LUNG CANCER AND COPD AMONG SAWFILERS AND THOSE EXPOSED TO ENDOTOXIN WHILE WORKING IN BC SAWMILLS

by

HANCHEN CHEN

B.Sc., NANJING UNIVERSITY, 2008

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

The Faculty of Graduate Studies

(Occupational and Environmental Hygiene)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

July 2011

Abstract

Background: Sawfilers are a sub-group of sawmill workers who repair and maintain saw blades, and are exposed to multiple inhalable occupational hazards some of which were carcinogens or have non-malignant respiratory effects. Sawmill workers in general may be exposed to endotoxins from gram-negative bacteria of the wood. Previous studies across different industries have shown that endotoxin would increase the risk of COPD, but may decrease the risk of lung cancer. The main goal of this thesis was to examine the associations between the two exposures (sawfiling employment and endotoxin) and two diseases (lung cancer and COPD) by using an existing cohort of 25,685 BC sawmill workers. *Method*: Sawfiling exposure was categorized into ever-exposed and never-exposed groups. For endotoxin, we used a previous endotoxin monitoring study of 216 samples in BC sawmills to build a predictive model through forward-stepwise linear regression, based on which we assigned quantitative endotoxin exposure values and calculated cumulative endotoxin exposure levels. Relative risk of lung cancer (ICD9=162) and COPD (ICD9=490,491,492,496) for each exposure group were assessed using Poisson regression, controlling for age, race, calendar period, and time since first exposure, with workers in lowest exposed category as the reference. *Results*: A total of 523 cases of lung cancer (follow-up period 01/01/1959 to 12/31/1995) and 120 cases of COPD (follow-up period 01/01/1985 to 12/31/1998) were included in the analysis. With respect to sawfiling, risk of lung cancer (lagged 20 years) and COPD (lagged 5 years) were slightly elevated (RR=1.4, 95% CI=0.9-2.2 and RR=1.3, 95% CI=0.6-2.5, respectively) but neither significantly. Decreased risk of lung cancer was observed among subjects with highest endotoxin exposure (RR=0.8, 95% CI=0.5-1.1), and the dose-response trend was borderline significant (p=0.059). Increased risk of COPD was observed among subjects with highest endotoxin exposure (RR=1.9, 95% CI=1.0-3.7), and the

dose-response relationship was again borderline significant (p=0.065). *Conclusion*: This study provided evidence of a link between cumulative endotoxin exposure and a decreased trend of lung cancer and an increased trend of COPD. However, the association between lung cancer, COPD and sawfiling employment remained unclear.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACGIH	—	American Conference of Industrial Hygienists
CI	—	Confident Interval
COPD	—	Chronic Obstructive Pulmonary Disease
FEV_1	—	Forced Expiratory Volume in 1 Second
FVC	—	Forced Vital Capacity
HR	—	Hazard Ratio
IARC	—	International Agency for Research on Cancer
ICD	—	International Classification of Diseases
LPS	—	Lipopolysaccharide
LTAS	—	Life Table Analysis System
NIOSH	—	The National Institute for Occupational Safety and Health
OR	—	Odds Ratio
OSHA	—	Occupational Safety and Health Administration
RR	—	Relative Risk
TLV	—	Threshold Limit Value
TSFE	—	Time Since First Exposure

Acknowledgements

I wish to express great thanks to my supervisor, Hugh Davies, and my committee members, George Astrakianakis, Paul Demers and Chris Carlsten, for their invaluable advice and assistance, which not only guide me through all the difficulties but also give me such a great learning process.

I would also like to thank WorkSafe BC for funding our research. Also sincere appreciation goes to Ron Corbeil, Jack McLemon, Norm Prevost and Rock Lamont in the union, for providing us with information with regard to sawfilers' occupational exposure to heavy metals.

Last but not least, I would like to show my sincere appreciation to my parents, for their unconditional support and encouragement through the years of my education, in so many ways.

Dedication

To My Parents

Chapter 1: Introduction

This chapter introduces the motivation of my study, summarizes the background information of the occupational hazards of sawfiling and endotoxin through peer-reviewed literature, such as sawmill workers' exposure and potential health effects. It also briefly introduces methods used for our study. The research questions of our study are introduced.

1.1 Sawmilling industry

Sawmills are facilities where raw logs are cut into timber (large pieces) and lumber (generally considered 4''×4'' or smaller).[19] Job tasks of workers who work in sawmills include the breakdown of logs into cants (the square centre of the log), slabs (rounded outer edges of the log) and large boards, processing the cants and slabs into functional lumber sizes, grading, sorting, drying and processing the lumber for industrial specific uses with preservatives, fire retardants or surface protection.[20] During their work, sawmill workers may be exposed to multiple chemical, physical and biological hazards, for example, wood dust, pesticides, fungicides, noise and so on. For this study, our targeted occupational hazards were sawfiling and endotoxin. Figure 1.1 sketches out the flow of job tasks of the sawmill departments. From the flow chart, we can see that sawfilers, who are responsible for keeping saw blades operational, are in the maintenance department, and the workshops are generally physically separated from the rest of the mill (i.e. the "filing loft"). Higher level of endotoxin exposure, which is a chemical component of the outer membrane of gram-negative bacteria growing on the surface of fresh-cut wood, may be expected primarily among workers of log processing, primary breakdown, and by-product department.

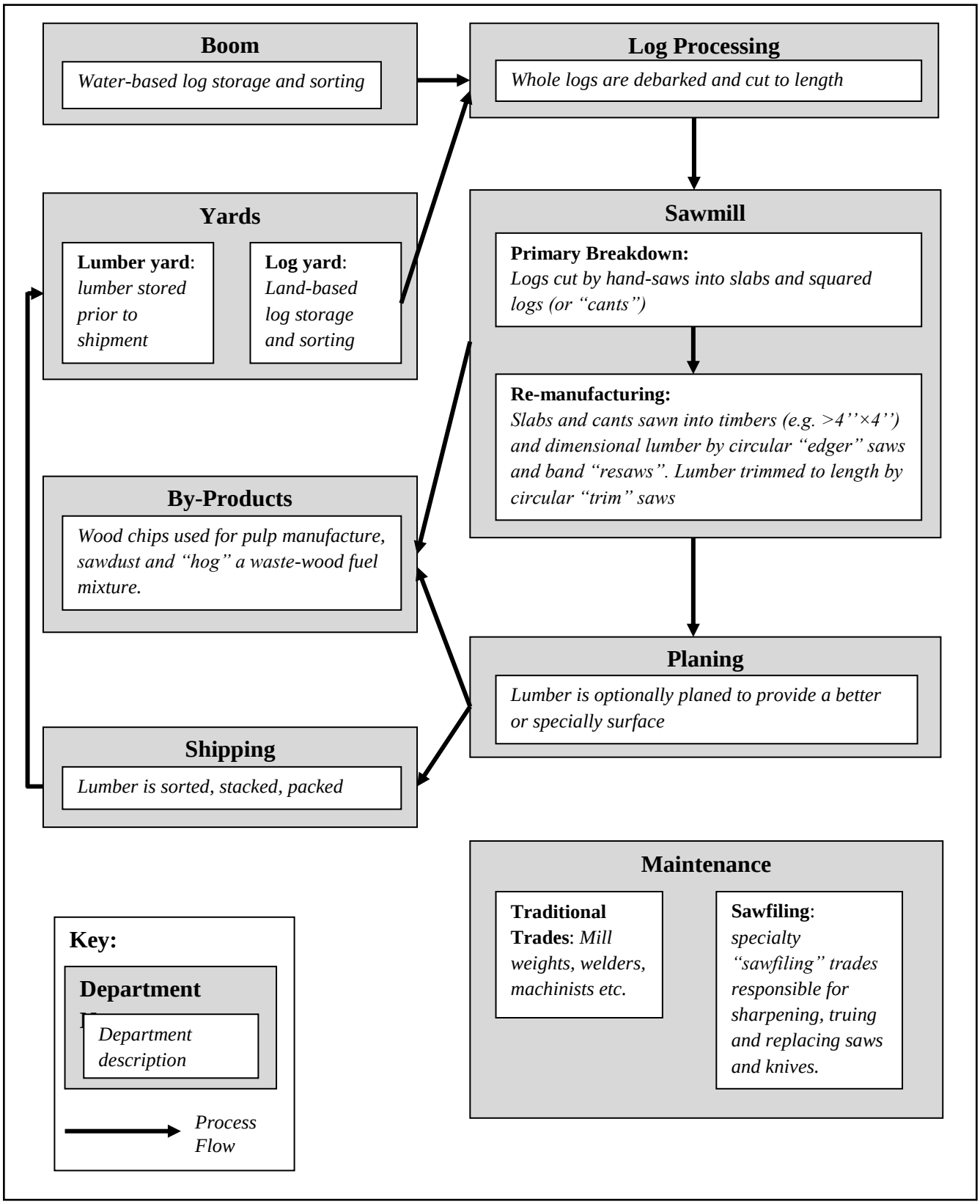

Figure 1.1 Department and job flow of the sawmilling industry

1.2 Study motivation

Since 1987, a group of researchers from the University of British Columbia has been studying the health of 26,000 workers employed in 14 sawmills of British Columbia. The overall goal of this research program was to investigate sawmill workers' occupational exposure to chemicals, dusts, and other potential exposures and association with work-related illnesses and injuries. All the sawmill workers in the cohort are anonymous in the database, but have full employment history available. The UBC sawmill study cohort has been linked with administrative health databases, including the BC Cancer Registry, Provincial Medical Plan data, hospital discharge and vital statistics (death registry). Because all subjects belong to a similar socio-economic group, potential confounding is reduced. Originally the dataset was used to examine the health effects of chlorophenate antisapstain fungicides. Then in order to fully utilize the cohort and investigate the health outcome of other occupational hazards, the researchers built more probabilistic linkage with other health databases.[173] After several such steps, the sawmill cohort data resource allows us to explore many exposure-disease relations in a well-defined and characterized cohort to answer new research questions as they arise.

In 1987, a sawmill worker had an accepted WCB claim for gastrointestinal cancer, and his occupational exposure to heavy metals was suspected as the cause of his initial cancer.[18] More specifically, the worker was a sawfiler in the mill, and it was suspected that the source of heavy metal exposure was from welding the carbon steel tips, and stellite, which is a range of cobalt-chromium-tungsten alloy. Another sawfiler in BC who ground tungsten carbide tips became totally 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.[30] However, there has been little epidemiologic research in this area. Therefore we

wished to study the existing sawmill cohort to examine whether sawfilers had higher risk of respiratory cancers and non-malignant respiratory diseases (mainly COPD) compared with the general sawmill workers, using internal comparisons with other sawmill workers within the BC sawmill cohort.

Furthermore, there has been consistent evidence linking endotoxin (which is a chemical component of the outer membrane of gram negative bacteria and considered to be one of the occupational bio-hazards in the sawmilling industry) with elevated risk of COPD. Perhaps surprisingly, there has been evidence the endotoxin might be protective against lung cancer, which will be summarized afterwards.

In 1997, a team of UBC researchers monitored personal endotoxin levels of several BC sawmills, as part of the UBC sawmill study. Therefore, as a second part of the current study, we used the available endotoxin monitoring data and sawmill workers' cohort health data to explore the health effects of exposure to endotoxin, specifically, with regard to COPD, and investigate it's potential protective effect against lung cancer.

1.3 Occupational exposure while sawfiling and its health effects

Sawfiling comprises the maintenance of cutting tools such as saw blades, knives, and planer heads. These maintenance activities may pose an occupational hazard for sawfilers, e.g., when the sawfilers fix the saw tips to saw bodies through soldering or welding, metal fumes may be generated from the heated metal components, and when wet grinding work is done with liquid lubricant to meet cutting specifications, ionized metal particulate may be generated. Saw blade tips and chipper knives used in BC may contain heavy metals such as cadmium, chromium, cobalt, iron, nickel and tungsten.[89-95] In April 1993, a study concerning sawfilers' occupational to heavy metals and evaluation of its effect on respiratory health was done by Teschke et al.[4]

Among the 278 air samples they took in their study, 3 cobalt samples exceeded the threshold limit value (TLV) of 0.05mg/m^3, and 2 chromium samples exceeded the WorkSafe BC permissible concentration of 0.1mg/m^3. In additional to the heavy metals, saw filers may also be exposed to chemicals in metalworking fluid, which may include mineral oil, as well as other organic contaminants, such as tri-ethanolamine and nitrosamines.[16]

Some of the heavy metals and organic chemicals are carcinogens, such as cadmium, cobalt and mineral oil. So compared with the general sawmill workers, saw filers may have higher risk of cancers, such as lung cancer, as a result of their unique occupational exposure to heavy metals and metalworking fluids.[5 6] In addition, exposure to aerosols of heavy metals was associated with a variety of adverse respiratory health outcomes: for example cadmium exposure was found to be associated with emphysema,[7] and cadmium exposure has been linked with asthma,[8-14] wheezing[8] and chronic bronchitis[9].

1.4 Occupational exposure to endotoxin and its health effects

Endotoxin is produced by gram-negative bacteria as a component of their outer-membrane, and exists ubiquitously in our environment. Sawmilling may expose sawmill workers at higher endotoxin exposure levels, as gram-negative bacteria may grow fast on wood, especially fresh cut wood.[55-57]

The reported health effects associated with endotoxin exposure may be both beneficial and harmful.

The beneficial side refers to its potential to reduce the risk of lung cancer.[72] The antitumoral effect of endotoxin was well demonstrated in animal models, as treatment of neoplasm in mice[96] [97], rats[98] [99] and rabbits[100] with lipopolysaccharides (or LPS, which refers to the purified endotoxin) increased survival of the host or slow the growth of the tumor. A downward dose-response trend has been observed among cotton textile and animal farming workers, who are exposed to endotoxin.[68] Early studies suggested that the underlying mechanism for the decreased cancer risk following endotoxin exposure/intervention was that endotoxin might stimulate a myriad of immunological agents that are considered active in prevention and inhibition of cancer,[101] [102] and the most possible bio-factor responsible for the antitumor effects of endotoxin was tumor necrosis factor-α (TNF-α)[71] [80], as TNF-α will stimulate the antitumoral response of the immune system[103-105]. However, more recent studies showed that cytokines other than TNF-α, such as interferon-γ (IFN-γ)[133], interleukin 1-β (IL1-β)[134], and interleukin-6 (IL-6)[135], as well as activated immune cells including neutrophilis[136], macrophages[137], and CD4 and CD8 T lymphocytes[138] [139] that infiltrated the tumor cells might be linked with the suppressing effect on cancer. Although all these studies suggested that immunomodulation is the primary anti-tumor mechanism, evidence for mechanistic pathways is still limited[142] [143.]

The harmful side refers to endotoxin's potential to decrease lung function and potential cause of COPD, a trend that was observed in occupational epidemiology studies of poultry slaughtering[64] and sawmill workers[53]. There were different perspectives into the underlying mechanism of endotoxin's potential to increase COPD risk: Murine models suggested that there was histological inflammation and airway hyperresponsiveness in the bronchoalveolar lavage fluid following acute LPS inhalation or instillation[106] [107]; while histological analyses of swine

confinement workers who developed symptomatic chronic airflow obstruction revealed thickening of the airway basement that was similar to COPD[108].

1.5 Research questions

1. Sawfilers may be exposed to heavy metal and organic chemicals, so we were interested in the question of: Is sawfiling employment associated with elevated risk of (a) lung cancer and (b) COPD among sawfilers? Chapter 2 of the thesis is aimed at answering this question.
2. Sawmill workers were also exposed to airborne endotoxin, thus for endotoxin, we were interested in the question of: Does endotoxin exposure (a) decrease the risk of lung cancer and (b) increase the risk of COPD? Chapter 3 of the thesis is aimed at answering this question.

1.6 Method overview

For both the exposure of sawfiling and endotoxin, we used a retrospective approach. We made use of the BC sawmill worker's cohort, which followed over 26,000 sawmill workers who worked at least one year between 1950 and 1995. Their disease outcome of lung cancer is ascertained from cancer registry, and COPD is ascertained from the hospitalization file. For the exposure assessment, we made use of the work history data, which included complete work histories in the 14 mills for all subjects.
For sawfiling, we calculated the total duration a subject worked as sawfiler or in the sawfiling department, and also categorized the subjects into ever-exposed vs. never-exposed groups.

For endotoxin, with the available exposure measurement result and work history data, we calculated the cumulative amount which took both the endotoxin level and exposure duration into account (unit: ng/m^3*day), then the workers were further categorized into five exposure groups based on endotoxin cumulative from low to high. From each exposure group, we calculated the relative risk of lung cancer and COPD through Poisson regression, adjusted for race, age, calendar period and time since first exposure. Since both diseases are chronic, we also took lag time into account.

Chapter 2: Lung Cancer and COPD among BC Sawfilers

Sawfilers are sawmill maintenance workers responsible for repairing and maintaining saw blades, knives and planer heads, which expose them to respiratory hazards with carcinogenic and non-carcinogenic effects. The goal of this study was to find if employment as a sawfiler was associated with elevated risk of lung cancer and of chronic obstructive pulmonary disease (COPD). We used the BC sawmill workers cohort (N=25,685) for lung cancer analyses and a sub-cohort (N=11,447) for COPD analyses. Exposure assessment was based on duration of sawfiling employment, and the subjects were categorized into non-exposed and exposed groups. Relative risk (RR) was calculated through Poisson regression adjusting for race, age, calendar period, and time since first exposure (TSFE), allowing for different lagging time. There was no excessive relative risk of lung cancer for the exposed group (RR=0.92, lag time set to 20 years), and a non-significant increased RR of COPD for the exposed (RR=1.14, lag time set to 20 years). The highest risks were observed for low exposed workers, suggesting a lack of dose-response relationship.

2.1 Introduction

2.1.1 Sawfilers' occupational exposure

Modern sawmills require sharp, well maintained saws. Sawfiling is a subcategory of sawmill maintenance workers, whose job tasks include examining saws for defects, keeping saws sharp and operational, repairing saw blades and sharpening chippers and planer heads. Saw tips made with tungsten carbide and stellite (trademarked name for a range of cobalt-chromium alloys which also contain tungsten) are used widely because of their better performance and wear resistance. Consequently, sawfilers are potentially exposed to heavy metal components of the

material, such as chromium, cadmium, lead, and cobalt[15]. One study analyzed metal composition of four common saw blade tips and chipper knives in BC sawmills based on MSDS datasheets[4], and is summarized in Table 2.1. There have been monitoring studies that measured the concentration of airborne heavy metals in the sawfiling department or where sawfiling work was done[21 23-27]. One study measured airborne cobalt level during a carbide tip grinding process in a small company which produced carbide tip blades for woodworking industry, and they found that the ambient cobalt levels in the grinding department approached the ACGIH TLV of 0.05mg/m3; urine samples also indicated elevated level of cobalt after the workers' are exposed at their work shift[21]. The welding of stainless steel and other high chromium containing alloys may result in the workers' exposure to airborne chromium oxide[24-27]. The chemical composition of the dust generated from grinding high alloyed steel contains chromium from 7% to 18%[23]. In additional to the heavy metals, sawfilers may be exposed to organic chemicals of the metalwork fluids they work with, such as triethanolamine, mineral oil and nitrosamines[16].

Table 2.1 Heavy metal composition of saw blade tips and chipper knives in BC sawmills (in percent) cited in MSDS (by Tescheke, et al [4])

Heavy metal \ Sawblade material	Tungsten carbide	Stellite	Saw Steel	Knife Steel
Chromium	--	23-33	0-0.12	7.3-8.8
Cobalt	2.4-30	50-63	--	--
Iron	--	0.5-1.5	--	0.2-0.5
Nickel	--	1-3	<1-2.1	--
Tungsten	60-99	7-13	--	0-1.8

2.1.2 Carcinogenic effects of exposure related to sawfiling

There is limited information regarding the lung cancer risk associated with the sawfiling occupation. However, the carcinogenicity of some of the heavy metals associated with sawfiling has been summarized by agencies such as ACGIH and IARC, and this is summarized in Table 2.2.

For the carcinogenicity of mineral oil, IARC categorized untreated or mildly treated mineral oil as "1, carcinogens to humans", while the highly refined mineral oil as "3, not classifiable as to its carcinogenicity to humans". For triethanolamines, although IARC categorized it as "not classifiable as to its carcinogenicity to humans", small excesses were observed for cancer risks of various sites, in particular, stomach, oesophagus and larynx from epidemiology studies which looked at cancer mortality or incidence among workers using metalworking fluids with ethanolamines as additives[28].

Table 2.2 Carcinogenicity classification of heavy 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)	*Soluble*: A4 (Not classifiable as a human carcinogen) *Insoluble*: A1 (Confirmed human carcinogen)

2.1.3 Non-malignant respiratory effects associated with sawfiling

There is limited information regarding respiratory effects associated with the range of occupational hazards resulting from sawfiling employment; few studies have been conducted to find if sawfiler workers have higher risk of lung cancer or respiratory diseases. One study, a cross-sectional study of 118 sawfilers that measured workers' personal exposure to heavy metals, evaluated respiratory function by spirometric test and questionnaires, and concluded that at levels below the permissible limit of 20 $\mu g/m^3$, cobalt exposure was associated with significant reduction in lung function, and saw filers had increased rate of phlegm, wheeze and cough[17]. In addition, the investigator found an association between cobalt exposure and tungsten carbide grinding, and chromium exposure and stellite welding[17]. Another study of workers engaged in the production of tungsten carbide tools found that exposure to heavy metals resulted in reduced lung diffusing capacity and reduced lung volumes[8]. There is comparatively more research that looked at the respiratory effects associated with the individual heavy metals. Increased risk of bronchitis was found in a study of cobalt-exposed metal industry workers, in addition, a measurable acute reduction in lung function was found among the most heavily-exposed[29]. Cadmium exposure was associated with emphysema among sawfiling tradesmen[7]. Exposure to aerosols of machining fluids was shown to be associated with a measurable acute decline in lung function[31].

In the province of British Columbia, researchers at the UBC School of Occupational and Environmental Health established the cohort of BC sawmill workers including sawfilers in the early 1990s. For each subject, we have complete work history, including job titles and start/end

date for each employment period. In this chapter, we address the following two research questions with the available data:

1) Does working as a sawfiler increase risk of lung cancer compared with other sawmill workers?

2) Does working as a sawfiler increase risk of non-malignant respiratory disease (specifically COPD) compared with other sawmill workers?

2.2 Materials and methods

2.2.1 Cohort enumeration

A cohort of BC sawmill workers (N=25,685) was followed from 01/01/1950 to 12/31/1995 for mortality and cancer incidence. There have been several previous publications with regard to the mortality and cancer incidence in the full cohort[154 155]. Cohort members were workers of 14 BC sawmills, who were employed as production or maintenance workers for at least one year. Work histories were derived from sawmill payroll records.

For lung cancer cohort, 11 workers were removed from the cohort because their vital status at the end of follow-up was unknown, and another 118 workers were removed because their death date was prior to 01/01/1970 (start of cancer registry) and we were not able to identify whether these subjects died of cancer, which left N=25,556 in the final cohort.

For COPD cohort we used a sub-cohort of workers, or which the follow up period was from 01/01/1985 to 12/31/1998, which was start and end of the time period for electronic hospitalization records. There are 11,289 sawmill workers in this sub-cohort.

2.2.2 Case definition and follow up

Each subject in the cohort was linked using probabilistic linkage to vital statistics records, and the cancer registry records; the sub-cohort was also linked to hospital discharge records. The cancer registry file, which started from 01/01/1970, had cancer diagnosis of the cohort subjects, which came from a national linkage with tumor registry data. The hospitalization file, which started from 01/01/1985, had disease diagnosis for hospital visits of the cohort subjects, which came from provincial hospitalization data. Our cases definition was based on International Classification of Diseases (ICD-9). Appropriate codes are shown in Table 2.3. Briefly, lung cancer included all cancers of trachea, lobe, bronchus and lung area of the respiratory system. COPD, by our definition, referred to chronic bronchitis, emphysema, and chronic airway obstruction, with the exclusion of asthma and extrinsic allergic alveolitis.

Table 2.3 Case definition of lung cancer and COPD

	Description	ICD-9 code
Respiratory cancer (Death registry and cancer registry)	Malignant neoplasm of trachea, bronchus, and lung	162
	Trachea	162.0
	Main bronchus	162.2
	Upper lobe, bronchus or lung	162.3
	Middle lobe, bronchus or lung	162.4
	Lower lobe, bronchus or lung	162.5
	Other parts of bronchus or lung	162.8
	Bronchus and lung, unspecified	162.9
COPD (Death registry and hospital discharge records)	Bronchitis, not specified as acute or chronic	490
	Chronic bronchitis	491
	Simple chronic bronchitis	491.0
	Mucopurulent chronic bronchitis	491.1
	Obstructive chronic bronchitis	491.2
	Other chronic bronchitis	491.8
	Unspecified chronic bronchitis	491.9
	Emphysema	492
	Emphysematous bleb	492.0
	Other emphysema	492.8
	Chronic airway obstruction, not elsewhere classified	496

Each worker was followed from start of study period or start of employment plus one year, whichever occurred later. Follow up ended at the end of study period, or diagnosis (first hospitalization), or cancer registry, or death date, or loss to follow up, whichever occurred the earliest.

2.2.3 Exposure assessment

Although sawfiling is not in itself an occupational hazard, in our risk assessment, it is a surrogate for exposure to a mixture of heavy metals and metal working fluid contaminants, which included known (e.g. chromium and nickel) and suspected carcinogens (e.g. cobalt and lead). More specifically, we assessed exposure based on the total duration of employment: (1) as a sawfiler; (2) in sawfiling related jobs or (3) in any other job categories that was conducted in the sawfiling department. Units were days. Examples of sawfiling and sawfiling related jobs (1 and 2) were benchman, grinderman, sawfiler, sawfiler, sawfitter, and fitter inspector. Examples of other jobs in sawfiling department (3) are clean-up, laborer and chargehand fitter.

2.2.4 Statistical analysis

The dataset was processed using the Life Table Analysis System (LTAS.NET 2.0.16) software developed by NIOSH, to calculate the cumulative dose (i.e. sawfiling employment days for each worker) and to group time at risk by covariates ready for Poisson regression. The dataset was stratified into 5 age groups, 5 calendar year groups and 5 TSFE (time since first exposure) groups, based on equal number of cases for each strata. Based on the subjects' surnames, we identified race as East Asian (mostly Chinese), South Asian (mostly Punjabi), and other-mostly Caucasian, and the process was validated in a sub-group of subjects who were surveyed. Since it

is generally believed that South Asians have lower cigarette consumption compared with the other two ethnic groups (thus potentially confounding the relation between exposure and lung cancer or COPD), we combined the races into two ethnic groups: Chinese & "other" (mostly Caucasian) and South Asian. For sawfiling exposure, cancer and COPD cohort was split into ever-exposed and never-exposed. Then internal analysis of comparing relative risk for the exposed group was performed using Poisson regression, with exposure variable and covariates. In addition, since lung cancer and COPD are chronic diseases, repeated analysis was performed allowing for the exposure lag of 5, 10, 15 and 20 years.

2.3 Results

2.3.1 Demographic summary of the lung cancer cohort and COPD cohort

Demographic information of the cohorts is summarized in Table 2.4. We can see that only a small fraction of the subjects (3.1% for lung cancer and 5.5% for COPD) had ever worked as sawfilers or in the sawfiling department. Correspondingly, the number of cases in the exposed group was small although we had a comparatively large total number of cases of the entire cohort. A potential problem associated with stratifying the exposed group is that there will be an even smaller number of workers and cases in each sub-group, thus reducing the stability of our analysis. So we presented the relative risk calculated based on the dichotomous groups ("ever-exposed" vs. "never-exposed) as the main result, and the RR calculated for sub-groups of exposed workers were used to discuss the dose-response relationship.

Table 2.4 Demographic information of lung cancer and COPD cohort

		Lung cancer cohort			COPD cohort		
		Exposed	Non-exposed	Total	Exposed	Non-exposed	Total
Number of workers		805	24,751	25,556	617	10,672	11,289
Vital status (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
Average age at the start of follow-up		33.1	34.5	34.5	43.1	39.0	39.2
Number of cases		20	513	533	9	112	121

2.3.2 Unadjusted relative risk

Among the 533 lung cancer cases, 20 were among the exposed (i.e., ever had sawfiling employment), which gave the unadjusted RR of lung cancer of the exposed workers 1.2 compared with non-exposed workers. Among the 121 total number of COPD cases, 9 had ever worked in sawfiling related jobs, which gave the unadjusted RR equal to 1.4.

2.3.3 Adjusted RR for lung cancer

Relative risk (RR) for lung cancer adjusted for race, age, calendar periods and time since first exposure is shown in Table 2.5. Compared with the unadjusted relative risk of 1.2, it has now increased to 1.4 but still not statistically significant. The relative risk for the South Asian ethnic group supported our assumption, as RR=0.3 compared with the reference group of Caucasian and Chinese (p=0.011).

Table 2.5 Relative risk of lung cancer for sawfiling exposed groups, adjusted for race, age and calendar period

Exposure group	N	RR	95% CI of RR	p-value
Never exposed	513	*reference*		
Ever exposed	20	1.38	0.88 2.17	0.163

2.3.4 Adjusted RR for COPD

Relative risk of COPD adjusted for age, calendar period, and time since first exposure is shown in Table 2.6. Race was not one of the covariates, as there was no COPD case among South Asian workers.

Table 2.6 Relative risk of COPD for exposure groups, adjusted for age, calendar period and time since first exposure

Exposure group	N	RR	95% CI of RR	p-value
Never exposed	112	*reference*		
Ever exposed	9	1.23	0.62—2.44	0.554

2.3.5 Adjusted RR with different lagging time

We repeated our analysis allowing for different lagging times (no lagging, 5 yr, 10 yr, 15 yr and 20 yr lagging). The results for lung cancer and COPD are shown in Table 2.7 and Table 2.8 respectively. From the tables we can see that increased lag time decreases the RR estimates towards null for both lung cancer and COPD.

Table 2.7 Adjusted RR of lung cancer allowing for different lag times

Lagging time (yr)	RR of exposed group	95% CI	p-value
0	1.38	0.88-2.17	0.163
5	1.29	0.80-2.07	0.301
10	1.30	0.80-2.13	0.286
15	1.12	0.65-2.00	0.699
20	0.92	0.45-1.84	0.804

Table 2.8 Adjusted RR of COPD allowing for different lag times

Lagging time (yr)	RR of exposed group	95% CI	p-value
0	1.23	0.62-2.44	0.554
5	1.26	0.64-2.50	0.509
10	1.08	0.50-2.32	0.852
15	0.87	0.35-2.15	0.763
20	1.14	0.46-2.82	0.779

2.3.6 Dose-response relationship between sawfiling and lung cancer

Our cohort number is relatively large for an occupational epidemiology study, and our total case number is also substantial, especially for lung cancer (N=523). However, since the exposed group (sawfiler) is only a small fraction of the whole job titles, case numbers among sawfilers are much smaller compared with the total case number. So, as was mentioned above, for the stability of the analysis, we categorized the workers into never-exposed vs. ever-exposed groups. However, we also categorized the ever-exposed workers into 3 exposure groups, based on approximately equal number of lung cancer cases for each exposure group, to investigate the dose-response relationship. The relative risk estimate for the multiple exposed groups adjusted

for race, age, calendar period, time since first exposure, with the 0, 10 and 20 years as lag time was shown in table 2.9. Generally, low exposed workers (i.e. subjects with non-zero but shorter sawfiling employment) have the highest risk of lung cancer, compared with both never-exposed and high-exposed subjects. The decreased risk for the high exposed group made the slope of trend line negative.

Table 2.9 Lung cancer RR estimates with 4 exposure groups, adjusted for race, age, calendar period, time since first exposure, and lag time set as 0, 10, 20 years.

	Never-exposed		Low			Medium			High		
Exposure*	0		0—2.5			2.5—12.6			>12.6		
	RR	N	RR	95% CI	N	RR	95% CI	N	RR	95% CI	N
no lag	1	513	1.81	0.85-3.84	7	1.40	0.66-2.98	7	1.07	0.48-2.40	6
10 years lag	1	516	1.81	0.85-3.82	7	1.37	0.64-2.90	7	0.75	0.16-2.57	3
20 years lag	1	525	1.30	0.48-3.48	4	0.58	0.15-2.34	2	0.90	0.22-3.60	2

* Sawfiling duration: year

2.3.7 Dose-response relationship between sawfiling and COPD

For COPD, we categorized the ever-exposed workers into 2 exposure groups, with approximately equal number of cases for each exposure group, to investigate the dose-response relationship. The relative risk estimate for the multiple exposed groups adjusted for race, age, calendar period, time since first exposure, with the 0, 10 and 20 years as lag time are shown in table 2.10. We can see from the table that the low-exposed subjects have higher risk estimates of COPD compared with high-exposed subjects, which also resulted in a decreased trend line.

Table 2.10 COPD RR estimates with 3 exposure groups, adjusted for race, age, calendar period, time since first exposure, and lag time set as 0, 10, 20 years.

Exposure group	Never-exposed		Low			High		
Exposure*	0		1.1—3.4			>3.4		
	RR	N	RR	95% CI	N	RR	95% CI	N
none	1	112	1.97	0.72-5.34	4	0.94	0.38-2.32	5
10 years	1	114	1.62	0.51-5.09	3	0.86	0.31-2.34	4
20 years	1	116	1.23	0.30-4.98	2	1.08	0.34-3.46	3

* Sawfiling duration (in year)

2.4 Discussion

2.4.1 Heavy metal and lung cancer

Sawfiling employment was a surrogate for the multiple heavy metals that sawfilers were potentially be exposed to, based on the hypothesis that workers in the sawfiling department had the unique exposure to metal components in the sawblade tips and chipper. Some of the metals were listed as “carcinogenic”, “probably carcinogenic”, or “possibly carcinogenic” by IARC (table 2.2). However, based on the result, the increase in the risk of lung cancer among workers who have ever been employed as sawfilers was not statistically significant, compared with workers without sawfiling employment, and there were no increase at all when disease lag was set to 20 years (the reason for highlighting risk estimates with 20 yr’s lag is that lung cancer is a chronic disease, and some occupational/environmental epidemiology studies considered 20 yr as the appropriate latent period[174-177]).

There were currently no previous studies which looked at the risk of lung cancer among sawfilers compared with the other sawmill workers. However, occupational epidemiology

studies of workers exposed to the similar heavy metal components were available: One industry-wide case-control studies comparing lung cancer mortality among hard-metal workers with the national general population found increased lung cancer mortality due to exposure to cobalt and tungsten carbide[162]. A job exposure matrix was built to quantify heavy metal exposure level for each subject, and the confounding effect of smoking was also adjusted, but disease lag was not taken into account[162]. Some of the studies which looked at lung cancer among workers exposed to stainless steel fumes found excessive risk[163 164] while others did not[165-167]. Reference subjects selected could have an impact on the risk estimates: Studies which observed excessive lung cancer SMR were based on comparison with the general population[162 163], while our study was based on internal comparison with another group of workers within the cohort. So it was possible that there might be a difference in the baseline disease risk between these two sorts of reference population, which influence the risk estimates calculated.

2.4.2 Heavy metal and COPD

Our study indicated a non-significant increase of COPD risk among sawfilers compared with the other sawmill workers. By comparison, although there were no previous studies that linked sawfiling employment with COPD, occupational epidemiology studies of workers exposed to heavy metal (e.g. metal welders[7 17], heavy metal production[8 29]) showed an association between heavy metal exposure and decreased lung function or increased respiratory disease. However, these studies were either case control studies among a small cohort group or case reports and they did not take disease latent time into account.

Ideally we want to identify reduced lung function in subjects; we choose COPD as a surrogate of decreased lung function, based on the consideration that COPD refers to airflow limitation of the

respiratory system[172] and COPD is a disease incorporated into the ICD system, we can use the hospitalization discharge dataset to define our cases. However, since we do not have spirometry tests information for the subjects, it was possible that the lung function of some workers might have been decreased because of occupational exposures but yet not developed into COPD, or been diagnosed as COPD. However, since we made internal comparisons, the misclassification would be non-differential between the exposed and non-exposed workers.

2.4.3 Dose-response relationship

For both lung cancer and COPD, the highest disease risk was observed among low-exposed workers (RR=1.30, 95%CI=0.48—3.48, lag=20yr and RR=1.23, 95%CI=0.30—4.98, lag=20yr), which was not the hypothesized pattern of dose-response. The reasons could be as follows: First, since our exposure assessment was based on employment duration as sawfilers and in sawfiling departments, we were actually assigning a homogeneous exposure level for all sawfilers, disregarding the subcategories of job titles (e.g., sawfiler, benchman, sawfitter, chargehand fitter and knife sharpener). It is likely that the actual exposure level differed between job types and individuals. During the analysis, we tried to re-evaluate exposure level by contacting an expert panel: we emailed a questionnaire to sawfilers contacted through their union, regarding the use of sawblade materials such as tungsten carbide, stellite and lead babbit among those subcategories of sawfiling jobs, and asked for their judgment of heavy metal exposure level. Their reply indicated that there could be a difference in the use of sawblade materials for different subcategories of sawfiling jobs (e.g., sawfitters were reported to have a higher exposure level of stellite compared with benchman), but there was insufficient data to quantify this difference in our analyses. A previous study showed that the type of alloy material that saw filers were working with could play a role in the heavy metal exposure level and consequent health

effects, for example, stainless steel welding could cause a higher risk of lung cancer compared with mild steel welding, because of the higher concentration of chromium in stainless steel[128 129]. Another source of exposure misclassification could be the change of sawblade material with time: since the follow-up period of the study spans several decades, it is possible that some sawblade materials which were considered to impose high occupational risk were either phased out or placed by new materials. One example would be lead babbit (lead alloy used for the bearing surface in a plain bearing), which was gradually replaced by tin babbit after 1987. Second, the decreased disease risk among highest exposed workers could be partly attributed to healthy workers' survivor effect, which refers to the continuing selection process such that workers who remain employed (i.e. survivors of the workforce) will tend to be healthier than those who leave employment.[169] Third, the small number of cases in the exposure categories could magnify random error. Although we have a substantial number of cases in the cohort (N=533 for lung cancer, N=121 for COPD), the case number among the sawfiling exposed workers were comparatively small (N=20 for lung cancer, N=9 for COPD). Thus it was expected that the number for each exposure sub-category would be further reduced when we stratify the exposed workers into low, medium and high exposure groups. In addition, when we set disease lagging time to non-zero values, we were ignoring the most recent exposure, and "pushing" cases from the exposed category into the non-exposed category, which would make the case numbers in exposure categories even smaller. Consequently, a small random change in the number of cases in the exposure group would cause a huge change in the risk estimates we calculated.

2.4.4 Confounding and control of confounding

For most occupational epidemiology studies with regard to cancer and non-malignant respiratory diseases, smoking can be a strong confounder. In United States, it was estimated that 85%-90%

of all lung cancer incidence was attributable to smoking[111-113], while approximately 80%-90% of the risk of developing and dying from COPD is attributable to smoking[109-110]. Regarding the lung cancer risk among sawfilers, the bias caused by smoking could be more substantial, because some authors have reported that workers with job tasks similar to sawfilers, such as welders and grinders, tended to smoke more than the general population[130-132]. However, in our study design, the bias caused by smoking is mitigated for two reasons: First, our analysis is based on internal comparison, so smoking would not be a significant confounder unless there was a substantial difference of cigarette consumption among sawfilers and non-sawfiler sawmill workers. Second, this issue was partly addressed by including race into our model, as South Asian are generally considered to smoke less because of their religious belief, and our results supported this assumption.

Difference in social/economic status, lifestyle and health worker's effect (HWE) are typical confounders of occupational epidemiology studies which compared disease risk among certain group of workers with the general population.[169] However, since our study design was based on internal comparison (i.e. comparing exposed and non-exposed workers within the particular sawmill cohort), it was expected that the uncontrolled confounding of social/economic status, lifestyle and HWE would be small.[170 172]

2.5 Conclusion

There was a non-significantly increased risk of both lung cancer and COPD among sawmill workers who have ever been employed as sawfilers compared with other sawmill workers. The risk appeared to decrease with increasing exposure, but the reason for this is not understood.

Chapter 3: Respiratory Health Effects of Endotoxin Exposure

Sawmill workers are exposed to airborne endotoxin at work. We made use of a cohort of sawmill workers (approximately N=26,000) and a previous endotoxin measurement study to obtain a cumulative exposure level for each subject, and built a Poisson regression model to test the association between endotoxin exposure and COPD risk. We also looked at the effect of endotoxin on lung cancer risk, which we hypothesized to be reduced as endotoxin has been suggested to have a protective effect. We included covariates such as race, age, calendar period, and time since first exposure, and 20 yr as lagging time for both diseases. We found that there was a 26% decrease of lung cancer risk for the highest endotoxin-exposed workers compared with the reference of lowest exposed when we allow 20 years lag, and for COPD, the risk increased by 87% for the highest exposed group. Based on the relative risk we calculated for all the endotoxin exposure groups, the risk of lung cancer decreased as the endotoxin cumulative dose increased. For COPD, increased risk was observed as the endotoxin cumulative increased.

3.1 Introduction

Endotoxin is produced by gram-negative bacteria as component of their outer membrane[32]. Endotoxin has been found in a large number of environments where gram-negative bacteria can grow, such as in the soil, on vegetation, in natural water and in house dusts of the indoor environment[33-35]. Some studies even found endotoxin in tobacco smoke[83] and particulate matter in air pollution[82].Endotoxin consists of three parts: the O-specific side chain composed of repeated oligosaccharide units, and oligosaccharide core, and lipid A consisting of a diglucosamine acylated by long chain fatty acids.[77 81] The lipopolysaccharide (LPS) component

is believed to be responsible for most of the biologic properties of bacterial endotoxins.[61] Health effects of endotoxin exposure are paradoxical, as there are both adverse and positive health outcomes following endotoxin exposure.[62 63]

3.1.1 Endotoxin and decreased lung function

The most well studied adverse effect of endotoxin exposure is decreased respiratory function. One occupational epidemiology study among sawmill workers found a dose-response relationship between endotoxin exposure and decrease in FEV_1 (forced expiratory volume in 1 second) at personal exposure levels below 20ng/m^3.[53] Studies of other occupations with high endotoxin exposure also observed such trend: One study found a cross-shift increase in respiratory symptoms, decreased lung function and bronchi damage among poultry slaughter house workers identified as highly exposed 400ng/m^3.[64] Textile workers with chronic occupational endotoxin exposure were observed to develop severe obstructive airway diseases.[78 85] Physiologically, inhaled endotoxin[86 88] and grain dust that contains endotoxin[79 87] can cause airflow obstruction or decreased FEV_1 in both previously never-exposed and ever-exposed subjects. In addition to decrease FEV_1, several studies also reported a decrease of FVC (forced vital capacity) in association with endotoxin exposure.[140 141] Study in animal models of mice found that chronic intra-tracheal exposure to LPS elicits lung pathologic changes similar to human COPD-associated inflammation.[84]

3.1.2 Endotoxin and asthma

There are conflicts regarding the potential effect of high endotoxin exposure on asthma, as both elevated and decreased asthma risk was observed across the studies. The inconsistency with regard to whether endotoxin would increase or decrease asthma risk could be attributed to the

fact that asthma can be classified into atopic asthma and non-atopic asthma, based on whether it is associated with allergic sensitization or not.[62] The risk of atopic asthma is decreased because endotoxin might suppress the eosinophilic response, which is common in asthmatic reactions.[62] However, the risk of non-atopic asthma is enhanced by endotoxin exposure, as endotoxin will cause neutrophilic airway inflammation, which is most responsible for the non-atopic asthmatic symptoms.[62 65]

3.1.3 Endotoxin and lung cancer

Endotoxin exposure has been reported to have an apparent potential to reduce cancer risk. Reduced lung cancer risk among cotton textile workers and farmers who are exposed to endotoxin has been recognized since 1936.[66 67] A meta-analysis of papers published in the 1970s and 1980s showed that lung cancer relative risk was significantly lower than 1.0 in workers exposed to cotton and wool dust.[68] Another meta-analysis with 28 studies that met predefined quality criteria, summarized a lung cancer risk of 0.72 (95% CI 0.57—0.90) for textile workers and 0.62 (95% CI 0.52—0.75) for agricultural workers.[142] In addition to the decreased overall lung cancer risk, dose-response relationship between increased level or duration of endotoxin exposure and decreased rate of lung cancer has been observed to be significant in the cotton textile industry[47] as well as agricultural section[69].

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-α), which will stimulate the antitumoral response of the immune system.[70-74]

At occupational settings, higher endotoxin level is found at work places where large amount of bioaerosols are generated, such as animal farming[36-41], waste industry[42-46], textile industry[47-51], and wood processing industry[52-57]. Animal farmers are considered to be one of the highest exposed jobs, for example, in dairy barns, endotoxin level could reach as high as 2800 ng/m^3,[36] by comparison, measurements of household indoor air endotoxin level ranges between 18 to 50 ng/m^3.[34] Currently, there's no threshold endotoxin exposure limits set by ACGIH, OSHA, NIOSH or WorkSafe BC, however, some scholars recommended that peak endotoxin level should not exceed 20 ng/m^3,[58] and the National Health Council of the Netherlands suggests an 8-hr endotoxin occupational exposure limit of 50EU/m^3, or approximately 5ng/m^3 [60] (EU/m^3 is another unit that is also often used in endotoxin concentration measurement, and 10EU≈1ng/m3)[34].

Since gram-negative bacteria grow on wood, in wood processing industry, endotoxin is generated along with wood dust when certain tasks are performed, such as cutting, sawing and trimming, and then can be inhaled by sawmill workers. Sawmill departments at the early stage of wood processing (such as log processing, primary breakdown) are expected to have higher endotoxin exposure level, as studies showed that endotoxin level are higher for fresh-cut wood[55-57], in addition, workers dealing with wood processing by-products (such as sawdust and "hog") are expected to have higher exposure level because of the airborne bio-aerosol generated. One study which measured endotoxin levels in British Columbia sawmills found an average personal exposure level of 2.09ng/m^3,[52] and 9% of the samples were above 5ng/m^3. Another study measured endotoxin levels in several sawmills, logging sites and joineries located in New South

Wales of Australia, and found that some personal exposure samples exceeds the threshold peak value of 20 ng/m^3.[59] Wood processing of the initial stage was related with higher endotoxin exposure, for example, the great level of endotoxin exposure among sawmill workers were noted at debarking of two measurement studies in Poland and Finland.[55 57]

3.1.4 Research question

The focus of our research was to explore both the positive and negative health effects of occupational endotoxin exposure:

1) Is endotoxin exposure among sawmill workers associated with reduced risk of respiratory cancer?

2) Is endotoxin exposure among sawmill workers associated with increased risk of COPD?

3.2 Materials and Methods

3.2.1 Cohort enumeration

A cohort of BC sawmill workers cohort (N=25,685) were followed from 01/01/1950 to 12/31/1995 for mortality. There have been previous publications with regard to the mortality and cancer incidence for the full cohort.[154 155] Cohort members were composed of workers of 14 BC sawmills who worked at least one year in production or maintenance. Work histories were derived from sawmill payroll records. Each subject was linked using probabilistic linkage to vital status records, cancer registry records[154], and hospital discharge records[161].

For the lung cancer cohort, 11 workers were removed from the cohort because their vital status at the end of follow-up was unknown, and another 118 workers were removed because their death date was prior to 01/01/1970 (start of cancer registry), which makes N=25,556 in the final cohort.

For COPD, we used a sub-cohort of workers, for which the study period was from 01/01/1985 to 12/31/1998, which is start and end date of hospitalization records. There were 11,447 sawmill workers in the sub-cohort.

3.2.2 Case definition

Each subject in the sub-cohort was linked using probabilistic linkage to vital statistics records, cancer registry records, or hospital discharge records, in which a disease code was assigned for each death cancer diagnosis or hospital discharge. The cancer registry file, which started from 01/01/1970, had cancer diagnosis of the cohort subjects, which came from a BC provincial linkage with tumor registry data. The hospitalization file, which started from 01/01/1985, had disease diagnosis for hospital visits of the sub-cohort subjects, which came from provincial hospitalization data. Lung cancer cases included all cancers of trachea, lobe, bronchus and lung area of the respiratory system. COPD, by our definition, referred to chronic bronchitis, emphysema, and chronic airway obstruction, with the exclusion of asthma and extrinsic allergic alveolitis. The complete list of the targeted disease was shown in Table 2.3, which was based on International Classification of Disease-9 (ICD-9) code.

Each worker was followed from start of study period or start of employment plus one year, whichever occurred later. Follow up ended at the end of study period, or diagnosis (first hospitalization) or death date, or loss to follow up, whichever occurred earlier.

3.2.3 Exposure assessment

1) Introducing the endotoxin monitoring study

An endotoxin monitoring study was conducted at 4 BC sawmills during the summer months of 1997, as part of the BC sawmill study. Each mill was located in a different region of the province: Northern interior, Southern coast, Vancouver Island, and Southern interior. A total number of 216 samples were collected, along with the worker's job title.[52] Consequently, it was possible to build an exposure model based on the monitoring dataset that would predict the endotoxin level of any subject in our cohort, given his job title and geographic location of the mill he was working, which we could identify from the work history file. However, we needed to reconfigure the datasets in order to do that: First, the job codes adopted in the endotoxin monitoring study were not consistent with the job titles in the work history file. Second, we needed an endotoxin concentration for each job-location combination, which was not available in the existing monitoring data.

2) Recoding jobs

Job information in the monitoring data was based on 107 four-digit job codes, each corresponding to one job titles. By contrast, there were 74 distinct job titles in the work history file. Figure 3.2 shows the relationship of the two job coding schemes. The key issue here was to make the two coding systems consistent with each other to facilitate exposure assessment. The 64 jobs which existed in both files were kept. The 43 jobs which were monitored but did not exist in the work history file were maintained, as there were only 216 observations in total and we would lose observations by doing so. Instead, the exposure levels were reassigned to a new job that exists in both files, one that we believe to have the closest endotoxin exposure based on

the job tasks they performed and department they worked. For the 10 jobs which existed in the work history data but not in the monitoring data, we found a corresponding substitute job from those existed in both files. The list of jobs before and after recoding is presented in Appendix I. After the recoding, there were 64 distinct jobs in both the monitoring and work history files, which was consistent with each other.

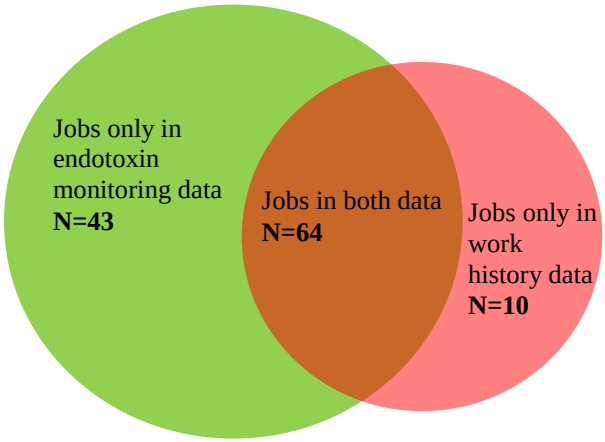

Figure 3.1 Jobs coding schemes of the endotoxin monitoring and work history data

3) Building the job exposure matrix

In the recoded endotoxin monitoring data, we had 64 jobs and 4 geographic locations of the sawmills, for a total of 256 combinations. However, there were 216 observations, which indicated that we did not have endotoxin concentration for certain jobs in a certain geographic location. Consequently, we needed to build a job exposure matrix to predict the endotoxin concentration for each job-location combination. Exposure were all measured in 1997, thus they did not represent the true time-varying nature of the exposure. Then for the purpose of standardization and keeping consistency, for the endotoxin exposure evaluation of all the subjects, we used the "modeled" result (instead of using the "actual" level for the subjects being

monitored and "modeled" level for those missing). In addition, by using endotoxin levels from regression model instead of individual monitoring values, it was expected that Berkson type error would increase while classical type of error would decrease, thus it shouldn't increase the total error or bias the relative risk towards the null value.[118]

The job exposure matrix was built based on a linear regression model: explanatory variables were the job codes and geographic location of the mills, and the outcome variable was the log-transformed endotoxin concentration (ng/m^3), as the concentration data follows log-normal distribution.

The categorical variable of jobs were converted it into 63 dummy variables, and geographical locations were converted into 3 dummy variables. Modeling was by manual forward-stepwise linear regression, considering p-value of 0.2 as the cut-off point of whether the dummy variable should be included or categorized as reference. The final model (shown in Table 3.1) had all the 4 geographic locations and 21 job codes out of the original 64.
The adjusted R^2 value for the overall model was 0.36, which indicates that 36% of the variance in endotoxin level could be explained by job and sawmill geographic location.

Based on the job exposure matrix, we can calculate endotoxin exposure level for each mill and job. E.g., endotoxin level for a carpenter at a southern coast mill is exp(-0.11-0.80+0.88)=0.97ng/m^3.

Table 3.1 Job exposure matrix of endotoxin

		Coefficient	*p-value*	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 attendent	-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

3.2.4 Statistical analysis

The dataset was processed using the Life Table Analysis System (LTAS.NET 2.0.16) software developed by NIOSH, to calculate endotoxin cumulative dose for each subject ($\sum_{j=1}^{N} concentration_{job\ j} \times duration_{job\ j}$) in the unit of ng/m^3*year, and group time at risk by covariates ready for Poisson regression. Then the dataset was stratified by LTAS into 5 age groups, 5 calendar period groups, 5 time since first exposure (TSFE) groups based on equal

number of deaths for each group. Based on the last name in the payroll, we were able to identify the race group of the Chinese and South Asian, the majority of all the other workers were Caucasian. The Chinese were merged with "other" races, so that we have two race groups: South Asian and others. This was based on a *priori assumption* that South Asian has comparatively less cigarette consumption compared with other races, because of their religion, thus potentially confounding the endotoxin-lung cancer/COPD relation. Endotoxin exposure was categorized into 5 groups, with approximately equal number of cases for each group. Then internal analysis of comparing relative risk among exposure groups was performed using Poisson regression of the cohort export, with exposure variable and covariates.

3.3 Result

3.3.1 Demographic summary of the lung cancer cohort and COPD cohort

Demographic information of the main cohort and the COPD sub-cohort are shown in Table 3.2.

The average age at the start of follow up was older for COPD (39.2) cohort compared with lung cancer cohort (34.5), as the follow up period started earlier for lung cancer. The cohorts were stratified into the exposure groups based on equal (or approximately equal) number of cases for each group, the number of total deaths for each exposure group varied: There were a downward trend in number of workers for each exposure group, and by comparison, the decreased trend was more obvious for the COPD cohort than the lung cancer cohort.

Table 3.2 Demographic information of the two cohorts

Exposure group		Vital status [1]		Race [2]		Number of workers	Number of cases	Average age [3]	Average follow-up years	Median cumulative dose [4]
		Dead	Alive	Chinese and other	South Asian					
Lung cancer cohort	1	885 (13.1%)	5,849 (86.9%)	6,513 (96.7%)	221 (3.3%)	6,734	105	30.0	20.6	0.89
	2	1,060 (15.5%)	5,779 (84.5%)	6,489 (94.9%)	350 (5.1%)	6,839	104	32.3	19.3	2.68
	3	915 (21.8%)	3,281 (78.2%)	3,953 (94.2%)	243 (5.8%)	4,196	105	36.0	18.9	5.52
	4	942 (26.7%)	2,592 (73.3%)	3,203 (90.6%)	331 (9.4%)	3,534	105	38.5	20.7	11.64
	5	1,080 (28.2%)	2,756 (71.8%)	3,466 (90.4%)	370 (9.6%)	3,836	104	40.9	21.4	19.84
	Total	4,882 (19.4%)	20,257 (80.6%)	23,624 (94.0%)	1,515 (6.0%)	25,139	523	34.5	20.1	3.99
COPD sub-cohort	1	209 (4.0%)	5,066 (96.0%)	4,943 (93.7%)	332 (6.3%)	5,275	24	33.6	10.3	2.88
	2	177 (9.4%)	1,716 (90.6%)	1,720 (90.9%)	173 (9.1%)	1,893	24	40.3	11.4	9.48
	3	180 (12.5%)	1,259 (87.5%)	1,259 (87.5%)	180 (12.5%)	1,439	24	44.5	11.8	13.38
	4	197 (12.8%)	1,248 (87.2%)	1,351 (87.4%)	194 (12.6%)	1,545	24	46.4	11.8	17.92
	5	153 (13.8%)	958 (86.2%)	990 (89.1%)	121 (10.9%)	1,111	24	47.1	11.8	28.12
	Total	906 (8.0%)	10,357 (92.0%)	10,263 (91.1%)	1,000 (8.9%)	11,263	120	39.2	11.0	8.14

[1]: At the end of follow up.

[2]: "W" White, "CHN" Chinese, "SA" South Asian.

[3]: At the start of follow-up.

[4]: Unit ng/m3*year

3.3.2 Risk estimates for lung cancer

Relative risk of lung cancer adjusted for race, age, calendar period and time since first exposure is shown in Table 3.3. The significance of the dose-response trend was 0.170, based on linear regression with median exposure level as the explanatory variable and RR as the outcome variable.

Table 3.3. RR of lung cancer among different exposure groups (Adjusted for race, age, calendar period, TSFE)

Endotoxin cumulative dose (ng/m^3*year)	Median exposure (ng/m^3*year)	N	RR	95% CI of RR	*p*-value
0—1.5	0.9	105	1.0	*(reference)*	
1.5—4.7	2.7	104	0.79	0.60—1.04	0.690
4.7—9.1	6.6	105	0.94	0.71—1.24	0.642
9.1—14.7	11.6	105	0.86	0.65—1.14	0.293
>14.7	19.9	104	0.73	0.55—0.98	0.186
Total		523			

RR for South Asian ethnic group supported our assumption, which was 0.3 and statistically significant compared with the reference group of "others" (p=0.011).

3.3.3 Risk estimates for COPD

Relative risk of COPD adjusted for age, calendar period and time since first exposure is shown in Table 3.4. Race was not controlled for, as there are no COPD cases among South Asian workers. The dose-response trend was borderline significant (p=0.065).

Table 3.4 Adjusted RR of COPD among different exposure groups (Adjusted for age, calendar period, TSFE.)

Endotoxin cumulative dose (ng/m^3*year)	Median exposure (ng/m^3*year)	N	RR	95% CI of RR	*p*-value
0—7.4	2.9	24	1.0	*(reference)*	
7.4—11.6	9.5	24	1.47	0.79—2.74	0.203
11.6—15.3	13.4	24	1.58	0.82—3.06	0.219
15.3—22.1	17.9	24	1.34	0.68—2.64	0.404
>22.1	28.1	24	1.87	0.95—3.67	0.069
Total		120			

3.3.4 Dose-response relationship and the effect of lagging time

For lung cancer, we repeated our analysis with the lag time set to 0, 5, 10, 15 and 20 years, the result is shown in Table 3.5, along with the slope of dose-response relationship based on the linear model with RR and median exposure level of each exposure group. From the slope of the trend, we can see that dose-response relationship of the decreased lung cancer risk was most significant when lag time was set to 20 years.

Table 3.5 Adjusted RR of lung cancer among different exposure groups (adjusted for age, calendar period, TSFE. Lag was set to 0, 5, 10, 15 and 20 yrs), and slope of the dose-response relationship based on the linear model with RR and medium exposure level of each exposure group.

Endotoxin	<1.5*		1.5-4.7		4.7-9.1		9.1-14.7		>14.7		Slope
	n	RR (reference)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	
0 yr lag	105	1.00	104	0.79 (0.60-1.04)	105	0.94 (0.71-1.24)	105	0.86 (0.65-1.14)	104	0.73 (0.55-0.98)	-0.0098
5 yr lag	112	1.00	107	0.87 (0.66-1.14)	110	1.03 (0.78-1.35)	100	0.90 (0.67-1.20)	94	0.79 (0.59-1.08)	-0.0088
10 yr lag	126	1.00	114	0.98 (0.76-1.30)	116	1.13 (0.87-1.74)	93	0.97 (0.72-1.30)	74	0.84 (0.60-1.16)	-0.0088
15 yr lag	155	1.00	120	1.02 (0.79-1.30)	113	1.06 (0.82-1.38)	79	0.89 (0.65-1.20)	56	0.77 (0.54-1.10)	-0.0138
20 yr lag	204	1.00	130	1.05 (0.83-1.32)	93	0.84 (0.65-1.10)	56	0.75 (0.54-1.05)	40	0.76 (0.51-1.14)	-0.0153

* Endotoxin cumulative dose in ng/m^3*year

For COPD, we also repeated our analysis with the lag time set to 0, 5, 10, 15, and 20 yr respectively, and the result is shown in Table 3.6, along with the slope of dose-response relationship based on the linear model with RR and median exposure level of each exposure group. From the slope, we can see that dose response relationship was most significant when lag time was set to 20 yr. We can also see that as lagging time was increased from 0 year to 15 years, the trend of elevated risk becomes less significant, but when lagging time was increased from 15 years to 20 years, the trend became more significant, as the slope rises from 0.0053 to 0.0461. There might be both physiological and analytical reasons which could explain the change of dose-response relationship with lagging time, which would be discussed below.

Table 3.6. Adjusted RR of COPD among different exposure groups (Adjusted for age, calendar period, TSFE. Lag was set to 0, 5, 10, 15 and 20 yrs), and slope of the dose-response relationship based on the linear model with RR and medium exposure level of each exposure group.

Endotoxin	<7.4*		7.4-11.6		11.6-15.3		15.3-22.1		>22.1		Slope
	n	RR (reference)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	
0 yr lag	24	1.00	24	1.47 (0.79-2.74)	24	1.58 (0.82-3.06)	24	1.34 (0.68-2.64)	24	1.87 (0.95-3.67)	+0.0228
5 yr lag	29	1.00	22	1.14 (0.62-2.09)	26	1.52 (0.80-2.88)	24	1.27 (0.65-2.47)	19	1.49 (0.74-2.98)	+0.0182
10 yr lag	36	1.00	29	1.62 (0.93-2.82)	20	1.35 (0.69-2.62)	21	1.52 (0.78-2.98)	14	1.52 (0.78-2.98)	+0.0158
15 yr lag	55	1.00	26	1.03 (0.59-1.80)	14	0.76 (0.37-1.53)	16	1.12 (0.56-2.21)	9	1.10 (0.48-2.52)	+0.0053
20 yr lag	71	1.00	21	0.80 (0.46-1.40)	10	0.80 (0.38-1.67)	10	1.09 (0.51-2.29)	8	2.09 (0.90-4.83)	+0.0461

* Endotoxin cumulative dose in ng/m^3*year

3.3.5 Risk estimates based on job grouping used in the endotoxin monitoring study

Our endotoxin job exposure matrix is based on a forward stepwise regression, in which the number of job categories decreased from 64 to 21. However, in the endotoxin monitoring study which was the base of our exposure assessment[52], results were presented by using a different scheme of job categories: Samples they took were divided into 6 job categories “front sawmill”,

"other sawmill", "planer mill", "clean-up", "maintenance", and "miscellaneous", based on the *a priori* hypothesis that potentially higher levels of endotoxin could be present in the front end of the sawmill because this is where whole logs or slabs are handled. We thus made a new job-exposure matrix based on the 6 major job categories adopted in their study and the 4 geographical locations, which was presented in Table 3.7 below. The adjusted R^2 is 0.28, which is lower than the adjusted R^2 of 0.36 in the job exposure matrix we used. Then we repeated the risk estimates calculation based on the job exposure matrix with 6 major job categories, and the results for lung cancer and COPD were shown in table 8 and table 9 respectively. There was a downward trend of lung cancer as endotoxin exposure level increased and an upward trend of COPD as endotoxin exposure increased, which were both in consistent with the trend we observed using our own job exposure matrix. In addition, the slope of trend was greatest when lag time was set to 20 years for both lung cancer and COPD, indicating the same influence of lag time on risk estimates. However, by comparing the absolute value of the slopes, we can see that the dose-response trend was not as obvious for the second exposure assessment method. The reason was that the job categorization of the new job exposure matrix was based on the *a priori* assumption that endotoxin exposure among front sawmill jobs would be higher than other sawmill jobs, however, the actual measurement showed that endotoxin concentration in the other sawmill group was slightly higher (0.71 compared to 0.90 ng/m^3).

Table 3.7 Job exposure matrix* of endotoxin concentration based on 6 major job categories and geographic locations.

	Southern Interior	Vancouver Island	Northern Interior	Southern Coast
Maintenance	1.34**	0.71	1.96	0.58
Clean-up	3.96	2.11	5.80	1.73
Front sawmill	0.95	0.50	1.39	0.41
Miscellaneous	0.74	0.39	1.08	0.32
Other sawmill	1.36	0.72	1.99	0.59
Planer mill	0.53	0.28	0.78	0.23

*Adjusted R^2=0.2755
** unit: ng/m^3

Table 3.8 Relative risk estimates of lung cancer for endotoxin exposure groups based on job exposure matrix of 6 major job categories

Endotoxin	<2.7*		2.7-6.5		6.5-11.4		11.4-18.5		>18.5		Slope
	n	RR (reference)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	
0 yr lag	105	1.00	104	0.83 (0.63-1.09)	105	0.99 (0.75-1.30)	104	0.82 (0.62-1.09)	105	0.78 (0.58-1.04)	-0.008
10 yr lag	129	1.00	117	1.04 (0.80-1.34)	108	1.12 (0.86-1.46)	95	0.96 (0.72-1.28)	74	0.88 (0.64-1.22)	-0.007
20 yr lag	218	1.00	107	0.86 (0.68-1.09)	94	0.90 (0.69-1.16)	68	0.81 (0.60-1.11)	36	0.73 (0.48-1.10)	-0.103

* Endotoxin cumulative dose in ng/m^3*year

Table 3.9 Relative risk estimates of COPD for endotoxin exposure groups based on job exposure matrix of 6 major job categories

Endotoxin	<8.8*		8.8-15.6		15.6-19.8		19.8-23.3		>23.3		Slope
	n	RR (reference)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	
0 yr lag	24	1.00	24	1.00 (0.54-1.86)	24	1.43 (0.76-1.98)	24	1.24 (0.89-1.78)	24	1.51 (0.91-2.39)	0.0203
10 yr lag	34	1.00	40	1.78 (1.05-3.02)	20	1.42 (0.82-1.90)	13	1.21 (0.88-4.17)	13	1.47 (0.67-3.20)	0.0194
20 yr lag	69	1.00	29	0.97 (0.59-1.61)	11	1.25 (0.58-2.67)	4	1.21 (0.40-3.62)	7	1.58 (0.65-3.83)	0.0237

* Endotoxin cumulative dose in ng/m^3*year

3.4 Discussion

For the protective effect of endotoxin against cancer, the trend we observed was consistent with those of most of the epidemiologic studies among animal farming workers and textile workers[47 69], believed to be "highest exposure workers", at levels reported as high as 360ng/m^3.[54] By contrast, for the sawmill workers of our cohort, their exposure level is much lower (mean concentration 2.09ng/m^3), so our result suggests that protective effect might occur at much lower levels than previous studies. However, we should be cautious when we compare the levels at which dose-response was observed in our study with those of other studies for three reasons: 1) According to some studies which compared intra-laboratory results of endotoxin measurements, the variation could be as much as an order of magnitude[160], which makes comparing endotoxin levels between different studies problematic. 2) For inter-laboratory comparisons, endotoxin monitoring in the grain industry was performed in the same laboratory (but using a different filter medium in the analysis), and the result of that study showed a mean endotoxin concentration 10 times higher than the highest concentrations observed in the sawmill industry endotoxin study[161]. However, since we made internal comparisons between the endotoxin exposure groups, with regard to our study, it should not affect the validity of dose-response relationship we observed. For the protective effect of endotoxin against lung cancer, most previous studies did external comparison with the general population, so the trend they observed may be questioned to be attributed to healthy worker effect, less exposure to carcinogenic substances, and reduced smoking[65 76 79]. However, in our study, thanks to the large number of cohort workers as well as cases we have, we can perform an internal comparison, which is expected to mitigate the health workers effect (HWE), and reduce the bias caused by confounders such as economic status, life style and smoking. 3) Our endotoxin exposure

assessment incorporated both concentration and exposure duration. It would be possible that once a worker was exposed to higher endotoxin concentration at the early stage of his employment history, his immune system response was triggered, after which a lower endotoxin concentration would be able to "maintain" the activated immuno-status, and develop protective effect against cancer. Thus a low endotoxin concentration of the later period of the workers' employment history could be sufficient to play a role in the anti-cancer effect.

For the elevated risk of chronic obstructive pulmonary disease, the trend in our study is also consistent with previous reports. In one study significant trend of decreased FEV1 and other increased respiratory symptoms may be observed at the exposure level as low as 20ng/m^3.[61] In another study, this trend was observed among sawmill workers whose exposure arithmetic level was 4.65ng/m^3 and 0.47ng/m^3 respectively for inhalable and respirable endotoxin[53], a level comparable with the data we used. Results of our study also suggested that the adverse effects might occur at a lower exposure level compared with the "beneficial" effect related to cancer.

The confounding of age on lung cancer risk could be substantial: As shown table 3.6, the 5 endotoxin exposure groups were defined based on approximately equal number of cases (N=523/5≈105), however, there was a clear decrease in the number of workers for each exposure group as endotoxin cumulative increased, so it was expected that when we calculate the unadjusted risk estimates, the RR would be larger than 1 because of the decrease in the denominator. By comparison, there was an increased trend in the risk estimate after adjusting for covariates. The paradox between unadjusted RR and adjusted RR could be attributed to the difference in the age distribution among the 5 exposure groups: higher endotoxin cumulative

dose might be due to longer employment duration, which in turn results in older age and higher risk of lung cancer. Actually, from Table 3.2 of this Chapter, we can see that the average age at the start point of follow-up increased from 30.0 for the lowest exposed to 40.3 for the highest exposed group, so by including age as our covariate, its confounding effect was adjusted, thus rendering the actual risk estimate. A more quantitative approach to assess the confounding effect of age was to compare the crude RR from univariate Poisson regression (i.e. endotoxin exposure as the only explanatory variable) with the partly adjusted RR from bivariate Poisson regression (i.e. with both endotoxin exposure and age as the explanatory variable): For the highest exposed group, RR from univariate model was 8.0 and RR from bivariate model was 0.85; for the second highest exposed group, it was 5.8 vs. 0.80.

The monitoring data we used were based on samples collected in the summer time, and did not take seasonal variation into account, which is a determinant of endotoxin exposure level.[34] The ideal exposure assessment would be based on a sufficiently large number of samples taken for each subjects in different seasons, so that both the inter-personal and intra-personal variation could be captured and taken into account in our calculation of endotoxin cumulative dose. However, in our analysis, endotoxin exposure groups were categorized based on equal number of cases (i.e. reference cumulative dose, but not absolute value), the exposure misclassification was mitigated.

Smoking is generally considered to be a confounder in many occupational epidemiology studies, as it was a confirmed risk factor for lung cancer and COPD.[109-113] Although we partly adjusted for the confounding of smoking by including race as one of the covariates in the lung cancer

analysis, it was still possible that there was a difference in the distribution of cigarette consumption among different endotoxin exposure groups, thus confounding the result.

Multiple exposures might influence the disease risk we calculated, as sawmill workers are potentially exposed to a variety of respiratory hazards besides endotoxin, such as wood dust, other chemical constituents of wood, moulds and bacteria.[52] In particular, wood dust concentration was found to be correlated with endotoxin concentration in the endotoxin monitoring study which was the base of our exposure assessment: correlation coefficient between the log-transformed concentrations was 0.69 (p<0.0001). For lung cancer, there have been limited studies which investigated the effect of "pure" wood dust, as multiple exposures always existed in sawmills. However, with regard to synthetic fiber, which is also a kind of inhalable dust, one study found increased lung cancer mortality among workers exposed to increasing levels of dusts,[144] and endotoxin levels were generally considered to be minimal in synthetic textile dusts.[145] Consequently, it can be expected that the combined effect of wood dust exposure will bias our results toward null (i.e., underestimated the anti-cancer effect of endotoxin). For COPD, the situation is different: according to some occupational epidemiology studies, wood dust were a risk factor for decreased lung function or COPD[119-122 146-150], while others did not find such trend[126-153], thus we still not could not determine whether the elevated COPD risk observed was the combined effect of endotoxin and wood dust (i.e., overestimated the COPD effect of endotoxin) or the actual effect of endotoxin alone.

3.5 Conclusion

For lung cancer, there was a decreased trend of risk as endotoxin exposure level increased. The trend was most obvious when lag time was set as 20 years.

For lung cancer, there was an increased trend of risk as endotoxin exposure level increased. The trend was most obvious when lag time was set as 20 years.

Chapter 4: Reflections and Future Work

4.1 Supplemental analysis of cancer of other sites

We thought, logically given the exposures of sawfiling, which impose sawfilers' on airborne heavy metal particulates and organic matters, lung cancer should be of primary concern. However, the initial motivation for this study was anecdotal information from the sawfilers' union relating exposure to gastrointestinal cancer, perhaps because it was suspected that the sawfilers' hands became contaminated with heavy metal through the course of their work and pose a hazard to the gastrointestinal tract.[1] In addition to the lung cancer cases, there were a smaller yet substantial number of gastrointestinal cancer cases in the cohort. Thus for the hazard of sawfiling, we repeated our analysis with colorectal cancer, the kind of gastrointestinal cancers with largest number of cases in our cohort.

Colorectal cancer refers to the neoplasm of colon, rectum, appendix and anus. It is the third most commonly diagnosed cancer in the world,[2] and is more common in the developed countries of the world.[3] We used similar methods as in Chapter 2, and exposure was ever vs. never worked as sawfiler. The ICD-9 code for colorectal cancer is 153.0-154.1. Table 4.1 shows the results of colorectal with 20 years as lagging time. Based on the repeated analysis with the lag time of 0, 5, 10 and 15 yrs, the corresponding relative risk is 1.61 (95% CI 1.01—2.57). 1.72 (95% CI 1.08—2.73), 1.88 (95% CI 1.18—3.00) and 2.02 (95% CI 1.25—3.26) respectively, from which we can see a more and more obviously elevated risk of colorectal cancer as we increase the lag time. The most significantly elevated risk with 20 years' lag could be explained that 20 year was closest to the actual lag time of sawfiling on colorectal cancer, although there has been no previous report with regard to this.

Table 4.1 Adjusted RR of colorectal cancer of sawfiling-exposed groups (Adjusted for age, calendar period, TSFE. Lag was set to 20 yrs)

	# of cases	# of workers	Adjusted RR	95% CI
Non-exposed	319	24,659	*reference*	
Exposed	15	897	2.06	1.22 –3.48
Total	334	25,556		

4.2 The effect of lag time on lung cancer

For the result of "protective effect" of endotoxin against lung cancer, the trend of dose-response relationship is more significant for the 20 yr lag. Same effect of lagging time on the increased trend of lung cancer was observed by one previous study, which found that the protective trend of lung cancer among cotton textile workers who were exposed to high level of endotoxin was most significant when they set the lagging time as 20 yrs, thus suggesting that the observed protective effect of exposure was acting at an early stage during lung carcinogenesis.

For sawfiling and lung cancer, since we are looking at multiple exposures of heavy metals and metalworking fluid chemicals, and the mechanism of initiating or promoting lung cancer might not be the same, thus it is hard to say that how long the lag time "should be". If we only look at the result of lung cancer with sawfiling, the elevated risk was highest if the lag time was set to 0 yr, and when the lag time was set to 20 yrs, it decreased the estimated relative risk of exposed group toward null (RR=1). The reason might be "analytical" rather than "physiological": there are already small number of lung cancer cases in the ever-exposed group, when we increase the lag time, we are "pushing" more cases from the ever-exposed group to the never-exposed group, consequently, the relative risk we calculated are more "vulnerable" to the small change in the case numbers. The trend that increased lagging time will push the risk estimate toward null was

also observed by other occupational epidemiology studies. One study which investigated the effect of synthetic metalworking fluid on lung cancer also found that the elevated risk was less significant when lag was set to 20 yr compared with no lag.[114]

4.3 The effect of lagging time on COPD

For the relationship between sawfiling employment and COPD, the elevated risk became less significant as we increase the lagging time from 0 to 20 years. This could be explained by the analytical reason, e.g., when we increase lagging time, we are actually "pushing" the ever-exposed subjects to the never-exposed group, thus the number of cases in the ever-exposed group became smaller, resulting in a magnified change in the relative risk we calculated when there is a change in the number of cases in the exposed group caused by some random factors. Similar effect of lagging time on Hazard Ratio (HR) estimates was observed in an industry cohort study exploring the effect of synthetic metalworking fluids on COPD mortality: Lagging exposure by 20 years raised the HR upwards towards null (i.e. HR=1).[114]

For endotoxin exposure and COPD, the elevated risk was more obvious when we set the lagging time to the maximum of 20 years and to the minimum of 0 year, based on the slope of trend line; the trend was not so obvious for medium lagging of 10 and 15 years. There was hardly any resource from the current literature with regard to how long the latent period should be from endotoxin exposure to the development of COPD, however, some studies exploring the relationship between smoking and COPD used 1to 5 years as the time lag in the analysis.[115-117] Thus it was possible that "analytical" reasons are more responsible for the effect of lagging time

on the trend, and it was expected to bias the relative risk estimates toward both overestimating and underestimating the real risk.

4.4 Scientific contributions of our study

The research questions were answered through the two parts of the study, and the results were in accordance with all our hypotheses: Sawfiling was associated with elevated risk of lung cancer and COPD, and endotoxin exposure was associated with decreased risk of lung cancer and increased risk of COPD.

By making use of the large cohort of BC sawmill study, our study relates to and contributes to the existing understanding of sawfiling and endotoxin as occupational hazards: First, although there are measurements of heavy metal levels and case reports of respiratory diseases following the heavy metal exposure at sawfiling shops, there is still lack of occupational epidemiology studies which relates sawfiling with lung cancer and COPD. Second, for the protective effect of endotoxin exposure against lung cancer, we can see a clear downward trend at low exposure levels like this, while most of the trends observed by previous studies were at higher exposure levels or among occupations with higher exposure than sawmill workers.

4.5 Recommendation for control measures

Engineering controls, administrative actions, and personal protection equipment (PPE) are the three major approaches to control occupational hazards. For endotoxin, although it has been linked with decreased risk of lung cancer over the lung term, still, it was generally seen as a biohazard in workplace, because of its effect to cause short-term discomfort and long term respiratory symptoms.[158 159] Here are the recommendations for controlling occupational exposure

from heavy metal particulates among sawfilers and endotoxin to reduce the negative health effects:

Engineering controls that eliminates or reduce the hazards are generally more preferable to the other two control methods:

- Substitute saw blade materials with chemical components that impose higher risk of lung cancer and respiratory diseases with lower risk ones. For example, use lead free babbit and cadmium free solder.
- Use enclosures and direct local ventilation when performing sawfiling job tasks which may generate airborne heavy metal, and test the ventilation system to ensure that contaminants are effectively drawn away at the grinding area.
- Change the metalworking fluid on a regular basis, to prevent the accumulation of heavy metal in the fluid. And 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.

Administrative controls involve management, workers' training and surveillance:

- Since there was one claimed case of gastrointestinal cancer because of hand contamination with heavy metal, we suggest that washing hands and face before eating to avoid ingesting traces of toxic metals that may be on the skin.
- Monitor for exposure to cobalt, chromium, lead, and cadmium on a regular basis when metals containing these substances are used.

Personal protection equipment should be used as the additional resort to engineering and administrative control measures, and should not substitute the previous two. Respiratory protection is needed when ventilation is not sufficient to remove welding fumes, and wearing a welder's face shield can protect the face from flying particles.[127]

4.6 Recommendation for future study

For future study regarding the health effects of sawfiling exposure, we might be able to do the following research:

First, in this study, we indirectly adjust the confounding of smoking by including race as one of the covariates, as the cigarette consumption of South Asians is much less than the other races. However, this might not totally be able to adjust the confounding of smoking. However, there was one study in the series of UBC sawmill study, which took a proportion of the cohort workers and surveyed about their smoking habit. So it is possible to compare the cigarette consumption between sawfilers and the entire sawmill workers, to see if there are any differences with regard to that. If there are no differences, we can conclude that smoking is not likely to be a confounder of our result. Otherwise, we may, have to include smoking as a separate covariate in our Poisson model.

Secondly, we can do an external comparison with the BC general population, to see if there is a difference with regard to the risk of lung cancer and COPD. In addition, we might be able to directly evaluate the confounding effect of smoking, as previous studies had interviewed a

representative portion of the cohort workers with regard to cigarette consumption and compared with the general British Columbia population.[156 157]

References

1 Email with Jack Mcleman on December 18, 2010, 1:33PM.

2 United Nations Population Division: World population prospects: The 2008 revision population database. Retrieved from http://esa.un.org/unpp/index.asp?panel=5 on April 11th, 2011.

3 Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. Annals of Oncology. 16(3), 481-488.

4 Teschke K, Kennedy SM, Marion SA, Chan-Yeung M, van Zuylen M, Lea J, Switzer T, Thompson K, Oja J. Saw filers exposed to cobalt and other metals: determinants of exposure and respiratory health evaluation. (1993). CHER research papers. Retrieved from https://circle.ubc.ca/dspace/bitstream/2429/827/2/saw-filers_report.pdf on September 20th, 2009.

5 Finkel AJ. Hamilton and Hardy's Industrial Toxicology. 4th Edition. John wright, PSG Inc, Boston, 1983.

6 Wright JL and Churg A. Disease caused by metals and related compounds, fumes, and gases. In: Churg A and Green FHY eds. Pathology of Occupational Disease. IGAKU-SHOIN Medical Publishers Inc, New York, 1988.

7 Stokingger HE. The metals. In: Clayton GD, Clayton FE, editors. Patty's Industrial Hygiene and Toxicology, 3rd Edition, Volume 2A: Toxicology. John Wiley and Sons, New York. 1981; 1493-2060.

8 Sprince NL, Oliver LC, Eisen EA, Greene RE, Chamberlin RI. Cobalt exposure and lung disease in tungsten carbide production. A cross-sectional study of current workers. Am Rev Respir Dis 1988; 138:1220-1226.

9 Kusaka Y, Ichikawa Y, Shirakawa T, Goto S. Effect of hard metal dust on ventilatory function. Brit J Ind Med 1986;43:486-489.

10 Roto P. Asthma, symptoms of chronic bronchitis, and ventilatory capacity among cobalt and zinc production workers. Scand J Work Environ Health 1980;6:1-49.

11 VanCutsem EJ, Ceuppens JL, Lacquet LM, Demedts M. Combined asthma and alveolitis induced by cobalt in a diamond polisher. Eur J Respir Dis 1987;70:54-61.

12 Gheysens B, Auxerx J, Van den Eeckhout A, Demedts M. Cobalt-induced bronchial asthma in diamond polishers. Chest 1985; 88:740-744.

13 Nemery B, Nagels J, Verbeken E, Dinsdale D, Demedts M. Rapidly fatal progression of cobalt lung in a diamond polisher. Am Rev Respir Dis 1990;141:1373-1378.

14 Davison AG, Haslam PL, Corrin B, Coutts II, Dewar A, Riding WD, Studdy PR, Newman-Taylor AJ. Interstitial lung disease and asthma in hard-metal workers: bronchoalveolar lavage, untrastructural and analytical findings and results of bronchial provocation tests. Thorax 1983;38:119-128.

15 WorkSafeBC. Hard metal hazard---Important health information for saw filers and knife grinders. Retrieved on Jan 25th, 2010 from http://www.worksafebc.com/publications/health_and_safety/by_topic/assets/pdf/hard_metal_hazard.pdf

16 Criteria for a Recommended Standard: Occupational Exposure to Metalworking fluids. DHHS (NIOSH) Pub. No. 98-102. NIOSH, Cincinnati, OH (1998).

17 Kennedy SM, Chan-Yeung M, Marion S, Lea J, Teschke K. Maintenance of stellite and tungsten carbide saw tips: health and exposure-response evaluations. Occup Environ Med 52(3):185-191. (1995)

18 Email communication with worker of a sawfilers' union.

19 Davies HW, Demers PA, Kauppinen T, Teschke K. Section 71.4 Major Section and Processes: Occupational Hazards and Controls. In International Labor Office: Encyclopedia of Occupational Health and Safety. Geneva. ILO. (1998)

20 Alamgir H, Tompa E, Koehoorn M, Ostry A, Demers PA. Cost and compensation of work-related injuries in British Columbia sawmills. Occup Environ Med. 2006;64:196-201.

21 Stebbins AI, Hortsman SW, Daniell WE, Atallah R. Cobalt exposure in a carbide tip grinding process. Am Ind Hyg Assoc J 1992;53(3):186-192.

22 US Department of Labor, OSHA. Office of Data Management System, Unpublished data. 1990

23 Koponen M, Gustafsson T, etc. Grinding dusts of alloyed steel and hard metal. Ann Occup Hyg 1981;24:191-204.

24 Finkel AJ. Hamilton and Hardy's industrial Toxicology. 4th Edition. John Wright, PSG Inc, Bonston, 1983.

25 Gray CN. Hexavalent chromium in welding fume and the role of ozone. Ann Occup Hyg 1987;31:269-270.

26 Zatka VJ. Speciation of hexavalent chromium in welding fumes interference by air oxidation of chromium. Am Ind Hyg Assoc J 1985;46:327-331.

27 Van der Wal JF. Exposure of welders to fumes, Cr, Ni, Cu and gases in Dutch industries. Ann Occup Hyg 1985;29:377-389

28 International Agency for Research on Cancer. Triethanolamine (IARC summary and evaluation). IARC monographs, Volume 77, 2000.

29 Kusaka Y, Ichikawa Y, Shirakawa T, Goto S. Effect of hard metal dust on ventilatory function. Brit J Ind Med 1986;43:486-489.

30 WorkSafe BC. Hard metal hazard: Important health information for saw filers & knife grinders. Retrieved from http://www.worksafebc.com/publications/ health_and_safety/ by_topic/assets/pdf/hard_metal_hazard.pdf on April 25th, 2011.

31 Kennedy SM, Greavers IA, ect. Acute pulmonary responses among automobile workers exposed to aerosols of machining fluids. Am J Indus Med 1989;15:627-641.

32 Jacek D, Leon J, Stephen AO. Occupational Biohazards: A Review. *Am J Ind Med* 1988;14:605-623.

33 Hudson AR, Kilburn KH, Halprin GM, McKenzie WN. Granulocyte recruitment to airways exposed to endotoxin aerosols. *Am Rev Respir Dis* 1977;115:89-95.

34 Ragnar R. Endotoxin in the environment – exposure and effects. *J Endo Res* 2002;8(4): 241-252.

35 Park JH, Spiegelman DL, Burge HA, Gold DR, Chew GL, Milton DK. Longitudinal study of dust and airborne endotoxin in the home. *Environ Health Perspect* 2000; 108: 1023-1028.

36 Kullman GJ, Thorne PS, Waldron PF. Organic dust exposures from work in dairy barns. *Am Ind Hyg Assoc J* 1998;59:403-413.

37 Olenchock SA, May JJ, Pratt DS, Morey PR. Endotoxins in the agricultural environment. *Am J Ind Med* 1986;10:323-324.

38 Radon K, Weber C, Iversen M, Danuser B, Pederson N, Nowak D. Exposure assessment and lung function in pig and poultry farmers. *Occup Environ Med* 2001; 58:405-410.

39 Smid T, Heedrik D, Houba R, Quanjer PH. Dust and endotoxin related respiratory effects in the animal feed industry. *Am Rev Respir Dis* 1992;146:1474-1479.

40 Clark CS, Rylander R, Larsen L. Airborne bacterial, endotoxin and fungi in dust in poultry and swine confinement buildings. *Am Ind Hyg Assoc J* 1983;44:537-541.

41 Schwartz DA, Thorne PS, Yagla SJ. The role of endotoxin in grain dust-induced lung disease. *Am J Respir Crit Care Med* 1995;152:603-608.

42 Clark CS, Rylander R, Larsson L. Levels of Gram-negative bacteria, *Aspergillus fumigatus*, dust and endotoxin at compost plants. *Appl Environ Microbiol* 1983;45:1501-1505.

43 Thorn J, Beijer L, Rylander R. Airways inflammation and glucan exposure among household waste collectors. *Am J Ind Med* 1998;33:463-470.

44 Thorn J, Beijer L, Jonsson T, Rylander R. Measurement strategies for the determination of airborne bacterial endotoxin in sewage treatment plants. *Ann Occup Hyg* 2002; 46: 549-554.

45 Laitinen S, Kangas J, Kotimaa M. Workers' exposure to airborne bacteria and endotoxin at industrial wastewater treatment plants. *Am Ind Hyg Assoc J* 1992;55:1055-1060.

46 Rylander R. Health effects among workers in sewage treatment plants. *Occup Environ Med* 1999;56:354-357.

47 Astrakianakis G, Noah SS, Roberta R *et al*. Lung cancer risk among female textile workers exposed to endotoxin. *J Natl Cancer Inst* 2007;99(5): 357-364.

48 Christiani DC, Wang XR, Pan LD *et al*. Longitudinal changes in pulmonary function and respiratory symptoms in cotton textile workers. A 15-year follow-up study. *Am J Respir Crit Care Med* 2001;163:847-853.

49 Chun DTW, Chew V, Bertlett K et al. Preliminary report on the results of the second phase of a round-robin endotoxin assay study using cotton dust. *App Occup Environ Hyg* 2000; 15: 152-157.

50 Castellan RM, Olenchock SA, Kinsley KB *et al*. Inhaled endotoxin and decreased spirometric values: an exposure-response relation for cotton dust. *N Eng J Med* 1987;317:605-610.

51 Christiani DC, Velazquez A, Wilcox M *et al*. Airborne endotoxin concentrations in various work areas within a cotton mill in Central America. *Environ Res* 1993;60:187-192.

52 Dennekamp M, Demers PA, Bartlett K, Davies HW, Teschke K. Endotoxin exposure among softwood lumber mill workers in the Canadian province of British Columbia. *Ann Agric Environ Med* 1999;6:141-146.

53 Mandryk J, Udeni AK, Hocking AD. Work-related symptoms and dose-response relationships for personal exposure and pulmonary function among woodworkers. *Am J Ind Med* 1999;35:481-490.

54 Duchaine C, Meriaux A, Thorne PS, Cormier Y. Assessment of particulates and bioaerosols in eastern Canadian sawmills. *Am Ind Hyg Assoc J* 2000;61:727-732.

55 Dutkiewicz J, Krysinska TN, Prazmo Z *et al*. Exposure to airborne microorganisms in Polish sawmills. *Ann Agric Environ Med* 2001;8:71-80.

56 Douwes J, McLean D, van der Maarl E, Heederik D, Pearce N. Worker exposure to airborne dust, endotoxin and β(1,3)-glucan in two New Zealand sawmills. *Am J Ind Med* 2000;38:426-430.

57 Sarantila R, Reiman M, Kangas J, Husman K, Savolainen H. Exposure to endotoxins and microbes in the treatment of waste water and in the industrial debarking of wood. *Bull Environ Contam Toxicol* 2001;67:171-178.

58 Rylander R. Health effects of cotton dust exposures. *Am J Ind Med* 1990;17:39-45.

59 Alwis KU, Mandryk J, Hocking. Exposure to biohazards in wood dust: bacteria, fungi, endotoxin, and (1-3)-beta-D-Glucans. *Appl Occup Environ Hyg* 1999;14(9):598-608.

60 American Thoracic Society. Respiratory health hazards in agriculture. *Am J Respir Crit Care Med* 1998;158:S1-S76.

61 Liebers V, Bruning T, Raulf-Heimsoth M. Occupational endotoxin-exposure and possible health effects on humans. *Am J Ind Med* 2006;49:474-491.

62 Radon K. The two sides of the "endotoxin coin". Occup Environ Med 2006;63:73-78.

63 Liu AH. Endotoxin exposure in allergy and asthma: Reconciling a paradox. *J Allergy Clin Immunol* 2002;109:379-392.

64 Hagmar L, Schutz A, Hallberg T, Sjoholm A. Health effects of exposure to endotoxins and organic dust in poultry slaughter-house workers. *Int Arch Occup Environ Health* 1990;62:159-164.

65 Douwes J, Gibson P, Pekkanen J *et al*. Non-eosinophilic asthma: importance and possible mechanisms. *Thorax* 2002;57:643-648.

66 Kennaway NM, Kennaway EL. A study of the incidence of cancer of lung and larynx. *J Hyg* 1936;36:236-267.

67 Enterline PE, Sykora JL, Keleti G *et al*. Endotoxins, cotton dust, and cancer. *Lancet* 1985;2:934-935.

68 Mastrangelo G, Fedeli U, Fadda E et al. Epidemiologic evidence of cancer risk in textile industry workers: a review and update. *Toxico Ind Health* 2002;18:171-181.

69 Lange JH, Mastrangelo G, Fedeli U, *et al*. Endotoxin exposure and lung cancer mortality by type of farming: Is there a hidden dose-response relationship? *Ann Agric Environ Med* 2003;10:229-232.

70 Rylander R. Environmental exposures with decreased risks for lung cancer. *Int J Epidemiol* 1990;19:567-572.

71 Lange JH. Reduced cancer rates in agricultural workers: a benefit of environmental and occupational endotoxin exposure. *Med Hyptheses* 2000;55:383-385.

72 Lange JH, Mstrangelo G, Thomulka KW. Will sewage workers with endotoxin-related symptoms have benefit of reduced lung cancer? Letter to the editor. *Occup Environ Med* 2003;60:142-149.

73 Maraveyas A, Baban B, Kennard D, *et al*. Possible improved survival of patients with stage IV AJCC melanoma receiving SRL 172 immunotherapy: correlation with induction of increased levels of intracellular interleukin-2 in peripheral blood lymphocytes. *Ann Oncol* 1999;10(7): 817-824.

74 Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. *Nat Rev Cancer* 2004;4(1):11-22.

75 Blair A, Malker H, Cantor KP, *et al*. Cancer among farmers. A review. *Scand J Work Environ Health* 1985,11:397-407.

76 Wang Y, Lewis-Michl EL, Hwang SA, *et al*. Cancer incidence among a cohort of female farm residents in New York State. *Arch Environ Health* 2002,57:561-567.

77 Reisser D, Pance A, Jeannin JF. Mechanisms of the antitumoral effect of lipid A. *BioEssays* 2002;24:284-289.

78 Singh J, Schwartz DA. Endotoxin and the lung: Insight into the host-environment interaction.

79 Kline JN, Cowden JD, Hunninghake GW, ect. Variable airway responsiveness to inhaled lipopolysaccharides. *Am J Respir Crit Care Med* 1999;160:297-303.

80 Carswell EA, Old LJ, Kassel RL, et al. An endotoxin-induced serum factor that causes necrosis of tumors. *Proc Natl Acad Sci USA* 1975;72:3666-3670.

81 Lane SR, Nicholls PJ, Sewell RDE. The measurement and health impact of endotoxin contamination in organic dusts from multiple sources: focus on the cotton industry. *Inhalation Toxicol* 2004;16:217-229.

82 Reed CE, Milton DK. Endotoxin-stimulated innate immunity: a contributing factor for asthma. *J Allergy Clin Immunol* 2001;108:157-166.

83 Hasday JD, Bascom R, Costa JJ, etc. Bacterial endotoxin is an active component of cigarette smoke. *Chest* 1999;115:829-835.

84 Vernoy JHJ, Dentener MA, van Suylen RJ, Buurman Wouters EFM. Long-term intratracheal LPS exposure results in chronic lung inflammation and persistent pathology. *Am J Respir Cell Mol Biol* 2002;26:152-159.

85 Liu AH. Endotoxin exposure in allergy and asthma: reconciling a paradox. *J Allergy Clin Immunol* 2002;109:379-392.

86 Rylander R, Bake B, Fischer JJ, Helander IM. Pulmonary function and symptoms after inhalation of endotoxin. *Am Rev Respir Dis* 1989;140:981-986.

87 Clapp WD, Becker S, etc. Grain dust-induced airflow obstruction and inflammation of the lower respiratory tract. *Am J Respir Crit Care Med* 1994;150:611-617.

88 Michel O, Ginanni R, etc. Inflammatory response to acute inhalation of endotoxin in asthmatic patients. *Am Rev Respir Dis* 1992;146:352-357.

89 Atlas Alloys/A.J. Forsyth & Co. Ltd. MSDS for Steel (Carbon & H.S.L.A.) Toronto, Ontario.

90 Kennametal Inc. MSDS for Kennametal Tungsten Carbide with Cobalt Binder. Latrobe, Pennsylvania, 1989.

91 Pacific/Hoe Saw and Knife. MSDS for Cemented Tungsten Carbide Grades. Portland, Oregon.

92 Latrobe Steel Company. MSDS for Chipper Knife. Latrobe, Pennsylvania, 1992.

93 Bayer AM, Vasco T, Walton LR. Wrought tool steels. In: Metals Handbook, 10th Edition. Vol 1: Properties and Selection: Irons, steels, and high-performance alloys. 1990:757-763.

94 Simonds Industries Inc. MSDS for Chipper Knife A 8 Modified. Delta, British Columbia, 1992.

95 Multi-Metals. MSDS for Cemented Tungsten Carbide Product with Cobalt Binder. Louisville, Kentucky, 1990.

96 Matsumoto N, Aze Y, Akimoto A, Fujita T. Restoration of immune response in tumor-bearing mice by ONO-4007, an antitumor lipid A derivative. Immunopharmacology 1997;36:69-78.

97 Shimizu T, Iida K, Iwamoto Y, et al. Biological activities and antitumor effects of synthetic lipid A analog linked N-acetylated serine. Int J Immunopharmacol 1995;17:425-431.

98 Jeannin JF, Onier N, Lagadec P, et al. Antitumor effect of synthetic derivatives of lipid A in an experimental model of colon cancer in the rat. Gastroenterology 1991;101:726-733.

99 Inagawa H, Nishizawa T, Takagi K, et al. Antitumor mechanism of intradermal administration of lipopolysaccharide. Anticancer Res 1997;17:1961-1964.

100 Jimbo T, Akimoto T, Tohgo A. Systematic administration of a synthetic lipid A derivative, DT-5461, reduces tumor blood flow through endogenous TNF production in hepatic cancer model VX2 carcinoma in rabbits. Anticancer Res 1996;16:359-364.

101 Rudbach JA, Cantrell JL, Ulrich JT, Mitchell MS. Immunotherapy with bacterial endotoxins. In: Friedman H., Klein TW, Nakano M, Nowotny., eds. New York: Plenum Press, 1990: 665-676.

102 Nakano Y, Shirai M, Mori N, Nakano M. Neutralization of microcystin shock in mice by tumor necrosis factor alpha antiserum. *Appl Environ Microbiol* 1991;57:327-330.

103 Van de Wiel PA, van der Pijl A, Bloksma N. Role of tumor necrosis factor in the tumor-necrotizing activity of agents with diverging cytotoxocity. *Cancer Immunol Immunother* 1991;33:115-120.

104 Hsu H, Shu HB, Pan MG, Goeddel DV. TRADD-TRAF2 and TRADD-FADD interactions define two receptor1 signal transduction pathways. *Cell* 1996;84:299-308.

105 Blondiau C, Lagadec P, et al. Correlation between the capacity to activate macrophages in vitro and the antitumor activity of lipopolysaccharides from different bacterial species. *Immunobiology* 1994;190:243-254.

106 O'Grady NP, Preas HL, Pugin J, et al. Local inflammatory responses following bronchial endotoxin installation in humans. *Am J Crit Care Med* 2001;163:1591-1598.

107 Cochran JR, Khan AM, Elidemir O, et al. Influence of LPS exposure on airway function and allergic responses in developing mice. *Pediatr Pulmonol* 2002;34:266-277.

108 Schwartz DA, Landas SK, Lassise DL, et al. Airway injury in swine confinement workers. *Ann Intern Med* 1992;116:630-635.

109 U.S. Surgeon General. The health consequences of smoking: Chronic obstructive lung disease. (DHHS publication 84-50205). Washington, DC: U.S. Department of Health and Human Services, 1984.

110 Bresnitz EA. Epidemiology of advanced lung disease in the United States. *Clin Chest Med* 1997;18:421.

111 Wu-Williams AH, Samet JM. Lung cancer and cigarette smoking. In: Samet JM, ed. Epidemiology of lung cancer. New York: Marcel Dekker, Inc., 1994.

112 Doll R, Peto R, et al. Mortality in relation to smoking: 40 years' observations on male British doctors. *Brit Med J* 1994;309:901.

113 U.S. Department of Health and Human Services. Women and smoking: A report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General, 2001.

114 Mehta A, Malloy E, et al. Lung cancer, COPD mortality, and exposure to synthetic metalworking fluids in the auto industry. Epidemiology 2007;18(5):162-163.

115 Keistinen T, Vilkman S, Tuuponen T, Kivela SL. Hospital admissions for chronic obstructive pulmonary disease in the population aged 55 years or over in Finland during 1972-1992. *Public Health* 1996;110:257-259.

116 Lapperre TS, Postma DS, Gosman MME, et al. Relation between duration of smoking cessation and bronchial inflammation in COPD. *Thorax* 2006;61:115-121.

117 Viegi G, Scognamiglio A, Baldacci S, et al. Epidemiology of Chronic Obstructive Pulmonary Disease (COPD). *Int J Thoracic Med* 2001;68(1):4-19.

118 Armstrong BG. Effect of measurement error on epidemiological studies of environmental and occupational exposures. *Occup Environ Med* 1998;(55):651-656.

119 Jacobsen G, Schlunssen V, et al. Longitudinal lung function decline and wood dust exposure in the furniture industry. *Eur Respir J* 2008;31:334-342.

120 Shamssain MH. Pulmonary function and symptoms in workers exposed to wood dust. *Thorax* 1992; 47: 84–87.

121 Noertjojo HK, Dimich-Ward H, Peelen S, Dittrick M, Kennedy SM, Chan-Yeung M. Western red cedar dust exposure and lung function: a dose response relationship. *Am J Respir Crit Care Med* 1996; 154: 968–973.

122 Mandryk J, Alwais KU, Hocking AD. Work-related symptoms and dose-response relationships for personal exposures and pulmonary function among woodworkers. *Am J Ind Med* 1999; 35: 481–490.

123 Talini D, Monteverdi A, Benvenuti A, et al. Asthma-like symptoms, atopy, and bronchial responsiveness in furniture workers. *Occup Environ Med* 1998; 55: 786–791.

124 Ahman M, Persson L, Lagerstrand L, So ̈derman E, Cynkier I. Lung function in woodworking teachers in Sweden. *Int J Occup Environ Health* 1996; 2: 204–210.

125 Borm PJ, Jetten M, Hidayat S, et al. Respiratory symptoms, lung function, and nasal cellularity in Indonesian wood workers: a dose-response analysis. *Occup Environ Med* 2002; 59: 338–344.

126 Bohadana AB, Massin N, Wild P, Toamain JP, Engel S, Goutet P. Symptoms, airway responsiveness, and exposure to dust in beech and oak wood workers. Occup Environ Med 2000; 57: 268–273.

127 Canadian Centre for Occupational Health and Safety. Personal Protective Equipment and Clothing. Retrieved from http://www.ccohs.ca/oshanswers/safety_haz/welding/ppe.html on June 2nd,2011.

128 Stern RH. Assessment of risk of lung cancer for welders. *Arch Environ Health* 1983;39:148-155.

129 Hansen KS, Lauritsen JM, Skytthe A. Cancer incidence among mild steel and stainless steel welders and other metal workers. *Am J Ind Med* 1996;30:373-382.

130 Sterling TD, Weinkam JJ. Smoking characteristics by type of employment. *J Occup Med* 1986;18:743-754.

131 Borgers D, Menzel R. Physicians, waitresses, welders: An analysis of smoking habits with regard to job and occupation. *Munchener Medizinische Wochenschrift* 1984;126:1092-1096.

132 Steenland K, Beaumont J, Elliot L. Lung cancer in mild steel welders. *Am J Epidemiol* 1991;133:220-229.

133 Dighe AS, Richards E, Old LJ, Schreiber RD. Enhanced in vivo growth and resistance to rejection of tumor cells expressing dominant negative IFN-γ receptors. *Immunity* 1994;1:447-456.

134 Blondiau C, Lagadec P, et al. Correlation between the capacity to activate macrophages in vitro and the antitumor activity in vivo of lipopolysaccharides from different bacterial species. *Immunobiology* 1994;190:243-254.

135 Inagawa H, Nishizawa T, et al. Mechanisms by which chemotherapeutic agents augment the antitumor effects of tumor necrosis factor: Involvement of the pattern shift of cytokines from Th2 to Th1 in tumor lesions. *Anticancer Res* 1998; 18(5D):3957-3964.

136 Inagawa H, Nishizawa T, et al. Antitumor mechanism of intradermal administration of lipopolysaccharide. *Anticancer Res* 1997;17(3C):1961-1964.

137 Shimizu T, Iida K, et al. Biological activities and antitumor effects of synthetic lipid A analog linked N-acylated serine. *Int J Immunopharmacol* 1995;17:425-431.

138 Onier N, Lejeune P, et al. Involvement of T lymphocytes in curative effect of a new immunomodulator OM 163 on rat colon cancer metastases. *Eur J Cancer* 1993;29A:2003-2009.

139 Onier N, Hilpert S, et al. Cure of colon cancer metastasis in rats with the new lipid A OM 174: Apoptosis of tumor cells and immunization of rats. *Clin Exp Metastasis* 1999;17:299-306.

140 Donham KJ, Cumro D, et al. Dose-response relationships between occupational aerosol exposure and cross-shift declines of lung function in poultry workers: recommendations for exposure limits. *J Occup Med* 2000;42:260-269.

141 Jacobsen G, Schlumssen V, et al. Longitudinal lung function decline and wood dust exposure in the Danish furniture industry. *Eur Respir J* 2008; 33:1268-1276.

142 Lenters V, Basinas I, Beane-Freeman L, et al. Endotoxin exposure and lung cancer risk: a systematic review and meta-analysis of the published literature on agriculture and cotton textile workers. *Cancer Causes Control* 2010;21:523-555.

143 Liebers V, Raulf-Heimsoth M, Bruning T. Health effects due to endotoxin inhalation (review). *Arch Toxicol* 2008;82:203-210.

144 Hours M, Fevotte J, Lafont S, Bergeret A. Cancer mortality in a synthetic spinning plant in Besancon, France. *Occup Environ Med* 2007;64:575-581.

145 Kateman E, Heederik D, Pal TM, Smeets M, Smid T, Spitteler M. Relationship of airborne microorganisms with the lung function and leucocyte levels of workers with a history of humidifier fever. *Scand J Work Environ Health* 1990;16:428-433.

146 Post WK, Heederik D, Kromhout H, et al. Occupational exposures estimated by a population specific job exposure matrix and 25 year incidence rate of chronic non-specific lung disease (CNSLD): the Zutphen Study. *Eur Respir J* 1994;7:1048-1055.

147 Douwes J, McLean D, Slater T, et al. Pine dust, atopy and lung function: A cross-sectional study in sawmill workers. *Eur Respir J* 2006;28,791-798.

148 Ashley MJ, Corey P, Chan-Yeung M, et al. A respiratory survey of cedar mill workers. II. Influence of work-related and host factors on the prevalence of symptoms and pulmonary function abnormalities. *J Occup Med* 1978;20:328-332.

149 Liou SH, Cheng SY, Lai FM, Yang JL. Respiratory symptoms and pulmonary function in mill workers exposed to wood dust. *Am J Ind Med* 1996;30:293-299.

150 Mandryk J, Alwais KU, Hocking AD. Work-related symptoms and dose-response relationships for personal exposures and pulmonary function among woodworkers. *Am J Ind Med* 1999;35:481–490.

151 Borm PJA, Jetten M, Hidayat S, et al. Respiratory symptoms, lung function, and nasal cellularity in Indonesian wood workers: a dose-response analysis. *Occup Environ Med* 2002;59:338-344.

152 Halpin DM, Graneek BJ, et al. Respiratory symptoms, immunological responses, and aeroallergen concentrations at a sawmill. *Occup Environ Med* 1994;51:165-172.

153 Halpin DM, Graneek BJ, et al. Extrinsic allergic alveolitis and asthma in a sawmill worker: case report and review of the literature. *Occup Environ Med* 1994;51:160–164.

154 Demers PA, Friesen MC, Davies HW, Hertzman C, Marion S, Ostry A, Teschke K. Cancer and occupational exposure to pentachlorophenol and tetrachlorophenol. *Cancer Causes Control* 2006;17(6):749-758.

155 Hertzman C, Teschke K Aleck O, et al. Mortality and cancer incidence among sawmill workers exposed to chlorophenate wood preservative. *Am J Public Health* 1997;87(1):71-79.

156 Davies HW, Teschke K, Kennedy SM, et al. Occupational exposure to noise and mortality from acute myocardial infarction. *Epidemiology* 2005;16(1):25-32.

157 Tobacco Use in British Columbia, 1997. Available at: http://www.healthplanning.gov.bc.ca/ tobacrs/index.html. Accessed December 3, 2003.

158 Park JH, Cox-Ganser J, et al. Fungal and endotoxin measurements in dust associated with respiratory symptoms in water-damaged office building. *Indoor Air* 2006;16:192-203.

159 Krajewski JA, Cyprowski M, et al. Health complaints from workplace exposure to bioaerosols: A questionnaire study in sewage workers. *Ann Agric Environ Med* 2004;11:199-204.

160 Chun DT, Chew V, Bartlett K, et al. Preliminary report on the results of the second phase of a round-robin endotoxin assay study using cotton dust. *Applied Occup Env Hyg* 2000;15(1):152-157.

161 Kennedy SM, Bartlett K, Keefe A, Ward H, Chan-Yeung M. Grain and endotoxin exposure monitoring. *Report to Labour Canada*. June 1997.

162 Moulin JJ, Wild P, et al. Lung cancer risk in hard-metal workers. *Am J Epidemiology* 1998; 148(3): 241-248.

163 Gerin M, Siemiatycki J, et al. Nickel and cancer associations from a multi-cancer occupation exposure case-referent study: preliminary findings. *IARC Sci Publ* 1984;53:105-115.

164 Sjogren B, Hansen KS, et al. Exposure to stainless steel welding fumes and lung cancer: a meta-analysis. *Occup Env Med* 1994;51:335-336.

165 Hansen KS, Lauritsen J. Lung cancer mortality in stainless steel and mild steel welders—A nested case-referent study. *Am J Ind Med* 1996;30(4): 383-391.

166 Kjuus H, Skjaerven R, et al. A case-referent study of lung cancer, occupational exposures and smoking. I. Comparison of title-based and exposure-based occupational information. *Scand J Work Environ Health* 1986;12:193-202.

167 Sjogren B, Gustavsson A, et al. Mortality in two cohorts of welders exposed to high- and low-levels of hexavalent chromium. *Scand J Work Environ Health* 1987;13:247-252.

168 Ronald LA, Demers PA. Occupational mould exposure and respiratory disease morbidity among BC lumber mill workers. UBC retrospective thesis digitization project. Retrieved from https://dspace.library.ubc.ca/handle/2429/11778.

169 Pearce N, Checkoway H, Kriebel D. Bias in occupational epidemiology studies. *Occup Environ Med* 2007;64:562-568.

170 Kriebel D, Zeka A, Esisen EA, et al. Quantitative evaluation of the effects of uncontrolled confounding by alcohol and tobacco in occupational cancer studies. *Int J Epidemiol* 2004;33:1040-1045.

171 Siemiatycki J, Wacholder S, Dewar R, et al. Smoking and degree of occupational exposure: are internal analyses in cohort studies likely to be confounded by smoking status? *Am J Ind Med* 1988;13:59-69.

172 Rabe KF, Hurd S, Anzueto A, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary. *Am J Respir Crit Care Med* 2007;176 (6): 532-555.

173 Teschke K, Ostry A, Hertzman C, et al. Opportunities for a broader understanding of work and health: Multiple uses of an occupational cohort database. *Can J Public Health* 1998;89(2):132-136.

174 Omenn GS, Goodman GE, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *The New England Journal of Medicine* 1996;334(18): 1150-1155.

175 Breslow L, Hoaglin FL, et al. Occupations and cigarette smoking as factors in lung cancer. *Am J Pub Health* 1954;44(2):171-181.

176 Gottlieb L, Husen L. Lung cancer among Navajo Uranium miners. *Chest* 1982;81:449-452.

177 Tochman MS. Airways obstruction and the risk for lung cancer. *Annals of Internal Medicine* 1987;106(4):512-518.

Appendix: Job Code

1) Jobs exist in both endotoxin monitoring and work history files (N=64)

Job code in monitoring file	Corresponding job title in work history file
1001	Shift boss
1007	Log loadoperator
1009	Boat orperater/Sidewinder
2003	Cut-off saw
2011	Barker
2016	Log deck
2095	Utility
2099	Clean-up
3001	Foreman/Chargehand/Shift supervisor/Studmill Foreman/Supervisor
3003	Headrig/Sawyer
3007	Offbearer/Tailsawyer
3011	Quadsaw operator
3013	Chip-n-saw operator
3017	#3 edger
3023	12" Edger
3025	10" Edger
3035	Lumber straightener
3037	Resaw operator
3045	Dropsort operator/Eliminate gate
3053	Slasherman
3057	Auto trimmer/Trimmer Operator
3067	Grader
3071	Bin patrol/J-bar attendent
3077	End stacker/Stacker operator
3079	Strip loader/Placer
3099	Clean-up
4003	Chipper Feeder/Clean up
4007	Chip screen tender
4013	Hog operator
5001	Planer chargehand/Planermill foreman
5003	Planer feeder/Hoist
5005	Planer feeder
5007	Planer technician/Planer set up/Planerman
5017	Strip picker
5057	Trimmerman
5067	Grader
5099	Clean-up
6003	Painter and sealer
6005	Paint spray/car blocker
6007	Bander operator/Banding room/Stacker
6015	Forklift/tallyman/shipping
6017	Quality control
6019	Weigh scale operator
7009	Crane operator

Job code in monitoring file	Corresponding job title in work history file
7019	Carrier driver
7025	Truck driver
7029	Kiln operator/chip loader
8003	Carpenter
8005	Electrician
8007	Machinist
8009	Mechanic
8011	Millwright
8013	Lubrication/Oiler
8017	Sheet metal
8019	Welder
8020	Antisapstain operator
8030	Power engineer
8031	Watchman
8032	Fireman
8040	Janitor
9003	Circular saw filer/Filer
9005	Benchman
9007	Fitter/Sawfitter
9011	Grinderman/Knife grinder

2) Jobs only exist in the endotoxin monitoring file but not in the work history file (N=43)

Jobcode in monitoring file	Job title in w/h file with closest endotoxin exposure level	Corresponding job code
2001	Shift boss	1001
2015	Log slasher	2003
2017	Deckhand/Deckman	2016
2045	Block sorter	2016
3002	Sorter Chargehand	3001
3005	Pony rig sawyer	3003
3009	Pony offbearer	3007
3014	#1 Timmer man	3057
3019	Board edger	3023
3039	Vertical resaw	3037
3027	12" edger	3023
3041	Horizontal resaw	3037
3043	Retrim/Reedger operator	3023
3051	Dropsort (front)/stencilman	3045
3058	Auto trimmer	3057
3059	#2 trim saw operation inspector	3057
3063	Trimmer spotter	3057
3073	Greenchain sorter	3071
3081	Conveyorman	3035
3095	Sawmill chaser	3035
4001	Chipper Chargehand/Utility	4003
4005	Splitter room	4003

Jobcode in monitoring file	Job title in w/h file with closest endotoxin exposure level	Corresponding job code
4011	Chip loaderman	7029
4015	Reject wood operator	4013
4017	Belt cleaner	4003
5071	Bin patrol	3071
5073	Dry chain/Dry chain puller	3071
5077	Autostacker operator/End stacker	3077
6001	Shippling Chargehand/Yard supervisor	6017
6009	Narrow loads	6015
6011	Tally/Yard inspector	6015
6018	Tally/Yard inspector	6017
7003	Log loader	7019
7004	Forklift driver/Forklift	7019
7007	Timber crane operator	7009
7013	Butt-n-top/Cherry picker	7009
7017	Forklift driver/Forklift	7029
7027	Strap puller	6007
7099	Yard clean-up	2099
8033	Fireman's Helper	8032
9001	Head filer	9003
9004	Filer/Fitter	9003
9012	Barkerman	9011

3) Jobs only exist in the work history file but not in the endotoxin monitoring file (N=7).

Jobs in the work history file	Substituting job code that share closest endotoxin exposure level
Boom man	1009
Bull edger	3023
Pony edger	3025
Stenciller	6003
Timber deck grader/Bullsaw	7009
Utility	2099
Pipefitter	8005