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## **Cancer and Lung Disease in relation to Sawfiling and Endotoxin among Sawmill Workers**

March 2012

Principal Investigator/Applicant  
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RS2008-DG06



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# **Cancer and lung disease in relation to sawfiling and endotoxin among sawmill workers**

**Report to the Research Secretariat of WorkSafeBC**

**October, 2011  
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## Main Research Findings and Policy Prevention Implications

- In a sample of 14 BC sawmills, work in the “sawfiling” trades was found to be associated with an increased risk of colorectal cancer (relative risk of 2.1), but not of lung cancer, nor Chronic Obstructive Pulmonary Disease (COPD).
- These findings represent some of the first studies of chronic respiratory disease in people employed in the sawfiling trades, but were limited by small number of cases, semi-quantitative exposure assessment, and lack of individual level confounder data.
- Exposure to endotoxin in BC sawmill workers was associated with an increased risk of Chronic Obstructive Pulmonary Disease (COPD) that reached a relative risk over 2 in those exposure above 28 ng/m<sup>3</sup>\*yr, but the increased RR was not statistically significant.
- High level of endotoxin exposure among BC sawmill workers was associated with a decreased risk of lung cancer; this apparent protective effect has been observed in other studies.
- Job title and duration of employment were accounted for in assessing hard metal exposure; on-site measurement and duration were used in assessing endotoxin exposure. However, our job exposure matrix models could be improved to increase statistical power.
- Reduction of exposure to hard metal fume/particulate is still advised because of earlier health findings; this can be achieved by substituting saw blade materials; using enclosures and local exhaust ventilation; monitoring ventilation systems and exposures; and changing metalworking fluid on a regular basis.
- Despite a possible “protective” effect against lung cancer, endotoxin is generally considered an indoor air pollutant, and exposure should be avoided. Identification of effective control measures should be the subject of further study.
- We recommend monitoring policy in the area of endotoxin exposure limits, but to be cognizant of the fact that we observed health effects at levels well below other published studies.

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## Executive Summary

*Background:* “Sawfilers” are a sub-group of sawmill workers who repair and maintain saw blades, and who may be exposed to hard metals present in metal alloys; some of which are carcinogens or have other, non-malignant respiratory effects. Sawmill workers in general may be exposed to endotoxin from gram-negative bacteria present on the wood stock. Previous studies across different industries have shown endotoxin associated with increased risk of COPD, but paradoxically, that it might decrease the risk of lung cancer. The main goal of this research project was to utilize an existing cohort of approximately 26,000 BC sawmill workers to: 1) examine associations between hard metals and endotoxin exposures and cancer of the lung and GI tract<sup>1</sup>; and 2) examine the associations between hard metal and endotoxin exposures and COPD in a sub-cohort of 11,289 sawmill workers for whom hospital discharge data was available.

*Method:* We used duration of employment as a sawfiler or in the sawfiling department as a surrogate for hard metal exposure because of a lack of measurement data. Endotoxin exposure was estimated using a predictive model built on previous monitoring (216 measurements) in BC sawmills. We then assigned quantitative endotoxin exposure values to jobs, and calculated cumulative endotoxin exposure levels as the sum of time spent in a job \* exposure level in that job. Relative risks of cancer and COPD for each exposure group were assessed using Poisson regression, controlling for age, race, calendar period and time since first exposure, with subjects in lowest exposed category as the reference.

*Results:* A total of 523 cases of lung cancer, 334 cases of colorectal cancer (follow-up period 01/01/1959 to 12/31/1995) and 121 cases of COPD (follow-up period 01/01/1985 to 12/31/1998) were included in the analyses. The risk of lung cancer and COPD (lagged 20 years) were not associated with hard metal exposure (RR=0.9, 95% CI=0.5-1.8 and RR=1.1, 95% CI=0.5-2.8, respectively). However, there was an association between hard metal exposure and colorectal cancer risk (RR=2.1 for the exposed, 95% CI=1.2-3.5, lagged for 20 years). For endotoxin, the observed point estimate of lung cancer risk among the highest exposed group was less than one yet not statistically significant (RR=0.8, 95% CI=0.5-1.1). The overall downward trend of lung cancer associated with endotoxin was statistically significant (coefficient = -0.086, 95% CI=-0.169 to -0.002). An

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<sup>1</sup> Cancer of the GI tract was added as a disease of a priori interest due to anecdotal case reports from BC sawfilers.

increased risk of COPD was observed among subjects with highest endotoxin exposure (RR=1.9, 95% CI=1.0-3.7), and there was an increasing trend between increasing endotoxin exposure and COPD risk (coefficient=0.104, 95% CI=-0.086-0.294).

*Discussion:* This study was the first to examine chronic health risks associated with sawfiling employment. While the findings for malignant and non-malignant respiratory disease were negative, these results should be interpreted with caution as the method of exposure assessment was fairly crude (duration of employment). The finding of an association between work as a sawfiler and colorectal cancer is novel and deserving of additional attention, but likewise is subject to possible exposure misclassification. The study used quantitative endotoxin exposure data and confirmed both a predicted “protective” effect against certain cancers, but also a positive association with COPD. In both cases the “effective” exposure levels were lower than seen in previous studies.

*Conclusion:* This study suggests a possible association between hard metal exposure and increased risk for colorectal cancer among sawmill workers. With regard to the respiratory effects of endotoxin exposure, our finding was in accordance with previous studies suggestive of a positive association with risk of COPD and a negative association with risk of lung cancer.

## Background and Literature Review

BC Sawmills have been the focus of previous occupational health studies that have resulted in a rich set of health, exposure and potential confounder information (Teschke *et al.*, 1998). These data permit us to look at novel research questions regarding occupational exposures and disease in a timely and cost-effective way. We recently too advantage of these resources to examine two occupational disease questions of particular interest to researchers and policy makers.

The first relates to “sawfiling”. This is a sawmill- specific trade, and “sawfilers” are responsible for maintenance of saws and knives. Sawfilers may be exposed to chromium, cadmium, lead, and cobalt, all known or suspected carcinogens. They have other exposures that are similar to the machinist trade, a group suspected of having an increased risk of cancer (Krstev *et al.*, 2007). Hard metal exposures have been associated with respiratory disease and in 1991 the Workers’ Compensation Board of BC (now WorksafeBC) funded a study of “hard” metal exposure (heavy metal alloys), respiratory symptoms and lung function among sawfilers (Kennedy *et al.*, 1995). However, no studies of cancer or other long-term health have been done in this occupational group to our knowledge. Several recent events heightened interest in this research area. In 1987, a BC sawfiler had an accepted claim for gastrointestinal cancer, and his occupational exposure to hard metals from welding the carbon steel tips and stellite was suspected as the cause of his initial cancer<sup>2</sup>. Another sawfiler in BC became disabled over a number of years because of lung damage; when he died at the age of 50, an autopsy attributed his death to lung disease caused by exposure to cobalt from grinding carbide (WSBC 2011).

The second research question relates to endotoxin. Endotoxin is a component of the outer cell walls of Gram-negative bacteria and is a common contaminant of organic dusts, including wood dust in sawmills (Dennekamp *et al.*, 1999). Adverse health effects associated with exposure to endotoxin are well recognized. These include septic shock at very high exposure levels and pneumonitis, decreased lung function, and respiratory symptoms at lower exposure levels, such as those observed in sawmills. However, recent studies have observed that populations exposed to endotoxins have a paradoxically *decreased* risk of lung and possibly other cancers. Several studies have examined endotoxin exposure among sawmill workers, including one in the

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<sup>2</sup> Personal communication with HSE advisor, United Steelworkers of America



BC sawmill cohort (Dennekamp *et al.*, 1999) but little work has been done to examine its relationship with lung disease in that setting, nor examined a hypothesized “protective” effect in relationship with cancer in that group.

## **Sawmills and the UBC Sawmill Study**

Sawmills are facilities in which raw logs are cut into timber (large pieces) and lumber (generally considered 4in × 4in or smaller; Davies *et al.*, 1998). Job tasks of sawmill workers include log handling and debarking, the breakdown of logs into cants (the square center of the log), slabs (rounded outer edges of the log) and large boards; sawing cants and slabs into functional lumber sizes; grading; sorting; drying; planing; and processing the lumber for industrial specific uses with preservatives, fire retardants or surface protection. During their work, sawmill workers may be exposed to multiple chemical, physical and biological hazards, which have the potential of causing several adverse health outcomes (Teschke *et al.*, 1998).

To better understand associations between such occupational exposures and health outcomes a group of occupational health researchers from the University of British Columbia has been following the health of 26,000 workers employed in 14 sawmills of British Columbia. The cohort was first enumerated in 1987; study subjects were linked with administrative health databases including the BC cancer registry, Provincial medical plan data, hospital discharge and vital statistics (death registry). Subject identity is kept anonymous but full and detailed employment history is available for all subjects. Exposure data has been developed for several hazards including chlorophenol antifungal agents, wood dust, noise, stress, and endotoxin (Demers *et al.*, 2006; Davies *et al.*, 2009; Freisen *et al.*, 2005; Dennekamp *et al.*, 1999; Ostry *et al.*, 2001)

## **Sawmill Workers' Exposure to Hard Metals and their Health Effects**

Occupational exposure to hard metals occurs when certain job tasks are performed, such as sharpening, grinding and welding saw tips, blades and knives. Airborne particulate that is generated could result in exposure by inhalation or skin contamination and ingestion. Those with greatest exposure potential are likely sawfilers, who are responsible for maintaining saws and knives. Saw blade material used in BC may contain hard metal components, many classified as carcinogens (see Table 1) or which have shown adverse respiratory effects (Teschke *et al.*, 1993; Kennedy *et al.*, 1995; Sprince *et al.*, 1988; Kusaka *et al.*, 1986; Kennedy *et al.*, 1989).

Further, exposure to aerosols of hard metals has been associated with a variety of adverse respiratory health outcomes, For example cadmium exposure was found to be associated with emphysema (Stokkinger *et al.*, 1981), and cadmium exposure has been linked with asthma (Sprince *et al.*, 1988; Kusaka *et al.*, 1986; Roto 1980; van Custem *et al.*, 1987; Ghysens *et al.*, 1985; Nemery *et al.*, 1990; Davison *et al.*, 1983), wheezing and chronic bronchitis (Sprince *et al.*, 1988; Kusaka *et al.*, 1986).

Table 1. Carcinogenicity classification of hard metal components of saw tips

Heavy Metal	IARC	ACGIH
Chromium, metallic	3 (Not classifiable as to carcinogenicity to humans)	A4 (Not classifiable as a human carcinogen)
Chromium VI	1 (Carcinogenic to humans)	A1 (Confirmed human carcinogen)
Cadmium, metallic	1 (Carcinogenic to humans)	A2 (Suspected human carcinogen)
Lead, metallic	2B (Possibly carcinogenic to humans)	A3 (Confirmed animal carcinogen with unknown relevance to humans)
Cobalt with tungsten carbide	2A (Probably carcinogenic to humans)	A3 (Confirmed animal carcinogen with unknown relevance to humans)
Nickel, metallic	2B (Possibly carcinogenic to humans)	A5 (Not suspected as a human carcinogen)
Nickel, compound	1 (Carcinogenic to humans)	<i>Soluble</i> : A4 (Not classifiable as a human carcinogen) <i>Insoluble</i> : A1 (Confirmed human carcinogen)

## Sawmill Workers' Exposure to Endotoxin and its Health Effects

Endotoxin is produced as a component of the outer membrane of gram-negative bacteria (Park *et al.*, 2000). Endotoxin is ubiquitous in our environment, found in soil, vegetation, natural water, indoor air and even tobacco smoke (Park *et al.*, 2000; Hudson *et al.*, 1977; Hasday *et al.*, 1999). In occupational settings such as sawmills, endotoxin may be present at higher concentration because of the growth of gram-negative bacteria on the surface of fresh-cut wood. One study that measured endotoxin levels in British Columbia sawmills found an average personal exposure level of 2.09 ng/m<sup>3</sup> (with 9% of samples above 5 ng/m<sup>3</sup>; Dennekamp *et al.*, 1999).

Health effects following endotoxin exposure are considered to be paradoxical, as there are both beneficial and harmful health outcomes following exposure. The harmful side of endotoxin exposure refers to its impact on respiratory function. The possible mechanism suggested by animal models is that chronic intra-

tracheal exposure to LPS elicits lung pathologic changes similar to human COPD-associated inflammation (Vernoy *et al.*, 2002). Decreased FEV<sub>1</sub> (Mandryk *et al.*, 1999), bronchi damage (Hagmer *et al.*, 1990), and COPD (Kline *et al.*, 1999) have been observed among workers who were exposed to endotoxin. The apparent benefit to endotoxin exposure is its potential to reduce cancer risk, which has been reported by several occupational epidemiology studies among workers who are exposed to high level of endotoxin, such as agriculture (Mastrangelo *et al.*, 2005), cotton textile ( Astrakianakis *et al.* 2007), and waste treatment workers (Lange 2003). A recent meta-analysis with 28 published occupational epidemiology studies showed an overall risk of lung cancer of 0.62 (95% CI 0.52—0.75) for agriculture workers and 0.72 (95% CI 0.57—0.90) for textile workers (Lenters *et al.*, 2010). The underlying mechanism of endotoxin's potential to reduce cancer risk may be the activation of the immune system with macrophage surveillance and increased secretion of cytokines, such as tumor necrosis factor alpha (or known as TNF- $\alpha$ ), which stimulate the anti-tumoral response of the immune system (Dranoff, 2004; Lange *et al.*, 2003).

## **Research Questions**

1. Sawfilers may be exposed to hard metals, other potentially carcinogens and respiratory toxins during the course of their work, therefore: Is work as a sawfiler associated with elevated risk of (a) lung cancer, (b) colorectal cancer, and (c) COPD?
2. Sawmill workers throughout the mill may be exposed to airborne endotoxin, and therefore: is endotoxin exposure associated with (a) increase in the risk of COPD and (b) decreases in the risk of lung cancer?

## Methodology

### **Cohort and Case Definition**

A cohort of BC sawmill workers (N=25,556) was followed from 01/01/1950 to 12/31/1995. A full description of cohort enumeration is described in a previous publication (Demers *et al.*, 2006). Subjects were employees of 14 BC sawmills employed in production or maintenance departments for at least one year. Here, the full cohort was used in studies of cancer incidence.

A sub-cohort of workers with the follow-up period from 01/01/1985 to 12/31/1998 was examined for non-malignant outcomes (i.e. COPD). Follow up was restricted because of the later start time of electronic hospitalization records. There were 11,289 sawmill workers in this sub-cohort.

Work histories for each cohort subject were derived from sawmill payroll records, and included standardized job title, sawmill department and the start and end date of each position held in the sawmill.

#### Case Definition and Follow-up

Every subject in the cohort was linked to vital statistics and cancer registry records using probabilistic linkage; fatal (1950–1995) and incident (1969–1995) cancers were identified using national registries. The sub-cohort was linked to vital status and provincial hospital discharge records (from 1985-1998). Although the number of prostate, bladder and skin cancer was not large enough to facilitate stratified analyses, there were substantial number of lung cancer cases in the cohort (N=533). In addition, because of the anecdotal report of GI cancer of a sawfiler, we repeated our analysis for colorectal cancer as a supplemental analysis. Briefly, in our definition of lung cancer we included all cancers of trachea, lobe, bronchus and lung area of the respiratory system (ICD-9=162); for colorectal cancer we included both the colon and rectum (ICD-9=153.0-154.1). Other cancer sites were considered for potential associations with hard metals, but could not be included because of insufficient numbers of cases. COPD by our definition referred to chronic bronchitis, emphysema, and chronic airway obstruction, with the exclusion of asthma and extrinsic allergic alveolitis (ICD-9=490, 491, 492 and 496).

Each worker was followed from the start of the study period or start of his or her employment plus one year, whichever occurred later. Follow up ended at the earliest of: end of study period, the date of death, the date of loss to follow up, the date of diagnosis (i.e. first hospitalization for non-malignant disease), or the date of registration of cancer (for malignant disease).

## Exposure Assessment

In the absence of measurement of hard metal exposures in BC sawmills, duration of employment in a sawfiling department was used as a surrogate of exposure. This was based on the *a priori* assumption that compared with other sawmill workers those working in sawfiling department were uniquely exposed to hard metals generated from tasks such as grinding, sharpening and welding. We defined “sawfiling job titles” as *benchman, grinderman, sawfiler, sawfiter, sawfitter, and fitter inspector*; in addition, those doing other jobs (such as *clean-up*) in the *sawfiling* department were considered to share similar hard metal exposure as sawfilers. Since most workers held several jobs in cohort mills, each for differing periods of time, we calculated a cumulative exposure metrics as the total number of years being employed in a sawfiling department.

Endotoxin exposure assessment was based on the available measurement data from a previous monitoring study (Dennekamp *et al.*, 1999). In that study, 216 subjects were monitored for personal endotoxin exposure level ( $\text{ng}/\text{m}^3$ ) along with information such as job title and geographic location of sawmill, of which  $N=106$  subjects had a measurement above LOD. A job exposure matrix was developed allowing us to link all sawmill job titles to endotoxin exposure levels. Missing data (where job and/or mill was not measured) was estimated through linear regression predictive modeling (Table 2). The adjusted  $R^2$  value for the model was 0.36, which indicates that 36% of the variance in endotoxin level could be explained by job and sawmill geographic location. Through modeling log-transformed endotoxin concentration with geographic area and job title, we made best use of the available data, and which we could then link to the work history file. It had the additional benefit that we were able to estimate endotoxin levels for job/location combinations that were not monitored in the study mentioned above. Further, modeling in this way tends to favour Berkson error which results in less biased estimates than measures with classical error.

Based on the job exposure matrix, we calculated endotoxin level for each mill and job. E.g., for a carpenter of a southern coast mill, the endotoxin level would be estimated as  $\exp(-0.11+0.88-0.80)=0.97 \text{ ng/m}^3$ .

We can then calculate the cumulative exposure metric as an endotoxin cumulative dose:

( ) in the unit of  $\text{ng/m}^3 \cdot \text{year}$ .

Table 2 Endotoxin exposure model, derived from 216 endotoxin measurements and associated determinant data. The coefficients in this model were then used to predict exposure levels for all cohort subjects.

	Coefficient	<i>p-value</i>	95% LCI	95% UCI	
Geographic location	Vancouver Island	-0.73	0.000	-1.10	-0.36
	Northern Interior	0.32	0.095	-0.06	0.70
	Southern Coast	-0.80	0.000	-1.17	-0.44
Job categories	Cutoff	-0.70	0.080	-1.49	0.08
	Clean-up	1.84	0.001	0.72	2.96
	Offbearer/Tailsawyer	0.93	0.181	-0.44	2.29
	Quad saw operator	1.42	0.040	0.07	2.77
	12" Edger	1.27	0.010	0.31	2.22
	Lumber Straightener	1.04	0.065	-0.07	2.14
	Dropsort Operator	1.00	0.013	0.21	1.79
	Bin Patrol/J-bar attendant	-0.62	0.154	-1.49	0.24
	Strip loader/placer	1.01	0.148	-0.36	2.37
	Clean-up	1.96	0.000	1.18	2.75
	Chipper Feeder/Clean-up	0.71	0.110	-0.16	1.58
	Planer chargehand	-0.98	0.081	-2.09	0.12
	Forklift/Tallyman/Shipping	-0.89	0.027	-1.68	-0.10
	Quality control	0.68	0.169	-0.29	1.65
	Carpenter	0.88	0.122	-0.24	1.99
	Oiler	1.19	0.016	0.23	2.14
	Power engineer	1.49	0.124	-0.41	3.40
	Janitor	1.29	0.061	-0.06	2.65
Fitter/Sawfitter	0.67	0.096	-0.12	1.47	
Grinderman/Knife grinder	0.80	0.034	0.06	1.53	

Reference: Southern Interior, End stacker. Intercept=-0.11

## Statistical Analysis

We used LTAS<sup>3</sup> to prepare data for analysis (Table 3). We conducted internal analyses among exposure groups using Poisson regression, with lowest exposure levels as the reference group.

Table 3. Stratification of cohort data

<b>Independent Variable</b>	<b>Rationale of stratification</b>	<b>Result of stratification</b>
Exposure	Main variable of interest.	Two hard metal exposure groups: Never exposed Vs. Ever exposed.
		Five endotoxin exposure groups with equal number of cases in each group.
Race	Covariate. South Asian workers smoked less, and cigarette consumption was a strong confounder of both lung cancer and COPD.	Two ethnic groups: South Asian and all others (identified by name algorithm and then validated in interviewed sub-group).
Age	Covariate. Risk of cancer and COPD occurs is higher at old age.	Five exposure groups with equal number of deaths <sup>[1]</sup> in each group
Calendar period	Covariate. Completeness of cancer registry and hospitalization record system and diagnosis might change within time.	Five exposure groups with equal number of deaths in each group
Time since first exposure (TSFE)	Covariate to account for: 1) For workers with same cumulative exposure, their exposure duration might be different; 2) For workers with intermittent employment, TSFE might be longer than those with continuous employment	Five exposure groups with equal number of deaths in each group

[1] For cancer cohort, number of deaths per group=4882/5≈976. For COPD cohort, number of deaths per group=906/5=181

<sup>3</sup> LTAS: Life-Table Analysis Software, NIOSH, Cincinnati, OH



## Research Findings

Demographic information of the full (cancer) and sub-cohorts (non-malignant disease) is summarized in Table 4. The “dead” row refers to the number of deaths from all deaths, and the “case” row refers to the number of targeted outcomes (cancer and COPD).

### Sawfiling and Cancer

Table 5 shows relative risk of lung cancer and colorectal cancer among hard metal exposed workers adjusted for race, age, calendar period, TSFE, and using a lag time of 20 years. Compared with non-exposed workers, there was a doubling of risk of colorectal cancer among workers employed as sawfilers (RR=2.1, 95% CI 1.2—3.5), but no excess of lung cancer was observed. We also examined dose-response relationships. Again with a 20 years lag, period and using never exposed as a reference, we found relative risks of 1.30, 0.58, and 0.90 in the <2.5 years, 2.5-12.6 year and >12.6 year exposure categories respectively; however these were based on small numbers (4, 2 and 2 cases, respectively).

Table 4. Demographic summary of cancer and COPD cohorts

		Cancer full cohort			COPD sub cohort		
		Exposed	Non-exposed	Total	Exposed	Non-exposed	Total
Number of workers		805	24,751	25,556	617	10,672	11,289
Vital status (at end of follow-up)	Dead	105	4,862	4,967	60	851	911
	Alive	700	19,889	20,589	557	9,821	10,378
Race	Chinese & South Asian	82	3,315	3397	69	1,936	2,005
	Others	723	21,436	22,159	548	8,736	9,284
Cases	Lung cancer	20	513	533	9	112	121
	Colorectal cancer	15	319	334			
Average age at start of follow-up		33.1	34.5	34.5	43.1	39.0	39.2

Table 5. Adjusted relative risk of lung cancer and colorectal cancer among sawmill workers exposed to hard metal\*

	Lung cancer			Colorectal cancer		
	N	RR	95% CI	N	RR	95% CI
<b>Non-exposed</b>	525	<i>reference</i>		319	<i>reference</i>	
<b>Exposed</b>	8	0.9	0.5 - 1.8	15	2.1	1.2 - 3.5
<b>Total</b>	533			334		

\*adjusted for race, age, calendar period and TSFE

### Sawfiling and COPD

Relative risk of COPD among workers employed as sawfilers is shown in Table 6; the results adjusted for race, age, calendar period and TSFE, and an exposure lag of 20 years. Again with a 20 years lag, period and using never exposed as a reference, we found relative risks of 1.23 and 1.08 in the <2.5 3.4 years and >3.4 year exposure categories respectively; however these were based on small numbers (2 and 3 cases, respectively).

Table 6. Adjusted relative risk of COPD for hard metal exposure groups\*

Exposure group	N	RR	95% CI
Never exposed	116	<i>reference</i>	
Ever exposed	5	1.14	0.46 - 2.82

\*adjusted for race, age, calendar period and TSFE

### Endotoxin and Lung Cancer

Lung cancer relative risk of endotoxin exposure groups is shown in Figure 1. Compared with the reference subjects with lowest endotoxin exposure, the risk estimate for the second lowest exposure group increased slightly above 1.0, but generally decreased as endotoxin exposure level increased. Although none of the point estimates were statistically significant, the overall dose-response trend was (-0.086, 95%CI: -0.169 to -0.002).

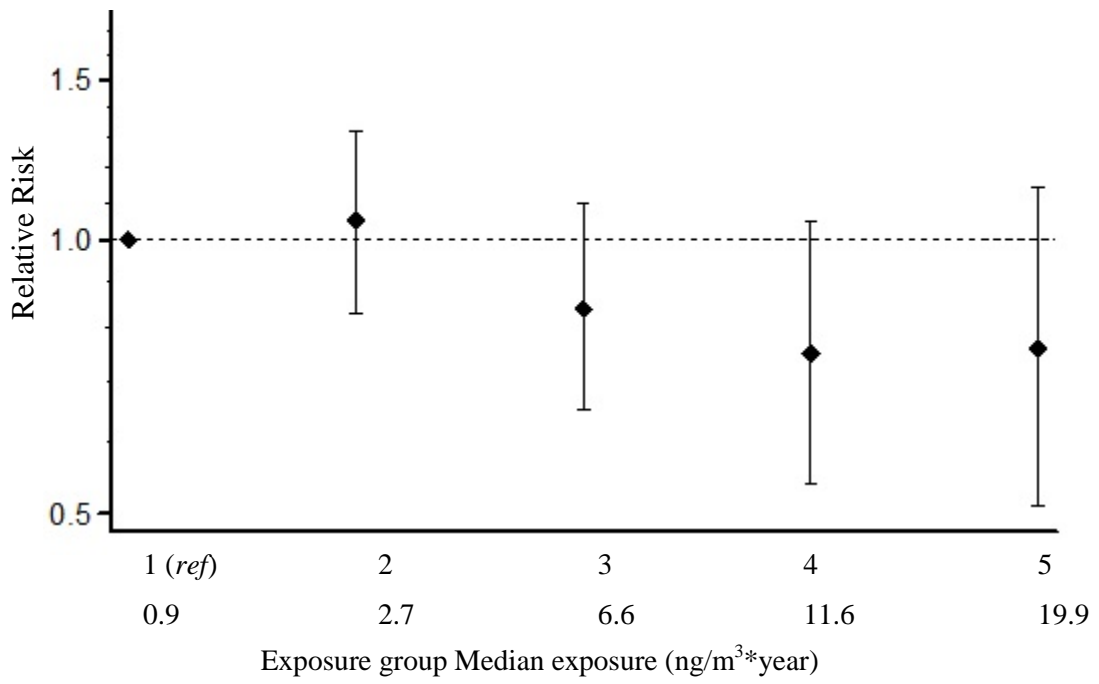


Figure 1. Risk of lung cancer with increased median endotoxin exposure for the 5 groups

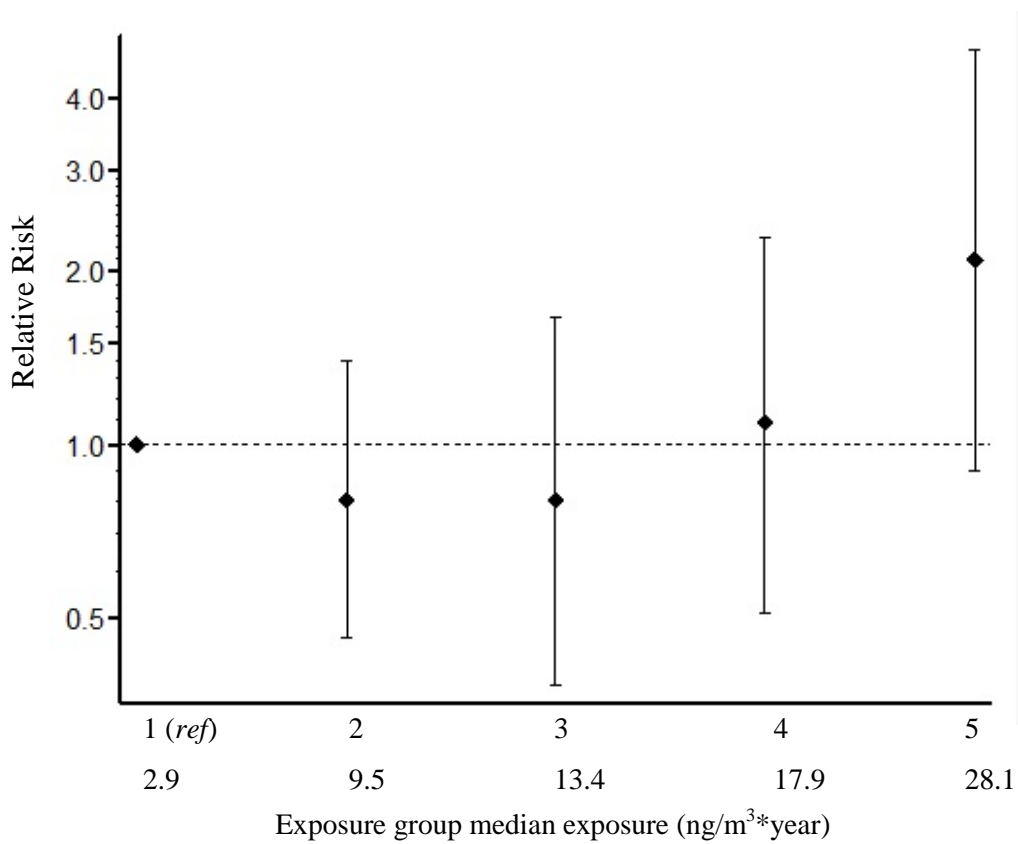


Figure 2. Risk of COPD with increased median endotoxin exposure for the 5 groups

## Endotoxin and COPD

The relative risk of COPD among endotoxin exposure groups is shown in Figure 2. Compared with the reference group with lowest exposure, risk estimates for medium exposures are around 1, but increased for the highest exposed group. The linear test for trend was not significant at  $\alpha = 0.05$

## Discussion

We studied work as a sawfiler and endotoxin exposures in 14 sawmills selected from Coastal and Interior BC. These findings should be generalizable to individuals who worked at other BC sawmills during the study time period.

In our examination of sawfiling and occupational disease, we found an excess risk of colorectal cancer for exposed subjects (RR=2.1) but no increase in risk of lung cancer (RR=0.9). With COPD we found was a slight, but non-significant elevation in risk (RR=1.2). There have been no previous studies with regard of cancer and respiratory risks among the sawfiler job group to our knowledge, and epidemiologic studies of other occupations (such as welding and hard metal production) that might be expected to have had similar exposures have shown inconsistent results. The reasons for the inconsistency across earlier studies may have been because workers were exposed to multiple types of hard metals, therefore difficult to study the independent effect of a single metal or because differences in reference populations might affect the risk estimates. Some studies reported that subjects with job tasks similar to sawfilers, such as welders and grinders, tended to smoke more than the general population (Sterling & Weinkam 1986), potentially confounding the cancer and COPD relation.

Although the risk of lung cancer associated with hard metal and endotoxin were studied separately, we did a summary of endotoxin cumulative exposure among sawfilers vs. non-sawfilers (Table 7). Sawfilers have a higher endotoxin cumulative dose compared with non-sawfilers, which may partially explain the non-significantly excess risk of lung cancer associated with hard metal exposure.

Table 7. Endotoxin exposure among sawfilers in the lung cancer cohort (unit: ng/m<sup>3</sup>\*year)

	<b>N</b>	<b>Range</b>	<b>AM</b>	<b>GM</b>	<b>GSD</b>
<b>Sawfilers</b>	805	0.4—85.2	15.2	11.6	0.006
<b>Non-sawfilers</b>	24334	0.006—107.1	7.0	3.7	0.01

Smoking is considered to be a potential confounder in occupational epidemiology studies, as it is a confirmed risk factor for lung cancer and COPD (Bresnitz EA 1997). In our study we did not directly control for

cigarette smoking because of a lack of individual smoking data. However, the confounding effect of smoking was indirectly addressed through two approaches: 1) We included race (South Asian Vs. Other) as covariate based on the *a priori* assumption that workers of South-Asian origin smoke less. The lung cancer risk of South Asian workers support this assumption (RR=0.3, 95% CI 0.2-0.5). 2) Our study design was based on an internal comparison approach, and avoided the data gap of smoking prevalence among workers and an external reference group. Also it helped to reduce impact of the healthy worker effect (that would be expected to result in underestimate the true risk of hard metal exposure; Arrighi & Picciotto 1994).

The finding of an elevated risk for colorectal cancer associated with sawfiling is novel. Occupational exposures previously investigated for association with colorectal cancer are: sedentary work (a high priority for future IARC review; IARC, 2008); polypropylene exposure and carpet workers, where the evidence was considered weak or non-supportive of a relation (Lagast *et al.*, 1995); and asbestos. Recently the evidence for a link between asbestos and colorectal cancer was reviewed by IARC (Straif *et al.*, 2009) who concluded evidence of an association between asbestos and colorectal cancer as “limited” though the monograph working group were “even split on whether the evidence was strong enough to warrant classification as ‘sufficient’”.

In our examination of the protective effect of endotoxin against lung cancer, we did observe a downward trend of risk estimates as endotoxin exposure increased, which was consistent with other studies. The direct endotoxin measurement method of our study contributes to the existing evidence as other studies were based on either occupation/employment duration (Mastranelo *et al.*, 2002; Lanfers *et al.*, 2010) or indirect measurement (such as cotton dust; Astrakianakis *et al.*, 2007). Additionally, subjects of most other “protective effect” studies were exposed to much higher endotoxin exposure level (ie geometric mean 6 ng/m<sup>3</sup>; Mutius *et al.* 2000). Our study indicated that exposure to much lower levels of endotoxin (mean concentration 2.09 ng/m<sup>3</sup>), for a long period of time might also be associated with decreased cancer risk. However, caution should be used when comparing cross-study endotoxin doses, as a study comparing intra-laboratory results of endotoxin measurements showed the variation of magnitude, indicating that the difference in the analysis method and laboratory condition could cause substantial differences in the reported concentration (Chun *et al.*, 2000). We

examined different lag times in our analysis, reflecting latent period in lung cancer development, which was not the case for some previous studies (Lenters *et al.*, 2010).

We observed a trend of increasing risk of COPD associated with increased endotoxin exposure level. Several previous studies have demonstrated increased risk of respiratory morbidity and mortality among farmers and farm workers who are potentially exposed to high level of endotoxin (Eduard *et al.*, 2009; Linaker & Smedley, 2002), and others observed decreased lung function, as measured by FEV<sub>1</sub> and FVC<sup>14</sup>. There have only been few occupational epidemiology studies that have investigated the association between measured endotoxin exposure level and decreased lung function. Again exposure levels in other studies - such as among poultry workers, N=257, that observed pulmonary function decrements - were at much high apparent exposure concentrations (61.4 ng/m<sup>3</sup>; Donham *et al.*, 2000).

## **Implications for Future Study**

Since endotoxin exposure was correlated with other respiratory toxins such as wood dust in occupational settings (Mutius *et al.*, 2000), future studies might include wood dust concentration in analysis, to study the combined and independent health effects of endotoxin and wood dust exposure.

The decrease in lung cancer risk for endotoxin-exposed workers was observed at dose levels lower than previous studies, thus more studies focusing on occupations and industries with borderline excessive endotoxin exposure are needed to confirm the dose-response relationship.

In our endotoxin exposure assessment, we included both concentration and duration into account. However, it is interesting to consider which of the two has a stronger influence on the dose-response relationship we observed.

Given the finding of adverse health effects at relatively low endotoxin exposure levels we recommend additional study of the health effects of low-level endotoxin exposure.

It may also be possible to examine the hypothesis that after a worker's exposure to high level of endotoxin that exceeded the threshold of triggering the immuno-response, a comparatively low level for a long duration would be able to "maintain" the anti-tumor effect.

Finally, an external comparison with the BC general population (i.e. SMR) would help assess the excess risk following occupational exposure to hard metal and endotoxin.

## **Policy and Prevention**

We found an elevated risk for colorectal cancer that was associated with sawfiling work, and that was potentially linked to hard metal exposures. Recommendations to minimize occupational exposure to hard metals are:

- Substitute saw blade materials with chemical components that infer higher risk of lung cancer and respiratory diseases with lower risk ones;
- Use enclosures and direct local ventilation when performing sawfiling job tasks that may generate airborne exposures; monitor ventilation systems to ensure that contaminants are effectively drawn away at the grinding area;
- Change metalworking fluid on a regular basis, to prevent the accumulation of hard metal in the fluid;
- Avoid mixing different types of metalworking fluids in use to prevent contamination. For example, mixing ethanolamine-based fluid with a nitrate-based one may generate nitrosamine contamination, which may cause cancer;
- Because of risk of hand contamination with hard metals, improve general hygiene - washing hands and face before eating to avoid ingesting traces of toxic metals.
- Monitor for exposure to cobalt, chromium, lead, and cadmium on a regular basis when metals containing these substances are used.
- For sawmill workers' occupational exposure to endotoxin, although our result suggested a "protective" effect against lung cancer, endotoxin is generally considered as an indoor air pollutant because of its



inflammatory respiratory effects. Identification of effective control measures should be the subject of further study.

- Currently however there are no exposure limits for endotoxins set by any of WorkSafe BC, ACGIH, OSHA, or NIOSH. However, some scholars recommended that peak endotoxin level should not exceed 20 ng/m<sup>3</sup> and the National Health Council of the Netherlands suggests an 8-hr endotoxin occupational exposure limit of 50 EU/m<sup>3</sup>, or approximately 5 ng/m<sup>3</sup> (Rylander 1990; ATS 1998). We recommend monitoring policy in this area, but to be cognizant of the fact that we observed health effects at levels well below other published studies.

## **Dissemination and Knowledge Transfer**

The major part of research was complete as Hanchen Chen's MSc thesis, under the supervision of Dr. Hugh W Davies (CIH) and members of the supervision committee: Dr. Paul Demers, Dr. George Astrakianakis and Dr. Chris Carlsten. As the thesis was in progress to the current date, we have to date only limited ability to present the research project to a wider audience:

- On January 26<sup>th</sup> 2011, the sawfiler aspects of the study were presented at the meeting of Western Canada health and safety meeting of the United Steelworkers of America, and representatives of sawfilers.
- On April 1<sup>st</sup> 2011, preliminary finding of the sawfiler and endotoxin study was presented at School of Occupational and Environmental Health weekly seminars, which are open to the UBC community and the public.
- On July 22<sup>nd</sup> 2011, completed thesis was submitted and published on UBC's online information repository, cIRcle.

In the future, after including smoking survey data into our analysis, we will write two separate papers based on exposure (sawfiling and endotoxin) and submit to academic journals for publication.

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