the largest studies ever conducted to examine the risk of cancer amongst workers exposed to chlorophenols and phenoxy herbicides and the largest to examine the risk specifically associated with pentachlorophenol and tetrachlorophenol. This is also the first cohort study of workers exposed to this family of chemicals to focus on dermal exposure and to attempt to quantify exposure through this route.

Conclusions

Previous analyses of data from this cohort found limited evidence of an increased risk of non-Hodgkin's lymphoma and less conclusive evidence for excesses of some other cancers. This study extended the follow-up and also examined the risk associated with pentachlorophenol and tetrachlorophenol independently and found much stronger associations between the risks of non-Hodgkin's lymphoma, multiple myeloma, and kidney cancer and level of dermal exposure to chlorophenol fungicides in sawmills, particularly with pentachlorophenol. This study did not find any evidence of an association between level of exposure to chlorophenols and increased risk of soft tissue sarcoma, lung cancer, sinonasal, or nasopharyngeal cancers.

References

- Axelsson O. Aspects of confounding in occupational health epidemiology. *Scand J Work Environ Health* 1978;4:98-102.
- Breslow NE, Day NE. *Statistical methods in cancer research. Vol. 2. The design and analysis of cohort studies.* (IARC scientific publication no. 32). Lyon, France: International Association for Research on Cancer, 1987.
- Eriksson M, Hardell L, Adami H-O. Exposure to dioxins as a risk factor for soft tissue sarcoma: a population-based case-control study. *J Natl Cancer Inst* 1990;82:486-490.
- Eriksson M, Hardell L, Berg NO, Möller T, Axelsson O. Soft tissue sarcoma and exposure to chemical substances: a case-referent study. *Br J Ind Med* 1981;38:27-33.
- Fenske RA, Horstman SW, Bentley RK. Assessment of dermal exposure to chlorophenols in timber mills. *Appl Ind Hyg* 1987;2:143-147.
- Garabedian MJ, Hoppin JA, Tolbert PE, Herrick RF, Brann EA. Occupational chlorophenol exposure and non-Hodgkin's lymphoma. *J Occup Environ Med* 1999;41(4):267-272.
- Hardell L, Eriksson M, Degerman A. Meta-analysis of four Swedish case-control studies on exposure to pesticides as risk factors for soft-tissue sarcoma including the relation to tumour localization and histopathologic type. *Int J Oncol* 1995;6:847-851.
- Hardell L, Eriksson M, Degerman A. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphomas. *Cancer Res* 1994;54:2386-2389.
- Hardell L, Eriksson M. The association between soft tissue sarcomas and exposure to phenoxyacetic acid. A new case-referent study. *Cancer* 1988;62:652-656.
- Hardell L, Johansson B, Axelsson O. Epidemiologic study of nasal and nasopharyngeal cancer and their relation to phenoxy acid or chlorophenol exposure. *Am J Indust Med* 1982;3:247-257.
- Hardell L, Bengtsson NO. Epidemiological study of socioeconomic factors and clinical findings in Hodgkin's disease and re-analysis of previous data regarding chemical exposure. *Br J Cancer* 1983;48:217-225.
- Hardell L, Sändstrom A. Case-control study: soft tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. *Br J Cancer* 1979;39:711-717.
- Hertzman C, Teschke K, Ostry A, Hershler R, Dimich-Ward H, Kelly S, Spinelli JJ, Gallagher R, McBride M, Marion SA. Mortality and cancer incidence among a cohort of sawmill workers exposed to chlorophenolate wood preservatives. *Am J Pub Health* 1997;87:71-79.
- Hertzman C, Teschke K, Dimich-Ward H, and Ostry A. Validity and reliability of a method for retrospective evaluation of chlorophenolate exposure in the lumber industry. *Am J Ind Med* 1988;14:703-713.
- Hooiveld M, Heederik DJ, Kogevinas M, Boffetta P, Needham LL, Patterson DG Jr, Bueno-de-Mesquita HB. Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. *Am J Epidemiol* 1998;147(9):891-901.
- Hoppin JA, Tolbert PE, Herrick RF, Freedman DS, Ragsdale BD, Horvat KR, Brann EA. Occupational chlorophenol exposure and soft tissue sarcoma risk among men aged 30-60 years. *Am J Epidemiol* 1998;148(7):693-703.
- Howe GR, Lindsay J. A generalized record linkage computer system for use in medical follow-up studies. *Comput Biomed Res* 1981;14:327-340.
- IARC Working Group. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, vol 77.* International Agency for Research on Cancer Lyon, 1999.
- Jappinen P, Pukkala E, Tola S. Cancer incidence of workers in a Finnish sawmill. *Scand J Work Environ Health* 1989;15:18-23.
- Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P, Bueno-de-Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Fingerhut M, Green L, Kauppinen T, Littorin M, Lyngge E, Mathews JD, Neuberger M, Pearce N, Saracci R. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. *Am J Epidemiol* 1997;145(12):1061-1075.

Kogevinas M, Kauppinen T, Winkelmann R, et al. Soft-tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-control studies. *Epidemiology* 1995;6:396-402.

Kontsas H, Rosenberg C, Tornaeus J, Mutanen P, Jäppinen P. Exposure of workers to 2,3,7,8-substituted polychlorinated dibenzo-p-dioxin (PCDD) and dibenzofuran (PCDF) compounds in a sawmill previously using chlorophenol-containing antistain agents. *Arch Environ Health* 1998;53:99-108.

Lampi P, Hakulinen T, Luostarinen T, Pukkala E, Teppo L. Cancer incidence following chlorophenol exposure in a community in southern Finland. *Arch Environ Health* 1992;47:167-175.

Mirabelli MC, Hoppin JA, Tolbert PE, Herrick RF, Gnepp DR, Brann EA. Occupational exposure to chlorophenol and the risk of nasal and nasopharyngeal cancers among U.S. men aged 30 to 60. *Am J Ind Med* 2000;37(5):532-541.

NIOSH. Life Table Analysis System for the PC. US Department of Health and Human Services, Cincinnati, OH, 2000.

Pearce NE, Smith AJ, Howard JK, Sheppard RA, Giles HJ, Teague CA. Non-Hodgkin's lymphoma and exposure to phenoxyherbicides, chlorophenols, fencing work, and meat works employment: a case-control study. *Br J Ind Med* 1986;43:75-83.

Pepelko WE, Gaylor DW, Mukerjee D. Comparative toxic potency ranking of chlorophenols. *Toxicol Indust Health* 2005;21(5-6): 93-111.

Ramlow JM, Spadacene NW, Hoag SR, Stafford BA, Cartmill JB, Lerner PJ. Mortality in a cohort of pentachlorophenol manufacturing workers, 1940-1989. *Am J Ind Med* 1996;30(2):180-194.

Smith AH, Pearce NE, Giles HJ, Teague CA. Soft tissue sarcoma and exposure to phenoxyherbicides and chlorophenols in New Zealand. *J Natl Cancer Inst* 1984;73:1111-1117.

Teschke K, Hertzman C, Dimich-Ward H, Ostry A, Blair J, Hershler R. A comparison of exposure estimates by worker raters and industrial hygienists. *Scand J Work Environ Health*. 1989;15:424-429.

Teschke K, Hertzman C, Fenske R, Jin A, Ostry A, van Netten C, Leiss W. A history of process and chemical changes for fungicide application in the western Canadian lumber industry: What can we learn? *Appl Occup Environ Hyg* 1994;9:984-993.

Teschke K, Marion SA, Ostry A, Hertzman C, Hershler R, Dimich-Ward H, Heacock H, Kelly S. Reliability of retrospective chlorophenol exposure estimates over five decades. *Am J Indust Med* 1996;30:616-622.

Teschke K, Ostry A, Hertzman C, Demers PA, Barroetavena MC, Davies HW, Dimich-Ward H, Heacock H, Marion S. Opportunities for a broader understanding of work and health: multiple uses of an occupational cohort database. *Canadian Journal of Public Health* 1998;89(2):132-136.

U.S. National Toxicology Program. Toxicology and carcinogenesis studies of pentachlorophenol in F344/N rats (NTP Tech Rep No 483; NIH Publ No 97-3973. Research Triangle Park, NC, 1997.

U.S. National Toxicology Program. Toxicology and carcinogenesis studies of two pentachlorophenol technical grade mixtures in B6C3F₁ mice (NTP Tech Rep No 349; NIH Publ No 89-2804). Research Triangle Park, NC, 1989.

Woods JS, Pollisar L, Severson RK, Heuser LS, Kulander BG. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. *J Natl Cancer Inst* 1987;78:899-910.

All rights reserved. The Workers' Compensation Board of B.C. encourages the copying, reproduction, and distribution of this document to promote health and safety in the workplace, provided that the Workers' Compensation Board of B.C. is acknowledged. However, no part of this publication may be copied, reproduced, or distributed for profit or other commercial enterprise or may be incorporated into any other publication without written permission of the Workers' Compensation Board of B.C.

Additional copies of this publication may be obtained by contacting:

Research Secretariat
6951 Westminster Highway
Richmond, B.C. V7C 1C6
Phone (604) 244-6300 / Fax (604) 244-6295
Email: resquery@worksafebc.com