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LUNG CANCER RISK ASSOCIATED WITH OCCUPATIONAL EXPOSURES TO CLEANING AGENTS AND BIOCIDES: ANALYSIS OF TWO CASE-CONTROL STUDIES IN MONTREAL, CANADA

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RÉSUMÉ

Contexte: Les agents de nettoyage sont des substances qui aident l'eau dans le processus de nettoyage. Les biocides comprennent les substances utilisées pour désinfecter, désodoriser, stériliser et assainir. L'utilisation d'agents de nettoyage, de biocides et d'autres produits liés au nettoyage est omniprésente. Certaines études suggèrent que l'exposition professionnelle à des substances liées au nettoyage peut être associée au cancer du poumon.

Objectif: Examiner l'association entre le risque de cancer du poumon et l'exposition professionnelle aux agents de nettoyage, aux biocides et à d'autres agents de nettoyage.

Méthodes: Cette étude utilise les données de deux études cas-témoins basées sur la population sur le cancer du poumon (étude 1: 1979-1986; étude 2: 1996-2001) menées à Montréal. Dans les deux études, les cas comprenaient des hommes ayant reçu un diagnostic de cancer du poumon confirmé histologiquement dans 18 hôpitaux métropolitains de Montréal. Dans les deux études, un ensemble de témoins de population sélectionnés au hasard à partir de la liste électorale du Québec a été établi (étude 2: 762 cas et 899 témoins); tandis que dans l'étude 1, un groupe témoin de cancer supplémentaire a été sélectionné à partir d'un groupe d'autres patients diagnostiqués avec un autre cancer incident (857 cas, 533 témoins de population, 1349 témoins de cancer). Dans les deux études, des antécédents professionnels détaillés ont été recueillis au cours des entretiens; une équipe de chimistes et d'hygiénistes industriels a ensuite évalué l'exposition professionnelle à de nombreuses substances professionnelles, notamment des agents de nettoyage, des biocides, des alcools aliphatiques, de l'ammoniac, de la soude caustique, des cires et des produits de polissage. Une régression logistique multivariée nonconditionnelle a été utilisée pour estimer les ratios des côtes et les intervalles de confiance à 95% du risque de cancer du poumon associé à diverses mesures de l'exposition professionnelle à ces six agents, tout en ajustant pour les facteurs de risque établis. Les interactions selon l'intensité du tabagisme et l'état d'asthme ont été explorées avec l'inclusion de termes de produits croisés.

Résultats: Dans l'ensemble, il n'y avait pas d'association cohérente soutenant le rôle de l'exposition professionnelle aux agents de nettoyage, aux biocides et à d'autres agents de nettoyage dans l'étiologie du cancer du poumon. Bien qu'il y ait eu des preuves que l'intensité du tabagisme peut modifier l'association entre la soude caustique et le risque de cancer du poumon dans l'étude 1; où, chez les fumeurs de faible intensité, une augmentation du risque par trois a été observée par rapport

à une association nulle observée chez les fumeurs d'intensité moyenne à forte ($p_{Interaction}$=0,03). Alors que, dans l'étude 2, les personnes exposées professionnellement à des alcools aliphatiques et qui ont déjà souffert d'asthme ont connu quatre fois du risque de cancer du poumon par rapport à une association nulle observée chez ceux qui n'ont jamais eu d'asthme ($p_{Interaction}$ = 0,04).

Conclusion: Pris ensemble, les résultats de cette étude ne soutiennent pas le rôle de l'exposition professionnelle aux agents de nettoyage, aux biocides et à d'autres produits de nettoyage dans l'étiologie du cancer du poumon.

Mots clés: Épidémiologie, cas-témoins, cancer du poumon, profession, exposition, lieu de travail, agents de nettoyage, biocides, produits de nettoyage.

ABSTRACT

Background: Cleaning agents are materials that aid water in the cleaning process. Biocides include materials used to disinfect, deodorize, sterilize, and sanitize. The use of cleaning agents, biocides, and other cleaning-related agents is ubiquitous. Some studies suggest that occupational exposure to cleaning-related substances may be associated with lung cancer.

Objective: To examine the association between lung cancer risk and occupational exposure to cleaning-related agents.

Methods: This study uses data from two population-based case-control studies on lung cancer (Study 1: 1979-1986; Study 2: 1996-2001) carried out in Montreal. In both studies, cases included men diagnosed with incident histologically confirmed lung cancer identified across 18 Montreal metropolitan hospitals. In both studies, a set of population-based controls randomly selected from the Quebec electoral list was established (Study 2: 762 cases and 899 controls); while in Study 1, an additional cancer control group was selected from a pool of other patients diagnosed with incident cancer (857 cases, 533 population controls, 1349 cancer controls). In both studies, detailed lifetime job histories were collected during interviews; a team of chemists and industrial hygienists then evaluated occupational exposure to many occupational substances including cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes. Unconditional multivariate logistic regression was used to estimate odds ratios and 95% confidence intervals for lung cancer risk associated with various metrics of occupational exposure to these six agents, while adjusting for established risk factors. Interactions by smoking intensity and asthma status were explored with the inclusion of cross-product terms.

Results: Overall, there was no consistent association supporting a role of occupational exposure to cleaning agents, biocides, and other cleaning-related agents in lung cancer etiology. Though there was some evidence that smoking intensity may modify the association between caustic soda and lung cancer risk in Study 1, where, among never-low intensity smokers, a threefold increase in risk was observed in comparison to a null association observed among medium-heavy intensity smokers ($p_{Interaction}$=0.03). While, in Study 2, those occupationally exposed to aliphatic alcohols and who have ever had asthma experienced a four-fold increase in lung cancer risk in comparison to a null association observed among those who have never had asthma ($p_{Interaction}$ = 0.04).

Conclusion: Taken together, the results of this study do not support the role of occupational exposure to cleaning agents, biocides, and other cleaning-related agents in lung cancer etiology.

Keywords: Epidemiology, case-control, lung cancer, occupation, exposure, workplace, cleaning agents, biocides, cleaning products.

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LIST OF ABBREVIATIONS

WHO	World Health Organization
IARC	International Agency for Research on Cancer
SCC	Small cell carcinoma
SCLC	Small cell lung cancer
NSCLS	Non small cell lung cancer
SqCC	Squamous cell carcinoma
ADC	Adenocarcinoma
RR	Relative risk
OR	Odds ratio
CI	Confidence interval (95% CI = 95% confidence interval)
CSI	Comprehensive Smoking Index
SEER	Surveillance, Epidemiology and End Results
SES	Socio-economic status
ISEI	International Socio-Economic Index of Occupational Status
ESEC	European Socio-Economic Classification
USA	United States of America
PM	Particulate matter
CCDO	Canadian Classification and Dictionary of Occupations

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1 INTRODUCTION

Globally, lung cancer is the second most commonly diagnosed cancer but remains the leading cause of cancer deaths with an estimated 1.8 million deaths (18%) in 2020.[1] In Canada, lung cancer is also the main contributor to cancer mortality accounting for 25% of all cancer deaths in 2020. The high mortality rate of lung cancer reflects its high incidence and low survival. The 5-year survival rate for lung cancer in Canada is 19%.[2] Considering the limited treatment options for lung cancer, the main strategy to reduce its burden is primary prevention. Each cancer case results from the combination of complex factors including genetic predisposition, environmental exposures and lifestyle habits which lead to the development of a tumour. Tobacco smoking is the strongest risk factor in the development of lung cancer, accounting for almost 90% of incident cases in men and 70-80% in women.[3] However, 10-25% of patients diagnosed with lung cancer have never smoked,[4] implying that other risk factors such as genetic susceptibility, exposures to environmental tobacco smoke (passive smoking), indoor and outdoor air pollution, and occupational exposures (e.g., to asbestos, silica, nickel, radon, diesel exhaust) may play a role in the etiology of the disease.[5]

Even among smokers, some occupational carcinogens may act in synergy with tobacco smoke to cause lung cancer,[6-8] thus, the study of occupational risk factors is still relevant for smoking-related lung cancers. Occupational risk factors play a major role in lung cancer.[9] It is estimated that 10% of lung cancer cases worldwide are attributable to occupational lung carcinogen exposure.[10]

Cleaning agents (comprising soaps and detergents) are materials with cleansing action that aid water in the cleaning process. Biocides are materials used to disinfect, deodorize, sterilize, and sanitize. While both cleaning agents and biocides have common application as a cleanser, disinfectant or preservative, biocides have additional function of controlling or killing harmful or unwanted organisms and microorganisms.[11-14] In many workplaces, individuals who routinely carry out cleaning tasks are exposed to cleaning agents, biocides and certain affiliated substances like aliphatic alcohols, ammonia, caustic soda, and waxes and polishes.[11, 12] There is extensive literature showing that cleaning agents and biocides are associated with an increased risk of chronic conditions including asthma and other respiratory disorders.[14-17] Asthma, characterized by chronic inflammation of the lungs, may predispose individuals to lung cancer.[18-20] However, despite

biological plausibility and the ubiquity of these exposures, the study of occupational exposures to cleaning agents and biocides and the risk of lung cancer has been relatively limited.

The purpose of this thesis is to determine the role of cleaning agents, biocides, and other cleaning-related substances in lung cancer etiology. In Chapter 2, a review of the literature on the epidemiology of lung cancer, highlighting the contribution of occupational exposures is presented, followed by the overall aim and specific objectives of the study in Chapter 3 and the methodology in Chapter 4. Results are presented in Chapter 5, followed by a discussion of results in the context of the current literature in Chapter 6. Finally, the conclusion of the study findings is presented in Chapter 7.

2 LITERATURE REVIEW

2.1 Descriptive epidemiology of lung cancer

In Canada, there were an estimated 29,800 lung cancer cases (representing 13% of all new cancer cases) and 21,200 deaths (representing 25% of all cancer deaths) in 2020.[2] There are two main histological types of lung cancer: small cell lung cancer (SCLC), and non-small cell lung cancer (NSCLC) which represent approximately 15% and 85% of all lung cancer cases, respectively.[21] SCLC is a highly malignant tumour[22] and strongly linked with tobacco smoking.[23] NSCLC has three main histological subtypes namely, large cell carcinoma, adenocarcinoma (ADC), and squamous cell carcinoma (SqCC). SqCC was the most common subtype of NSCLC in the 1970s but has been replaced by ADC, the incidence of which has increased steadily over the past decades.[23] The shift in histology from SqCC to ADC may be due to the introduction of filter vents in low tar cigarettes, making it easier for the smoker to draw in smoke, and allowing deeper inhalation than older, unfiltered cigarettes. Inhalation transports carcinogens from cigarette smoke more distally toward the bronchoalveolar junction where ADC often arises.[22, 23]

The histological classification of lung cancer is primarily used to guide treatment and estimate prognosis, as evidence suggests that lung cancer represents a group of histologically and molecularly heterogeneous diseases even within the same histological subtypes.[23-26] With respects to lung cancer etiology, there is evidence to suggest that risk factors for lung cancer do not necessarily have the same impact on all histological types.[23-26]

2.2 Lung cancer risk factors

The most important risk factor in lung carcinogenesis is tobacco smoking. However, since lung cancer also develops among non-smokers and not all smokers develop lung cancer, genetics, socio-demographic factors, lifestyle, environmental and occupational factors have also been implicated in the development of lung cancer. Of the 160 exposures classified by the International Agency for Research on Cancer (IARC) as definite human carcinogens (Group 1), 51 are lung carcinogens.[27] The key findings from meta-analyses and systematic reviews of the risk factors for lung cancer are presented in the following sections. However, individual studies are also discussed if meta-analyses and systematic reviews are few or are not available.[28]

2.2.1 Tobacco smoking

Tobacco smoking is the strongest known risk factor for lung cancer,[3] it is estimated to account for 70-90% of incident cases.[3] In a meta-analysis of 99 cohort studies comprising data from more than 7 million participants, and over 50,000 incident cases of lung cancer from January 1, 1999 to April 15, 2016, a higher risk of lung cancer associated with smoking was observed in men, relative risk (RR) of 7.33 (95% CI: 4.90-10.96; I^2 =98.8%) than in women, RR of 6.99 (95% CI: 5.09-9.59; I^2 =97.1%).[29]

Examining the risk of lung cancer in relation to various metrics of smoking history, Remen *et al.* (2018) reported similar associations (odds ratio (OR) of 7.42 (95% CI: 4.59-13.30) for men and an OR of 11.76 (95% CI: 7.50-18.42) for women). Specifically, the odds of lung cancer increased with every 10 unit increase in exposure duration (OR ranging from 1.23–28.94 for 20 to > 50 yr of exposure) and intensity (3.18–11.87 for 20 to > 40 cigarettes per day).[30]

Another meta-analysis using epidemiological evidence before 2000 conducted by Lee *et al.*, comprising 287 cohort and case-control studies, examined the impact of quitting smoking on lung cancer risk. When compared to never smokers, the study reported a RR of 5.50 (95% CI: 5.07-5.96) for ever smokers of cigarettes, a RR of 8.43 (95% CI: 7.63-9.31) for current smokers of cigarettes, and a RR of 4.30 (95% CI: 3.93-4.71) for former smokers of any tobacco product(s). By histological type, the current versus never smokers association is stronger for SqCC (RR of 16.91 (95% CI: 13.14-21.76)) than for ADC (RR of 4.21 (95% CI: 3.32-5.34).[31]

2.2.2 Demographic and socio-economic factors

The incidence of lung cancer is strongly dependent on age. In Canada, the age-specific incidence rates for lung cancer increases steadily from ages 45-54 (24 cases per 100,000 in men; 30 cases per 100,000 in women), 55-64 (118 cases per 100,000 in men; 108 cases per 100,000 in women), 65-74 (288 cases per 100,000 in men; 254 cases per 100,000 in women) and 75-84 (478 cases per 100,000 in men; 354 cases per 100,000 in women).[2]

Socioeconomic status (SES) has been associated with lung cancer in several studies, with people from lower socioeconomic backgrounds experiencing the highest incidence rates.[32-37] SES reflects one's position in societal hierarchies and is generally assessed by the interrelated dimensions of education, occupation, and income. However, the concept of SES includes many factors that are difficult to measure and distinguish from each other. SES is related to health/disease

through multiple interacting pathways in terms of material and social resources, physical and psycho-social stressors, and health-related behavior.[38, 39] The socioeconomic gradient in lung cancer likely reflects differences in exposures and risk factors such as smoking, occupational and environmental exposure to inhaled carcinogens, air pollution, and dietary factors among people with different SES.[40-42] Though SES is strongly associated with smoking behavior,[43] many studies on lung cancer and SES do not adequately control for smoking behavior.[44]

Perhaps the most compelling published evidence regarding the impact of SES on lung cancer comes from the international pooled SYNERGY study of 12 case-control studies from Europe and Canada (comprising 17,021 cases and 20,885 controls). The investigation of the association between lung cancer and occupation-derived SES revealed that SES remained a risk factor for lung cancer after adjustment for smoking behavior. Based on occupational codes derived from job histories of study participants the investigators measured SES using the International Socio-Economic Index of Occupational Status (ISEI) and the European Socio-economic Classification (ESeC). Comparing the lowest versus the highest SES category in men yielded: ISEI OR =1.84 (95% CI: 1.61–2.09) and ESeC OR =1.53 (95% CI: 1.44–1.63). ORs for women were slightly lower: ISEI OR =1.54 (95% CI: 1.20–1.98) and ESeC OR=1.34 (95% CI: 1.19–1.52).[45]

2.2.3 Lifestyle factors

Accumulating evidence supports the consumption of fruits and vegetables, and physical activity as lifestyle determinants of lung cancer risk. A systematic review and meta analysis of 29 prospective studies examining fruit and vegetable intake, and lung cancer risk , revealed an inverse association; specifically, comparing the highest versus the lowest intakes of fruits and vegetables, the summary RR estimates yielded 0.86 (95% CI: 0.78– 0.94; I^2=37%) for fruits and vegetables, 0.92 (95% CI 0.87–0.97; I^2=0%) for vegetables and 0.82 (95% CI 0.76– 0.89; I^2=32%) for fruits.[46] But, the protective association with fruit and vegetable intake was marginally significant in analysis restricted to current smokers only. Moreover, the investigators reported that their findings were consistent among the different types of fruits and vegetables, but that the strength of the association differed across geographic locations.

Findings from a systematic review and meta-analysis (comprising 28 studies) on leisure-time physical activity and lung cancer risk conducted by Brenner *et al.*[47] indicated an overall inverse association between recreational physical activity and lung cancer risk (RR = 0.76; 95%

CI: 0.69-0.85; I^2=86.6%). Similar inverse associations were found for all evaluated histological types of lung cancer, including ADC (RR = 0.80; 95% CI: 0.72-0.88), SqCC (RR = 0.80; 95% CI: 0.71-0.90) and SCLC (RR = 0.79; 95% CI: 0.66-0.94). When they examined effects by smoking status, inverse associations between recreational physical activity and lung cancer risk were observed among former (RR =0.77; 95% CI: 0.69-0.85) and current smokers (RR = 0.77; 95% CI: 0.72-0.83), but not among never smokers (RR = 0.96; 95% CI: 0.79-1.18).

2.2.4 Genetic factors

The literature on genetic risk factors for lung cancer is vast and of limited relevance to this study as data on genetic factors was not available. However, family history of cancer is an established risk factor for lung cancer.[48] From the most recent meta-analysis by Ang *et al*. (2020),[49] the pooled summary estimate for familial risk of lung cancer was 2.05 (95% CI: 1.78-2.35; I^2=56.3%) for women and 2.00 (95% CI: 1.65-2.42; I^2=54.6%) for men. Alterations in some oncogenes and tumour suppressor genes may trigger lung cancer. Tumour protein p53 (TP53) is a tumour suppressor gene which encodes a protein that regulates cell division, growth, and apoptosis, and inhibits cancer development. Mutations in the TP53 gene have been shown to occur in 50% of NSCLC cases , and they were more dominant in SqCC than in ADC among NSCLC cases [50, 51]. Besides, recent genome-wide association studies (GWAS) have identified multiple genetic polymorphisms that cause lung cancer. The three main susceptibility loci are found are in the 15q25, 5p15 and 6p21 regions [52-54]. Nevertheless, GWAS explain only a small proportion of the overall genetic variance with lung cancer but the fact that only a few smokers develop cancer supports the fact that genetic susceptibility might contribute to carcinogenesis [55].

2.2.5 Environmental risk factors

The term environmental exposure is defined "as having contact with chemical, biological, or physical substances found in air, water, food, or soil that may have a harmful effect on a person's health."[56] Environmental risk factors for lung cancer include outdoor and indoor air pollution, and second-hand smoke.

Major contributors to outdoor air pollution are emissions from industrial production, power plants and motor vehicles. Some substances present in vehicular emission exhaust are classified

by IARC as carcinogenic to humans (Group 1 for diesel exhaust) and possibly carcinogenic to humans (Group 2B for gasoline exhaust).[27] Many studies have indicated a higher lung cancer risk in urban areas compared to rural areas.[57] In the U.S., Europe, Russia and East Asia, agricultural emissions contribute considerably to particulate matter (PM) 2.5 (i.e. particles ≤2.5 μm in diameter). The risk of developing lung cancer increases as the level of PM2.5 in the air increases.[58]

A meta-analysis of 36 case-control studies evaluated the association between traffic-related air pollution and lung cancer risk: positive associations between lung cancer risk and exposure to nitrogen dioxide (OR=1.06; 95% CI: 0.99–1.13; I^2=59%), nitrogen oxide (OR=1.04; 95% CI: 1.01–1.07; I^2=46%), sulfur dioxide (OR=1.03; 95% CI: 1.02–1.05; I^2=0%), and fine PM (OR =1.11; 95% CI: 1.00–1.22; I^2=64%) were found.[59]

A meta-analysis of seven case-control studies evaluated the risk of lung cancer from indoor air pollution for the Chinese population. Domestic coal use for heating and cooking was associated with increased lung cancer risk, where the pooled OR values were 1.83 (95% CI: 0.62-5.41) and 2.66 (95% CI: 1.39-5.07) for women and both sexes, respectively. For indoor exposure to coal dust, the OR values were 2.52 (95% CI: 1.94-3.28) and 2.42 (95% CI: 1.62-3.63) for women and both sexes, respectively.[60]

2.3 Occupational epidemiology: Overview

The occupational environment has proved an important area for the discovery of carcinogens. Exposure to agents in the workplace is often higher than in the general population, considering not only the concentration of exposures but also the frequency and duration.[61]

In the 16th century Bernadino Ramazzini, a physician, noted several medical conditions that appeared to be more frequent in specific types of trades than in general and his treatise, De Morbis Artificum Diatriba[62] is considered to be one of the first attempts to document occupational disease. Subsequently, various cohorts of workers came to the attention of discerning physicians, such as silicosis among miners in Germany in the 16th century. In the 18th century[63], Percival Pott discovered that chimney sweeps had a high incidence of scrotal cancer due to exposure to soot. Through the late nineteenth and twentieth centuries, the retrospective cohort study emerged as the most important study design in occupational epidemiology.[64] The typical approach to retrospective cohort design involves collecting information from company records and obtaining disease status

(incidence or mortality) after a period of follow-up, ascertained through company medical records or record linkage (e.g., to cancer and other disease registries or mortality records).[65] Notwithstanding the practicality of the historic cohort design, one prominent limitation is its inability to enumerate multiple exposures, including occupational and residential exposures throughout a subject's lifetime, as well as medical and lifestyle factors (such as smoking habits, alcohol use, diet, and environmental exposures), that may confound or modify an exposure-disease association.[66] Thus, the absent or incomplete data on subjects' lifetime occupational histories may result in invalid conclusions for occupational exposures and cancer associations.

One of the earliest case-control studies of cancer was conducted by Doll and Hill on the relationship between tobacco smoking and lung cancer.[67] Mantel and Haenszel compared the case-control (or retrospective) study design with the cohort design (forward or prospective) study and stated that "a primary goal is to reach the same conclusions in a retrospective study as would have been obtained from a forward study, if one had been done." [68, 69] Since then, the development of appropriate statistical methods and the fact that case-control studies do not require lengthy follow-up, resulting in less costly studies, has increased the frequency of the use of the case-control study design. In a case-control study, despite some limitations due to the need to limit patient burden for cases, it is possible to collect information on a far wider array of factors than is generally possible in a retrospective industrial cohort. This includes obtaining full occupational histories and descriptions of tasks and other factors.

The key to observational epidemiology is the ability to characterise, as accurately as possible, the exposures of interest, be they lifestyle factors such as smoking, alcohol consumption, diet, or exposures to agents in the workplace. However, methods need to be devised to determine what the study subjects may have been exposed to in the occupational environment. Exact measurements of historic levels of exposure for an individual in a given situation are effectively non-existent. Several approaches to assessing occupational exposure retrospectively have been used: self-assessed exposure, job title-based assessment, the use of job exposure matrices, all of which have serious limitations.[11, 70] In the early 1980's, Siemiatycki and Gérin developed an approach to exposure assessment using full occupational histories. The detailed methodology has previously been described.[11, 71] This has since become the "gold standard" for retrospective exposure assessment.

The expert-based assessment of exposure in case-control studies, though expensive and difficult to implement, has been used over the past several decades by Siemiatycki and his research team in Montreal, Canada, to ascertain a subject's lifetime exposure to occupational and physical agents in population-based case-control studies of cancer including lung cancer.[71 72 11]

Briefly, trained interviewers obtained from each subject detailed socio-demographic and lifestyle characteristics information (e.g. smoking history, education, family income, education, as well as information for each job in the working lifetime of the subject including the company, its products, the nature of the worksite, equipment maintenance, presence of dusts, fumes or gases, use or presence of oils or solvents, exposure to radiation, use of personal protective equipment (PPE) e.g. masks, aprons, boots, eye/face protective glasses, and the use of subject's tasks and those of nearby workmates, among others. The experts then evaluated each job held by each subject to determine the confidence (possible, probable, or definite), frequency and concentration of exposure to a predetermined list of 294 substances for each job ever held. For each job in which a subject was exposed to a chemical agent, the experts used the number of years exposed as the work duration, and a set of ordinal values for confidence, frequency and concentration of exposure.[73], in which took into account whether any PPE was used while the subject was working, and the mode of contact between the substance and the worker: i.e. respiratory only, cutaneous only, both respiratory and cutaneous or radiation.[71] Thus, the experts factored in the impact of PPE to indicate the occurrence and extent of exposure.

2.4 Known occupational risk factors for lung cancer

Evidence from the literature suggests that between 5% to 14% of lung cancer incidence is attributable to exposure to workplace substances,[10] and lung cancer is the leading malignancy as a result of these exposures. In Canada, the estimated lung cancer population attributable risk for concurrent occupational exposures to lung carcinogens was found to be 14.9% (24% in men and 5% in women).[74] IARC has classified several occupational exposures as lung carcinogens based on sufficient evidence of carcinogenicity in humans (Group 1) including arsenic, beryllium, cadmium, chloromethyl ethers, chromium VI, nickel compounds, radon, silica, soot, coal combustion products, coal tar and pitch, inorganic acids, and benzo[a] pyrene.

2.5 Occupational exposure to cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes

Cleaning products in general (including cleaning agents, biocides and the additional four agents under study) are usually classified into categories according to how they are applied or used[75] (e.g. disinfectants, antioxidants, corrosion inhibitors, preservatives, algicides, bactericides, fungicides).[75, 76 77 11, 12] This thesis is aimed at examining the association between cleaning agents, biocides, and selected cleaning-related agents (namely, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes) and lung cancer risk. The selection process of cleaning-related agents is detailed in the Methodology section 4.3. This is quite challenging due to the complexity of the products' formulations and the co-exposure (overlaps) to different agents. Moreover, cleaning products are constantly changing in composition because of ecological, economic, and consumer demands.[78] Furthermore, exposures might have occurred in numerous jobs, where various chemical agents were used and whose levels of intensities might have changed over time with the introduction of government regulations and new technologies.[70]

Exposure to cleaning products has been implicated in different cutaneous and respiratory conditions, including work-related asthma.[16] Asthma, characterized by chronic inflammation of the lungs, causing airway hyper-reactivity, excessive mucous formation, and respiratory obstruction might lead to the development of lung cancer.[18] Azad *et al*. [19] indicated that chronic inflammation-induced production of reactive oxygen/nitrogen species in the lung may predispose individuals to lung cancer. Some studies have reported an association between asthma and the risk of lung cancer, but the results are inconclusive.[79-84] However, there is little evidence concerning the carcinogenic potential of occupational exposure to cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes.

In the following sections we discuss the main components of the two main agents, cleaning agents and biocides; definition and uses of each of the six agents (i.e., cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes); and epidemiologic evidence in relation to all the six agents.

2.6 Substantive background of cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes

2.6.1 Main chemical components of cleaning agents and biocides

Cleaning agents and biocides are mixtures of many chemicals, which are usually classified according to their application. The main chemical components (ingredients) of cleaning products are disinfectants, detergents, alkaline agents(e.g., sodium hydroxide, ammonia), acids, complexing agents(water softeners), solvents, corrosion inhibitors(e.g., monoethanolamine), film formers and polishes(e.g. acryl polymers, polyethylene), preservatives(e.g.benzalkonium chloride, isothiazolinones, formaldehyde), and perfumes and scents. [75, 76 77] Specifically, cleaning agents are materials such as soaps and detergents which have cleansing action, and aid water in the cleaning process, and biocides include products used to disinfect, deodorize, sterilize, and sanitize.[11, 12]

2.6.2 Definitions and uses of cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes

2.6.2.1 Definition and uses of cleaning agents

Cleaning agents are materials such as soaps and detergents which have cleansing action. Their main function is to aid water in the cleaning process. They can be divided into two categories: soaps and detergents. They may be simple sulfonated fatty acids or complex synthetic materials and may include anti-septic agents. Organic solvents are not included in the classification of cleaning agents. They may include some of the same components of the biocides. Soaps are used for cleaning, washing and textile processing, and detergents are applied to all synthetic washing compounds.[11, 12] Cleaning agents are ubiquitous in the occupational environment particularly of janitors, those working in the hospitality and food preparation industry, nurses, and cashiers.

2.6.2.2 Definition and uses of biocides

Biocides include products used to disinfect, deodorize, sterilize, and sanitize. They are capable of killing micro-organism (algae, bacteria, viruses, etc.). Agricultural pesticides are not included in the biocide group.[11, 12, 85] Biocides are used/applied as disinfectants (e.g. for human skin or scalp), as preservatives (e.g. for products during storage, for wood, leather, construction

materials), and to control infection.[86, 87] Janitors, painters, barbers and hairdressers, and nurses are examples of occupational groups that are exposed to biocides.

2.6.2.3 Definition and uses of aliphatic alcohols

Aliphatic alcohols represent a family of organic compounds containing one or more hydroxyl group (–OH) bonded to an alkyl group. The most common types of aliphatic alcohols are ethyl alcohol (ethanol), isopropyl alcohol (isopropanol), and methanol. Ethanol and isopropanol are used mainly as skin antisepsis and as disinfectants,[88] as well as components of commercial solvents and paint removers.[89] Exposure is found in a wide variety of occupations including motor vehicle mechanics and barbers and hairdressers.

2.6.2.4 Definition and uses of ammonia

Ammonia (NH_3) is a colourless, pungent gas composed of nitrogen and hydrogen.[90] It is a widely used chemical with many applications in agriculture, industry, commercial products, including various cleaning products.[91]

2.6.2.5 Definition and uses of caustic soda

Caustic soda (sodium hydroxide) is a by-product of chlorine production, and it is widely used in soap and detergent production.[92]

2.6.2.6 Definition and uses of polishes and waxes

A polish is a substance used to produce a smooth and shiny, often protective surface.[93] Wax refers to any of a class of pliable substances of animal, plant, mineral, or synthetic origin. Wax is used as a lubricant and in waxing the surfaces of materials (e.g. wooden floor or car parts) after cleaning and polishing to give shiny surfaces.[94, 95]

2.7 Epidemiologic evidence for occupational exposure to cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes related to lung cancer

There has been limited research on the role of occupational exposure to cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes, in lung cancer etiology. Nevertheless, a few studies have suggested a possible association between the development of lung cancer and occupational exposure to cleaning-related agents among cleaning workers. Table 2.1 presents the main characteristics of the nine studies (eight case-control and one retrospective cohort) identified.

Majority of epidemiologic studies examining the role of cleaning-related agents in lung cancer etiology used job-titles as a proxy of exposure. Specifically, nine studies examined cleaning-related occupations in relation to lung cancer risk, eight reported an increased risk of lung cancer associated with a cleaning-related occupation. Cleaning-related occupations that experienced an increased lung cancer risk included those ever employed as cleaners or in cleaning services: Ronco *et al*,[96] Brüske-Hohlfeld *et al*, [97] Matos *et al*,[98] Richiardi *et al*,[99] and Amr et *al*; [100] as building care takers, charworkers and cleaners: Menvielle et *al.* [101]; as hairdressers: Olsson et *al* [102]; and as waitresses, bartenders, and related work: Xu *et al*.[103] Only two studies which focussed on exposure to specific cleaning-related agents and lung cancer risk were identified: Garcia *et al,* [104] and Xu *et al*.[103] Xu *et al*., examined the role of occupational exposures in lung cancer risk among women[103]. No association was found between lung cancer risk and exposure to cleaning agents (OR=1.0; 95% CI: 0.7-1.4), biocides (OR=1.0; 95% CI: 0.3-1.0), aliphatic alcohols (OR=1.0; 95% CI: 0.7-1.5), and ammonia (OR=1.1; 95% CI: 0.5-1.5). However, the study found that ever employed as waitresses, bartenders and related work for more than 10 years was associated with a significantly increased risk of lung cancer (OR=2.7; 95% CI: 1.2-6.5).[103] Finally, in a retrospective cohort study of workers in three automobile manufacturing plants in Michigan, USA, lung cancer risk in relation to exposure to synthetic metalworking fluids (MWF) was examined by Garcia *et al*.[104] MWF is widely used to cool and lubricate industrial machining and grinding operations, have been linked with an increased risk of lung cancer, albeit with inconsistent results.[104] Several studies have indicated decreased lung cancer risk associated with the water-based synthetic fluids[105-107] due to the protective effect from endotoxins, which are thought to have antitumour activity.[108] The water-based MWFs may be contaminated by bacteria, so biocides are

routinely added to the fluids to prevent the growth of bacteria in the short term, thus, serving as a temporal indicator of exposure to bacterial and endotoxin contamination.[105, 106] In contrast to the case-control studies which supported an increased risk of lung cancer associated with working in a cleaning-related occupation, Garcia *et al.,* reported an inverse association between exposure to biocides and lung cancer risk (OR=0.54, 95 % CI: 0.34-0.86) among autoworkers working with synthetic MFW. However, the authors speculated that endotoxin contamination of the synthetic MWF, rather than the fluid itself, may have caused the apparent protective effect of biocide exposure on lung cancer risk.[104]

Table 2. 1. Summary of the epidemiologic literature on exposure to cleaning-related occupations and agents, and lung cancer risk

Author Last name, Publication Year	**Study Design[a]**	**Study Population**	**Exposure Assessment**	**Exposure Definition**	**Risk Estimate; 95% CI**
Ronco *et al*., 1988[96]	Case-control (M)	126 male lung cancer cases from cause of death registers in 2 industrialized areas of Northern Italy. 384 male population controls randomly selected from causes of death registries in the municipalities where death occurred.	Job titles	Ever engaged in selected jobs for at least 6 months: Cleaning services	OR=4.56; 95 % CI: 1.11-18.62
Brüske-Hohlfeld *et al.* 2000[97]	2 case-control studies (Pooled for joint analysis) (M)	3498 males diagnosed with lung cancer; cases were of German nationality from the Bremen, Frankfurt, East and West Germany municipal areas: 3541 male population controls randomly selected from mandatory registries and random digit dialing	Job titles	Ever employed in selected jobs: Cleaner	OR=2.06; 95 % CI: 1.37-3.11
Matos *et al.,* 2000[98]	Case-control (M)	193 males diagnosed with incident lung cancer in any the four Buenos Aires participating hospitals in Argentina: 393 hospital controls hospitalized for conditions unrelated to tobacco and residing in the same areas as cases	Job titles	Ever employed in an industry or occupational category: Cleaner	Ever employed as a cleaner: OR=2.0; 95 % CI: 0.9-5.0

Menvielle *et al.* 2003[101]	Case-control (M,F)	228 incident lung cancer cases identified from New Caledonia Cancer registry: 305 population controls randomly selected from electoral rolls.	Job titles	Ever exposed men in occupation and industry: Building care takers, Charworkers and Cleaners	OR=3.7; 95 % CI: 0.8-17.4
Richiardi *et al.* 2004[99]	Case-control (M, F)	1171 incident primary histologically or cytologically confirmed lung cancer cases identified participating hospitals in two areas of Northern Italy. 1553 population controls randomly selected from local registries	Job titles	Ever employed in an occupational category: Cleaner	OR=2.7; 95% CI: 1.0-7.4
Amr *et al.* 2009[100]	Case-control (M, F)	655 cases with histologically confirmed non-small cell primary lung tumors selected from seven hospitals in the metropolitan Baltimore area. 457 population controls recruited from the same Maryland counties of residence as the lung cancer cases by screening information obtained from the Department of Motor Vehicles.	Job titles	Longest job ever held in working life: service jobs including cleaners	Women OR=2.04; 95% CI: 0.98-4.23 Men OR=1.25; 95% CI: 0.64-2.45

Olsson *et al.,* 2013[102]	Pool of 16 case-control studies (Synergy Study)	19,369 lung cancer cases recruited from hospitals or cancer registries in Europe, Canada, China, and New Zealand. 23,674 controls recruited from the general population or hospitals	Job titles	Ever employed as Hairdressers	OR=1.65; 95% CI: 1.16-2.35
Garcia *et al.,* 2018.[104]	Retrospective Cohort (M,F)	All 38,560 hourly workers hired between 1938 and 1982 who worked for at least 3 years at any of three automobile manufacturing plants in Michigan, USA. Follow-up began 3 years after hire and ended at death, age 86 (age of oldest case), or the end of 1994, whichever occurred first.	Employment records and job exposure matrix	Annual average daily and cumulative exposure to synthetic metal working fluid and biocides. Workers with 8.52 or more years of biocide exposure	Ever exposed to biocides: RR= 0.54; 95% CI: 0.34–0.86

Xu *et al.,* 2021[103]	Case-control (F)	361 incident lung cancer cases diagnosed in one of the Montreal hospital, Quebec, Canada. 521 population controls randomly selected from Quebec Electoral list	Expert assessment	Ever exposed to selected occupational agents: cleaning agents, biocides, aliphatic alcohols, ammonia Ever employed in any cleaning related occupation for more than 10 years: waitresses, bartenders, and related work	Ever exposed to: Cleaning agents: OR=1.0; 95% CI: 0.7-1.4 biocides: OR=1.0; 95% CI: 0.3-1.0: Aliphatic alcohols: OR=1.0; 95% CI: 0.7-1.5 Ammonia : OR = 1.1; 95% CI: 0.5-1.5 Ever employed as waitresses, bartenders, and related work for > 10 years: OR = 2.7; 95% CI: 1.2-6.5

[a]M: men only study; F: women only study; M, F: men and women were included.

2.8 Summary and rationale

Persons involved in cleaning related activities, especially those who clean occupationally or often, might encounter excessive exposures to cleaning product emissions.[109] Some epidemiologic investigations have reported that cleaning workers have an increased risk of asthma.[15, 110] Asthma, marked by chronic inflammation of the lungs, might lead to the development of lung cancer. [18] The molecular pathways activated in chronic inflammation may contribute to lung carcinogenesis.[20] Some studies have reported an association between asthma and the risk of lung cancer, but the results are conflicting.[79-84]. Though previous investigations have reported some suggestive associations between cleaning work and the risk of lung cancer, majority of these studies were job-title based and thus, it is difficult to extrapolate such findings to pinpoint the contribution of individual cleaning product on the risk of lung cancer. Cigarette smoking was adjusted for in a few of the previous studies; thus, the possibility of residual confounding for smoking remains, as well as uncontrolled confounding by other lung cancer risk factors (e.g., income, education, underlying medical conditions, lifestyle factors). Moreover, none of the studies evaluated the associations between cleaning agents and biocides in relation to the major histological types of cancer namely SCC, SqCC and ADC resulting in further gaps in knowledge.

This present work aimed to improve upon the limitations of previous research by assessing lifetime exposure to specific occupational agents, evaluated using an expert-based approach, in relation to lung cancer risk using existing data from two case-control studies conducted in Montreal, Canada. The results of this thesis will contribute to the limited evidence base, informing future evaluations on occupational exposures to cleaning-related agents and the risk of lung cancer.

3 AIM OF STUDY

The overall aim of this MSc. thesis was to examine the associations between occupational exposure to cleaning-related agents, and the risk of lung cancer among men.

3.1 Study objectives

Primary objectives:

1. To determine whether a relationship exists between lung cancer risk and occupational exposure to:
    a) Cleaning agents
    b) Biocides
    c) Cleaning-related agents: namely, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes.

Secondary objectives

2. To evaluate effect modification by smoking intensity on the associations between cleaning-related agents and lung cancer risk.
3. To evaluate effect modification by asthma status on the associations between cleaning-related agents and lung cancer risk.
4. To investigate the associations between cleaning-related agents and lung cancer risk according to the major histological types of lung cancer, namely ADC, SqCC and SCC.
5. To investigate whether employment in certain cleaning-related occupations and durations in those occupations are associated with lung cancer.

4 METHODOLOGY

4.1 Study design and population

This study uses data from two population-based case-control studies carried out in Montreal, Quebec, Canada. Eligible subjects were restricted to Canadian citizens in the Montreal area (i.e. Montreal and its surrounding cities, also referred to as Greater Montreal). In both studies, cases included patients with incident histologically-confirmed lung cancer identified across all the major Montreal metropolitan hospitals.

Study 1 (1979-1986) evaluated 19 different cancer sites, including lung cancer among men aged 35-70 years. Of the 1,082 eligible lung cancer cases, 857 (79%) participated. As this study included cancers at several different sites, they served as an additional control group for the lung cancer cases. Thus, two sets of controls were available for Study 1. First, a population-based non-diseased control group (n=740) in which 533 (72%) participated; population controls were randomly selected from the Quebec electoral list. Second, a cancer control group (n=1,349) selected from a pool of other patients diagnosed with incident cancers. The main cancer sites considered in the cancer control group included cancers of the bladder, colon, prostate, stomach, lymphoma, kidney, and rectum. In Study 2 (1996-2001), considering only men aged 35-75 years, 762 cases and 899 population controls were recruited with response rates of 86 % and 69 % respectively. Study 2 only established a population-based non-diseased control group, which consisted of participants randomly selected from the Quebec electoral list. In both Studies 1 and 2, controls were frequency matched to the distribution of the cases by age.

Ethics approval was obtained for both studies from each participating hospital and university. All participating subjects provided informed consent. Figure A.1 of Appendix A presents the ethics approval letter of the study.

4.2 Exposure assessment

4.2.1 Data collection

Each eligible participant was invited by mail to participate in the study, along with a brief self-administered questionnaire. A short section on occupational history was included in the questionnaire and was used for interview preparation. Face-to-face interviews were performed

by trained interviewers who were not blinded to the lung cancer status of the participants. If study participants were unavailable (deceased, too ill, or other reasons), the interview was conducted with a surrogate or proxy respondent, for example a close family member. The interview comprised two parts: (i) a structured section, which was used to gather information on sociodemographic factors (e.g. ethnicity, income, education, and occupation), passive and active smoking, medical history (e.g. ever had asthma), residential cooking and heating methods and; (ii) a semi-structured section, which elicited a detailed description of occupations held by the subjects in their working life including job titles and company, products used, the nature of the work sites, work duration, the subjects' main and subsidiary tasks, equipment maintenance, use of protective equipment and activities of co-workers that could provide clues about work exposures and their intensities. For example, information solicited from participants who worked as janitors included whether soap, detergents, ammonia, deodorants, disinfectants, and insecticides were used during their cleaning duties and if yes, the number of weeks/year and hours/week they used these products. An excerpt of the questionnaire used for janitors is shown in Figure B.1 of Appendix B.

4.2.2 Expert assessment of occupational exposure

Following the interview, the detailed description of each job held by the subjects was examined by a team of experts, comprising chemists and industrial hygienists, who were blinded to subjects' disease status, to ascertain occupational exposures. First, each job was coded according to the 1971 Canadian Classification and Dictionary of Occupations (CCDO).[111] Subsequently, based on their knowledge and the literature, experts translated each job into a list of potential exposures using a checklist of 294 agents. For each agent considered present for a particular job, the experts classified exposure based on three exposure metrics: (i) Degree of confidence (reliability) of exposure occurrence (possible, probable, definite); (ii) Relative concentration of agent (low, medium, high) and (iii) Frequency of exposure in a typical 40-h work week in Study 1 as < 5 %, 5%-30%, > 30% and in Study 2 as a percentage on a continuous scale. The duration of exposure was defined based on the number of years of the job held, and the job description provided by the participants.

4.3 Variables of interest

4.3.1 Selection of exposures of interest related to cleaning agents and biocides

Cleaning agents and biocides are the primary exposures of interest for this thesis. However, cleaning workers are exposed to a wide variety of products such as waxes and polishes, and chemicals that contain sensitizers such as disinfectants and fragrances as well as irritants such as bleach (sodium hypochlorite), hydrochloric acid, and alkaline agents (ammonia and sodium hydroxide)[75, 76, 112, 113], 16 agents were thus, additionally considered from the literature based on their routine use in cleaning-related activities in the occupational setting[13, 130-132], and which were present in our database (see list of agents in Table 4.1).[114] We prioritized the additional 16 agents based on the prevalence of exposed jobs in our database. Specifically, three criteria were used: 1) overall prevalence ≥5%; 2) percentage co-exposure ≥15% among jobs exposed to cleaning agents and 3) percentage co-exposure ≥15% among jobs exposed to biocides. These *a priori* cut off-points were selected to ensure adequate statistical power in the main analyses. An agent was retained if it satisfied all three of the criteria in both Studies 1 and 2. Tables 4.1 and 4.2 present the distribution of the exposed jobs to the chemical agents of interest in Studies 1 and 2, respectively. Table 4.3 presents the summary of the selection procedure. Four of the sixteen agents (namely aliphatic alcohols, ammonia, caustic soda, and waxes and polishes) were retained based on the criteria. Therefore, six agents namely cleaning agents and biocides (main exposures of interest), aliphatic alcohols, ammonia, caustic soda, and waxes and polishes were the exposures of interest considered for this thesis.

To avoid confusion about the use of the term “cleaning agents” and “cleaning products” it should be noted that theses terms may be synonymous to a layman and are used interchangeably by investigators evaluating cleaning-related activities, and asthma and other respiratory conditions.[15, 75-77, 115, 116]. To them, cleaning agents/products are basically materials used to clean and/or to disinfect the working environment. For this thesis, however, we used the names of the agents assigned by the experts (chemists and industrial hygienists) i.e. cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes, as they based these classifications mainly on how these agents are used and the specific components (ingredients) they contain. [71 11 12]

Table 4.1. Prevalence of exposed jobs to the selected 16 cleaning-related agents and their co-exposure to cleaning agents and biocides in Study 1

	Total jobs in Study 1 (N = 5361 jobs)					
Chemical Agents	**N exposed jobs**	**% exposed jobs**	**N of jobs co-exposed to cleaning agents**	**% of jobs co-exposed to cleaning agents**	**N of jobs co-exposed to biocides**	**% of jobs co-exposed to biocides**
Organic solvents	3048	57	243	8	239	8
Formaldehyde	1515	28	233	15	212	14
Benzene	1126	21	123	11	75	7
Cleaning Agents	**941**	**18**			329	35
Toluene	847	16	39	5	46	5
Xylene	708	13	38	5	42	6
Biocides	**606**	**11**	329	54		
Ammonia	594	11	226	38	246	41
Aliphatic alcohols	573	11	106	19	129	23
Hydrochloric acid	483	9	94	20	98	20
Caustic Soda	440	8	137	31	80	18
Waxes and Polishes	316	6	206	65	156	49
Hypochlorites	300	6	234	78	217	72
Isopropanol	234	4	74	32	61	26
Acetic acid	213	4	42	20	50	24
Chlorine	135	3	75	56	53	39
Styrene	100	2	36	36	30	30
Phosphoric acid	74	1	6	8	14	19

Table 4.2. Prevalence of exposed jobs to the selected 16 cleaning-related agents and their co-exposure with cleaning agents and biocides in Study 2

	Total jobs in Study 2 (N = 3226 jobs)					
	N exposed jobs	**% exposed jobs**	**N of jobs co-exposed to cleaning agents**	**% of jobs co-exposed to cleaning agents**	**N of jobs co-exposed to biocides**	**% of jobs co-exposed to biocides**
Organic solvents	1828	57	376	21	281	15
Cleaning Agents	**952**	**30**			415	44
Toluene	708	22	112	16	69	10
Ammonia	654	21	317	48	209	32
Formaldehyde	624	19	159	26	93	15
Biocides	**569**	**18**	415	73		
Benzene	558	17	73	13	51	9
Aliphatic alcohols	540	17	190	35	194	36
Xylene	418	13	51	12	50	12
Isopropanol	348	11	163	47	160	46
Hydrochloric acid	325	10	66	20	41	13
Caustic Soda	181	6	86	48	55	31
Waxes and Polishes	160	5	120	75	77	48
Hypochlorites	151	4	124	82	123	81
Acetic acid	77	2	25	32	21	27
Styrene	51	2	16	32	1	2
Phosphoric acid	47	1	11	23	43	91
Chlorine	38	1	15	39	4	11

Table 4.3. Selection of agents based on prevalence of exposed jobs to cleaning agents and biocides and their co-exposures in Studies 1 and 2

	Study 1			**Study 2**		
Chemical agents	criterion	criterion	criterion	criterion	criterion	criterion
	1[a]	2[b]	3[c]	1[a]	2[b]	3[c]
Aliphatic alcohols	**x**	**x**	**x**	**x**	**x**	**x**
Isopropanol		**x**	**x**	**x**	**x**	**x**
Benzene	**x**			**x**		
Xylene	**x**			**x**		
Toluene	**x**			**x**	**x**	
Styrene		**x**	**x**		**x**	
Organic solvents	**x**			**x**	**x**	**x**
Formaldehyde	**x**	**x**		**x**	**x**	**x**
Hypochlorites	**x**	**x**	**x**		**x**	**x**
Ammonia	**x**	**x**	**x**	**x**	**x**	**x**
Chlorine		**x**	**x**		**x**	
Caustic Soda	**x**	**x**	**x**	**x**	**x**	**x**
Phosphoric acid			**x**		**x**	**x**
Acetic acid		**x**	**x**		**x**	**x**
Hydrochloric acid	**x**	**x**	**x**	**x**	**x**	
Waxes and polishes	**x**	**x**	**x**	**x**	**x**	**x**

[a] Overall prevalence: **≥ 5 %**.
[b] Co-exposure with cleaning agents: prevalence **≥ 15 %**.
[c] Co-exposure with biocides: prevalence **≥ 15 %**.

4.3.2 Parameterization of exposure to selected occupational agents

Each agent, namely, cleaning agents and biocides (main exposures of interest), aliphatic alcohols, ammonia, caustic soda, and waxes and polishes, was considered as a separate exposure. Two parameterizations of exposure were considered. First, participants were considered exposed to a selected agent only if the exposure confidence assigned by the experts was probable or definite (hereafter referred to as "Ever exposed"). Those who were exposed to the agent of interest but for whom the degree of confidence that the exposure occurred was rated as 'possible (uncertain)' by the experts were excluded from each analysis, in conformity to research conducted by Vizcaya *et al*. [117] and Lacourt *et al.* [118] This exclusion was used to eliminate certain jobs which may have had limited information elicited during the interviews which would have left the experts with an inadequate description of what the workers actually did.[71]

The "Never exposed" category encompassed participants who were not exposed to the agent of interest at any point in their working life. We further categorized those Ever exposed into two groups: (i) Substantial exposure: participants who had been exposed to a medium or high concentration of exposure for more than 5% of their workweek and for at least 5 years and: (ii) Non-substantial exposure: participants who were ever exposed to a selected agent but who did not meet the criteria of substantial exposure.

4.3.3 Covariates

A priori, established risk factors for lung cancer were considered as covariates, namely smoking, age, ethnicity, SES (i.e., income and education), and respondent status. These covariates were selected based on the literature and are routinely adjusted for in previous analysis of numerous occupational exposures and lung cancer risk in the two existing case-control studies[119] [120]. Additional potential confounders were considered and included residential fire-cooking and fire-heating after 20 years of age as well as occupational exposures to asbestos, diesel exhaust, silica, cadmium, chromium, and nickel.

4.3.3.1 Comprehensive smoking index (CSI)

Tobacco smoking is the strongest risk factor for lung cancer[121], and has been shown to act in synergy with other occupational carcinogens[6, 122]. Smoking history was adjusted for in this thesis

using the cumulative smoking index (CSI) [123]developed by Leffondré *et al*[124]. The CSI combines different smoking variables namely, smoking status (ever/never), number of years since quitting smoking, and the pack years (in logarithm) of smoking into a single aggregate measure. The index parsimoniously captures the confounding nature of smoking since it considers the timing of smoking exposure, and not just the duration and intensity. For this thesis, the CSI was considered as a continuous variable.

4.3.3.2 Demographic factors (age and ethnicity)

Age and ethnicity were selected *a priori* due to their association with lung cancer risk from past studies[119 11, 120]. Age was analyzed as a continuous variable. In the questionnaire, participants were asked to self-identify their ethnicity based on 14 ethnic groups. The majority self-identified as French and English Canadians (83% cases and 78 % controls for Study 1) and (82% cases and 71% controls in Study 2), thus, the remaining 12 ethnic groups were grouped into an 'Other' category.

4.3.3.3 Socio-economic factors (income and education)

Socioeconomic status (SES) has been associated with lung cancer in several studies, with people from lower socioeconomic backgrounds having the highest incidence rates [32-37]. As a result, two SES-related covariates considered in the analysis were income (median family income in Canadian dollars), and education. Income was categorized into three categories based on the tertile distribution in each study. Education was based on the number of years of schooling and was categorized into 0-7 years, 8-12 years and ≥ 13 years.

4.3.3.4 Respondent status

Proxy respondents were used if subjects were unavailable or too ill to respond to questions. However, responses from proxies are prone to errors and more cases than population controls were represented by proxies in both studies. Proxy was considered as a dichotomous variable *a priori* to adjust for this potential misclassification.

4.3.3.5 Residential cooking and heating and occupational exposures to IARC group 1 carcinogens

Residential cooking and heating after 20 years of age were considered as potential covariates in the analysis as studies have established that increasing level of smoke inside the home is associated with an increasing risk of lung cancer[125]. These variables were parameterized in categories of: Never exposed, exposed for 1-9 years, and exposed for at least 10 years.

IARC has classified asbestos, diesel engine exhaust, silica dust, cadmium, chromium VI, and nickel compounds as a Group 1 carcinogens for lung cancer. Occupational exposure to these Group 1 carcinogens was parameterized by the addition of the total duration in years that each subject was exposed to any of the six occupational carcinogens (asbestos, diesel exhaust, silica, cadmium, chromium, and nickel) at a reliability (confidence) of probable or definite. It was then analyzed as a continuous variable.

4.4 Confounder assessment

The six *a priori* covariates were included in all models: age, CSI, income, education, ethnicity, and respondent status. Three additional variables were then considered including: (a) total duration of occupational exposure to asbestos, diesel exhaust, silica, cadmium, chromium, and nickel; (b) residential exposure to fire-cooking; (c) residential exposure to fire-heating. To assess the impact of potential confounders, the change-in-estimate (CIE) procedure was used. Specifically, the CIE procedure entailed the addition of a potential confounder one-at-a-time to the model that included the six *a priori* covariates; the ORs were then compared and a threshold of 10% was used to define a meaningful change.

The independent associations between each *a priori* covariate and lung cancer risk are presented in Appendix C (Tables C1.1 and C1.2 for Study 1 and 2, respectively). To evaluate the three additional variables, two CIE procedures were conducted using population controls: Table C1.3 presents the CIE approach for cleaning agents and biocides and lung cancer in Study 1 and Table C1.4 presents the CIE approach for cleaning agents and biocides and lung cancer in Study 2 (Appendix C). Briefly, the addition of the three additional covariates did not appreciably change the ORs for cleaning agents and biocides. Thus, the final models for this thesis included only the six *a priori* covariates namely, age, CSI, income, education, ethnicity, and respondent status.

4.5 Statistical analyses

All statistical analyses were carried out using the Statistical Analysis System (SAS) University Edition (SAS Studio) 5.1.[126]

4.5.1 Analyses for primary objectives

4.5.1.1 Objective 1: Occupational exposure to cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes and lung cancer risk

Separate unconditional multivariate logistic regression was used to estimate the odds ratio (ORs) and 95 % CIs for the association between lung cancer and cleaning agents, biocides, and the other related agents among men, while adjusting for the six *a priori* covariates, in Studies 1 and 2. Six cleaning-related agents were considered: (1) cleaning agents (2) biocides (3) aliphatic alcohols (4) ammonia (5) caustic soda and (6) waxes and polishes. For each job ever held by a participant, exposure to each of the six agents was parameterized as never vs. ever exposed. The ever-exposed subjects were also further classified into substantial and non-substantial exposures. If a participant was exposed to the chemical agent in two or more jobs, then the average lifetime values of confidence, frequency and concentration weighted by the durations of exposures across jobs were used to assign substantial vs. non-substantial exposure. Jobs with uncertain (possible) exposures were excluded from all analyses; similarly, analyses were undertaken when a contrast had at least 5 exposed cases and 5 controls. Further, in Study 1, three sets of control groups were considered: namely, cancer controls, population controls and pooled controls.

In the main set of analyses, the reference category (reference group A (ref A)) consists of participants who were never exposed to the cleaning-related agent under analysis. Thus, in this case, the reference group changed for each agent under consideration. For example, in Study 1, the number of never exposed population controls was 431 for cleaning agents and 471 for biocides.

4.5.2 Analyses for secondary objectives

Secondary analyses considered the associations between lung cancer risk and the six agents under study by smoking intensity and asthma status. We further considered the main relationships of interests by histological types of lung cancer. For all secondary analyses, only ref A was used; further in Study 1, secondary analyses only considered pooled controls as the comparator group.

4.5.2.1 Objective 2: Analysis by smoking intensity

Tobacco smoking, being the strongest risk factor for lung cancer[121], has been shown to act in synergy with other occupational carcinogens[6, 122]. The associations between our selected cleaning-related agents, and lung cancer risk were assessed in two smoking strata of our study population. Two categories of smoking were created using the distributional cut-off points of the CSI: 'never/light' smokers versus 'medium/heavy smokers.' Lifetime low-intensity smokers, who occupied the lowest 25th percentile of the CSI, were categorized with never smokers due to the low prevalence of never smokers in our study population. Moderate/high intensity smokers were subjects with CSI values greater than the 25th percentile. Interaction by smoking was assessed with the inclusion of cross-product terms in the regression models.

4.5.2.2 Objective 3: Analysis by asthma status

As occupational exposures to cleaning-related agents have been associated with asthma, and asthma, characterized by chronic inflammation of the lungs may predisposed individuals to lung cancer[18], an analysis was conducted to determine whether having had asthma was an effect modifier on the association between lung cancer risk and exposures to our selected cleaning-related agents. Interaction by asthma status was assessed with the inclusion of cross-product terms in the regression models.

4.5.2.3 Objective 4: Analysis by histological types of lung cancer

Associations between our selected cleaning-related agents and the major histologic types of lung cancer were examined using polytomous logistic regression to determine if there were differences by histological subtypes of lung cancer (namely, SCC, SqCC and ADC).

4.5.3 Sensitivity analyses using reference group B

In the main set of analyses, the reference category (ref A) consisted of participants who were never exposed to the specific cleaning-related agent under study. In a sensitivity analysis of Objective 1, a second reference group was considered; reference group B (ref B) included the participants who were never exposed to any of the selected agents of interest. Thus, in this case,

the reference category was the same for all agents of interest. For example, in Study 1, the never exposed population controls was 319 for both the cleaning agents and biocides analyses.

4.5.3.1 Occupational exposure to cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes and lung cancer risk using ref B

Analyses using ref B employed the same procedure as in analyses using ref A. Briefly, separate unconditional multivariate logistic regression was used to estimate the ORs and 95 % CIs for the association between lung cancer and cleaning agents, biocides, and the other related agents among men, while adjusting for the six *a priori* covariates, in Studies 1 and 2.

4.5.4 Analysis of employment in cleaning-related occupations and durations in those occupations and lung cancer risk

4.5.4.1 Selection of the main occupations exposed to cleaning-related agents

In addition to our analysis focusing on occupational exposures in lung cancer etiology, we contrasted lung cancer risk among cleaning-related occupations and the duration in years spent in such occupations. In order to define broad occupational categories that would be exposed to many cleaning related agents, we first identified the top 10 most prevalent occupations that were exposed to 'cleaning agents' in Study 1 using the 4-digit code of the Canadian Classification and Dictionary of Occupations (CCDO). These same occupations were selected in Study 2. The occupational groups selected were: (1) Janitors, Charworkers and Cleaners; (2) Chefs and Cooks; (3) Labourers, Services; (4) Fire Fighting Occupations; (5) Supervisors, Food and Beverage Preparations and Related Occupations; (6) Supervisors: Sales and Occupations, Commodities; (7) Barbers, Hairdressers and Related Occupations; (8) Laundering Occupations; (9) Service Station Attendants and (10) Farm Workers.

Then we retained the occupational groups in which at least 25% of the jobs were assigned a probable/definite exposure to "Cleaning agents" and at least five cases and controls worked in that job. These criteria were met by the following five occupational groups: (1) Janitors, Charworkers and Cleaners; (2) Chefs and Cooks; (3) Labourers, Services; (4) Supervisors, Food and Beverage Preparations and Related Occupations and: (5) Service Stations Attendants

4.5.4.3 Objective 5: Employed in five cleaning-related occupations and durations in those occupations, and lung cancer risk

For each of the five selected occupations, separate unconditional multivariate logistic regression for lung cancer risk were performed comparing those who have ever worked in such occupation versus those who have never worked in such occupation. Further, we considered the duration of job held, among those who worked in a selected occupation dichotomized as those working in the job for up to 10 years and more than 10 year

5 RESULTS

5.1 Selected Characteristics of Study 1 Population

Select characteristics of Study 1 participants are presented in Table 5.1. Population controls were frequency matched to cases and thus, the mean age was similar across cases, population controls and cancer controls i.e., 59.3 years, 59.6 years, and 58.3 years respectively. In terms of ethnicity, French Canadians were the predominant group across cases (69%), population controls (64%) and cancer controls (58%). Population and cancer controls were more educated and had a higher family income than cases, with 22% of population controls and 20% of cancer controls compared to 14% of cases having had at least 13 years of schooling. Overall, proxy respondents were more commonly used among cases than controls (29 % of cases versus 19% of cancer controls and 13 % of population controls). Never smokers were rare among cases (2% cases versus 20% population and 18% cancer controls); the mean-pack years for cigarette smoking were 74.3, 49.9 and 52.3 for cases, population controls and cancer controls respectively. Among the lung cancer cases, SqCC (42%) was the most common histological type of lung cancer, followed by ADC (20%).

Table 5.1. Selected characteristics of Study 1 subjects

	Study 1		
Characteristics	Cancer Cases **(N=857)** **n (%)**	Population Controls **(N=533)** **n (%)**	Cancer Controls **(N=1349)** **n (%)**
Age (mean ± sd*)	59.3 ± 7.0	59.6 ± 7.9	58.3 ± 8.4
Age categories			
<55 years	195 (22.8%)	134 (25.1%)	398 (29.5%)
55-64 years	431 (50.2 %)	227 (42.6%)	566 (42.0%)
65-75 years	231 (27.0%)	172 (32.3%)	385 (28.5%)
Ethnicity			
French Canadian	592 (69.1%)	342(64.2%)	782 (58.0%)
English Canadian	116 (13.5%)	75 (14.0%)	217 (16.0%)
Other	149 (17.4%)	116 (21.8%)	350 (26.0)
Education			
0-7 years	435 (50.8%)	178 (33.4%)	543 (40.3%)
8-12 years	306 (35.7%)	236 (44.3%)	533 (39.5%)
≥ 13 years	116 (13.5%)	119 (22.3%)	273 (20.2%)
Family income (in tertiles ᵗ)			
Low	345 (40.3%)	159 (29.8%)	449 (33.3%)
Medium	291(34.0%)	204 (38.3%)	414(30.7%)
High	221 (25.7%)	170(31.9%)	486(36.0%)
Respondent status			
Self	605 (70.6%)	466(87.4%)	1090 (80.8%)
Proxy	252 (29.4%)	67(12.6%)	259 (19.2%)
Cigarette smoking			
Never	13 (1.5%)	105 (19.7%)	234 (17.4%)
Ever	259 (30.2%)	197(37%)	445(33.0%)
Current	585 (68.3%)	231 (43.3%)	670 (49.6%)
Mean-pack years ǂ (mean ± sd*)	74.3 ± 40.4	49.9 ± 32.4	52.3 ± 35.2
Histology			
Small (oat) cell carcinoma	159 (18.6%)	(-)	(-)
Squamous cell carcinoma	359 (41.9%)	(-)	(-)
Adenocarcinoma	167 (19.5%)	(-)	(-)
Other	172 (20.0%)	(-)	(-)

*sd = standard deviation.

ᵗ **Tertiles family income** were determined among the total study population.

ǂ Mean-pack (cigarette) years = mean (average) number of packs (20 cigarettes) smoked per day multiplied by the duration of smoking in years.

5.2 Selected Characteristics of Study 2 population

Table 5.2 presents select characteristics of Study 2 participants. The mean age of cases and control was 64.2 years and 65.0 years, respectively. In terms of ethnicity, there were more French Canadians cases (78%) than population controls (64%). Population controls were more educated and had higher family income than cases, with 35% of population controls compared to 24% of cases having had at least 13 years of schooling. Overall, proxy respondents were commonly used among cases than controls (40% of cases versus 10% of population controls). Never smokers were rare among cases (3% cases versus 18% of population controls). The mean-pack years for cigarette smoking were 77.4 for cases and 50.3 for population controls, respectively. Among the lung cancer cases, SqCC (34%) was the most common histological type of lung cancer, followed by ADC (32%).

Table 5.2. Selected characteristics of Study 2 subjects

	Study 2	
Characteristics	Cancer Cases **(N=762)** **n (%)**	Population Controls **(N=899)** **n (%)**
Age (mean ± sd*)	64.2 ± 7.9	65.0 ± 7.6
Age categories		
<55 years	93 (12.2%)	98 (10.9%)
55-64 years	243 (31.9%)	245 (27.3%)
65-75 years	426 (55.9%)	556 (61.8%)
Ethnicity		
French Canadian	593 (77.8%)	579 (64.4%)
English Canadian	35 (4.6%)	57 (6.3%)
Other	134 (17.6%)	263 (29.3%)
Education		
0-7 years	338 (44.4%)	316 (35.2%)
8-12 years	244 (32.0%)	264 (29.4%)
≥ 13 years	180 (23.6%)	319 (35.4%)
Family income (in tertiles ⁑)		
Low	290 (38.1%)	264(29.4%)
Medium	246 (32.3%)	308(34.3%)
High	226 (29.6%)	327(36.3%)
Respondent status		
Self	458 (60.1%)	810(90.1%)
Proxy	304(39.9%)	89 (9.9%)
Cigarette smoking		
Never	23(3.0%)	163(18.1%)
Ever	445 (58.4%)	503(56.0%
Current	294 (38.6%)	233(25.9%)
Mean-pack years ǂ (mean ± sd*)	77.4 ± 43.8	50.3 ± 38.3
Histology		
Small (oat) cell carcinoma	127 (16.7%)	(-)
Squamous cell carcinoma	261 (34.3%)	(-)
Adenocarcinoma	241 (31.6%)	(-)
Other	133 (17.4%)	(-)

*sd = standard deviation.

⁑ **Tertiles family income** were determined among the total study population.

ǂ Mean-pack (cigarette) years = mean (average) number of packs (20 cigarettes) smoked per day multiplied by the duration of smoking in years.

5.3 Distribution of lifetime occupational exposures to cleaning agents, biocides, aliphatic acids, ammonia, caustic soda, and waxes and polishes

The distribution of the lifetime occupational exposures to our six selected agents (namely, cleaning agents, biocides, aliphatic alcohols and ammonia, and caustic soda and waxes and polishes), according to the four metrics of exposure (i.e., confidence, concentration, frequency, and duration) found in Studies 1 and 2 are presented in Tables 5.3 (cleaning agents and biocides), 5.4 (aliphatic alcohols and ammonia) and 5.5 (caustic soda, and waxes and polishes).

From Table 5.3, ever exposure to cleaning agents in Study 1 was highest among population controls (19%) followed by cases (17%) then cancer controls (16%). Among Study 2, similarly, ever exposure to cleaning agents was also higher among populations controls (35%) than among cases (33%). Ever exposure to biocides followed the same trend as in ever exposure to cleaning agents in both studies.

Table 5.3. Distribution of lifetime occupational exposure to cleaning agents and biocides in Studies 1 and 2

	Cleaning agents					Biocides				
	Study 1			Study 2		Study 1			Study 2	
Exposure metrics	Cancer Cases **N=857** n(%)	Population controls **N=533** n(%)	Cancer controls **N=1349** n(%)	Cancer Cases **N=762** n(%)	Population controls **N=899** n(%)	Cancer cases **N=857** n(%)	Population controls **N=533** n(%)	Cancer controls **N=1349** n(%)	Cancer cases **N=762** n(%)	Population controls **N=899** n(%)
Never exposed	711 (83.0%)	431 (80.9%)	1129 (83.7%)	498 (65.4%)	570 (63.4%)	771 (90.0%)	471 (88.4%)	1205 (90.0%)	609 (80.0%)	679 (75.6%)
Ever exposed	145 (16.9%)	102 (19.1%)	218 (16.2%)	245 (33.0%)	312 (35.4%)	74 (8.8%)	57 (10.8%)	136 (10.1%)	138 (18.5%)	188 (21.7%)
Non-substantial	51 (6.0%)	39 (7.3%)	71 (5.3%)	216 (29.1%)	290 (32.9%)	38 (4.5%)	30 (5.9%)	86 (6.4%)	115 (15.4%)	169 (19.5%)
Substantial	94 (11.0%)	63 (11.8%)	147 (10.9%)	29 (3.9%)	22 (2.5%)	36 (4.3%)	27 (5.1)	50 (3.7%)	23 (3.1%)	19 (2.2%)
Confidence										
Probable	15 (1.8%)	9 (1.7%)	27 (2.0%)	45 (6.1%)	40 (4.5%)	38 (4.5%)	29 (5.5%)	86 (6.4%)	68 (9.1%)	81 (9.3%)
Definite	130 (15.2%)	93 (17.5%)	191 (14.2%)	200 (26.9%)	272 (30.8%)	36 4.3%)	28 (5.3%)	50 (3.7%)	70 (9.4%)	107 (12.3%)
Concentration										
Low	2 (0.2%)	4 (0.8%)	8 (0.6%)	208 (28.0%)	281 (31.9%)	19 (2.3%)	14 (2.7%)	58 (4.3%)	102 (13.7%)	162 (18.7%)
Medium	76 (8.9%)	65 (12.2%)	101 (7.5%)	35 (4.7%)	29 (3.3%)	51 (6.0%)	40 (7.6%)	69 (5.2%)	32 (4.3%)	21 (2.4%)
High	67(7.8%)	33 (6.2%)	109 (8.1%)	2 (0.3%)	2 (0.2%)	4 (0.5%)	3 (0.6%)	9 (0.7%)	4 (0.5%)	5 (0.6%)
Frequency										
<2 hours	9 (1.1%)	10 (1.9%)	15 (1.1%)	21 (2.8%)	30 (3.4%)	14 (1.7%)	9 (1.7%)	30 (2.2%)	18 (2.4%)	16 (1.9%)
2-12 hours	72 (8.4%)	52 (10.0%)	123 (9.1%)	156 (21.0%)	202 (22.9%)	48 (5.7%)	36 6.8%)	84 (6.3%)	81 (10.8%)	120 (13.8%)
>12 hours	64 (7.5%)	40 7.5%)	80 (8.9%)	68 (9.2%)	80 (9.1%)	12 (1.4%)	12 2.3%)	22 (1.6%)	39 (5.2%)	52 (6.0%)
Duration										
< 5 years	43 (5.0%)	32 (6.0%)	54 (4.0%)	67 (9.0%)	81 (9.2%)	16 (1.9%)	13 (2.5%)	26 (1.9%)	39 (5.2%)	50 (5.8%)
5-20 years	73 (8.5%)	53 (9.9%)	101 (7.5%)	101 (13.6%)	128 (14.5%)	36 (4.3%)	26 (4.9%)	51 (3.8%)	48 (6.4%)	76 (8.8%)
> 20 years	29 (3.4%)	17 (3.2%)	63 (4.7%)	77 (10.4%)	103 (11.7%)	22 (2.6%)	18 (3.4%)	59 (4.4%)	51 (6.8%)	62 (7.2%)

Column percentages are estimated based on dividing by the total sub-population (i.e., N=857 for cancer cases in Study 1).

From Table 5.4, ever exposure to aliphatic alcohols in Study 1 was highest among population controls (12%) followed by cases (10%) then cancer controls (9%). In Study 2, ever exposure to aliphatic alcohols was similar among cases (18.1%) and population controls (18.0%). Ever exposure to ammonia in Study 1 was also similar among cases (10.7%), population controls (10.4%) and cancer controls (10.5%). In Study 2, however, ever exposure to ammonia was higher among population controls (25.4%) than among cases (22.8%).

Table 5.4. Distribution of lifetime occupational exposure to aliphatic alcohols and ammonia in Studies 1 and 2

	Aliphatic alcohols					**Ammonia**				
	Study 1			**Study 2**		**Study 1**			**Study 2**	
Exposure metrics	Cancer Cases **N=857** n(%)	Population controls **N=533** n(%)	Cancer controls **N=1349** n(%)	Cancer Cases **N=762** n(%)	Population Controls **N=899** n(%)	Cancer cases **N=857** n(%)	Population controls **N=533** n(%)	Cancer controls **N=1349** n(%)	Cancer cases **N=762** n(%)	Population controls **N=899** n(%)
Never exposed	768 (89.6%)	463 (86.9%)	1225 (90.8%)	610 (80.1%)	715 (79.5%)	762 (88.9%)	473 (88.7%)	1200 (89.0%)	572 (75.1%)	650 (72.3%)
Ever exposed	85 (10.0%)	61 (11.6%)	119 (8.9%)	135 (18.1%)	157 (18.0)	91 (10.7%)	55 (10.4%)	140 (10.5%)	169 (22.8%)	221 (25.4%)
Non-substantial	48 (5.6%)	33 (6.3%)	60 (4.5%)	119 (16.0%)	137 (15.7%)	59 (6.9%)	38 (7.2%)	71 (5.3%)	157 (21.2%)	188 (21.6%)
Substantial	37 (4.3%)	28 (5.3%)	59 (4.4%)	16 (2.2%)	20 (2.3%)	32 (3.8%)	17 (3.2%)	69 (5.2%)	12 (1.6%)	33 (3.8%)
Confidence										
Probable	39 (4.6%)	29 (5.5%)	55 (4.1%)	60 (8.1%)	59 (6.8%)	40 (4.7%)	19 (3.6%)	54 (4.0%)	103 (13.9%)	99 (11.4%)
Definite	46 (5.4%)	32 (6.1%)	64 (4.8%)	75 (10.1%)	98 (11.2%)	51 (6.0%)	36 (6.8%)	86 (6.4%)	66 (8.9%)	122 (14.0%)
Concentration										
Low	28 (3.3%)	19 (3.6%)	31 (2.3%)	111 (14.9%)	128 (14.7%)	44 (5.2%)	24 (4.6%)	51 (3.8%)	151 (20.4%)	181 (20.8%)
Medium	44 (5.2%)	33 (6.3%)	65 (4.8%)	21 (2.8%)	23 (2.6%)	45 (5.3%)	26 (4.9%)	74 (5.5%)	14 (1.9%)	35 (4.0%)
High	13 (1.5%)	9 (1.7%)	23 (1.7%)	3 (0.4%)	6 (0.7%)	2 (0.2%)	5 (1.0%)	15 (1.1%)	4 (0.5%)	5 (0.6%)
Frequency										
<2 hours	22 (2.6%)	11 (2.1%)	24 (1.8%)	49 (6.6%)	62 (7.1%)	15 (1.8%)	9 (1.7%)	19 (1.4%)	13 (1.8%)	30 (3.4%)
2-12 hours	50 (5.9%)	37 (7.1%)	68 (5.1%)	57 (7.7%)	64 (7.3%)	59 (6.9%)	35 (6.6%)	98 (7.3%)	71 (9.6%)	90 (10.3%)
>12 hours	13 (1.5%)	13 (2.5)	27 (2.0%)	29 (3.9%)	31 (3.6%)	17 (2.0%)	11 (2.1%)	23 (1.7%)	85 (11.5%)	101 (11.6%)
Duration										
< 5 years	15 (1.8%)	11 (2.1%)	20 (1.5%)	34 (4.6%)	30 (3.4%)	19 (2.2%)	14 (2.7%)	26 (1.9%)	60 (8.1%)	56 (6.4%)
5-20 years	37 (4.3%)	28 (5.3%)	46 (3.4%)	48 (6.4%)	57 (6.5%)	33 (3.9%)	21 (4.0%)	54 (4.0%)	65 (8.8%)	106 (12.2%)
> 20 years	33 (3.9%)	22 (4.2%)	53 (3.9%)	53 (7.1%)	70 (8.0%)	39 (4.6%)	20 (3.8%)	60 (4.5%)	44 (5.9%)	59 (6.8%)

Column percentages are estimated based on dividing by the total sub-population (i.e., N=857 for cancer cases in Study 1).

With regards to Table 5.5, ever exposure to caustic soda in Study 1 was similar among cases (8%) cancer controls (7%) and population controls (7%). Among Study 2, ever exposure to caustic soda was slightly higher among populations controls (8%) than among cases (6%). Ever exposure to waxes and polishes in Study 1 followed the same trend as in ever exposure to caustic soda in Studies 1 and 2.

Table 5.5. Distribution of lifetime occupational exposure to caustic soda, and waxes and polishes in Studies 1 and 2

	Caustic soda					Waxes and polishes				
	Study 1			Study 2		Study 1			Study 2	
Exposure Metrics	Cancer Cases **N=857** n(%)	Population Controls **N=533** n(%)	Cancer controls **N=1349** n(%)	Cancer Cases **N=762** n(%)	Population Controls **N=899** n(%)	Cancer Cases **N=857** n(%)	Population Controls **N=533** n(%)	Cancer controls **N=1349** n(%)	Cancer cases **N=762** n(%)	Population controls **N=899** n(%)
Never exposed	777 (90.7%)	496 (93.1%)	1251 (92.7%)	709 (93.0%)	810 (90.1%)	814 (95.0%)	512 (96.1%)	1291 (95.7%)	709 (93.0%)	822 (91.4%)
Ever exposed	70 (8.3%)	35 (6.6%)	95 (7.1%)	45 (6.0%)	68 (7.7%)	40 (4.7%)	20 (3.8%)	56 (4.2%)	51 (6.7%)	73 (8.2%)
Non-substantial	46 (5.4%)	25 (4.7%)	62 (4.6%)	38 (5.0%)	57 (6.5%)	22 (2.6%)	14 (2.6%)	36 (2.7%)	41 (5.4%)	71 (7.9%)
Substantial	24 (2.8%)	10 (1.9%)	33 (2.5%)	7 (0.9%)	11 (1.3%)	18 (2.1%)	6 (1.1%)	20 (1.5%)	10 (1.3%)	2 (0.2%)
Confidence										
Probable	27 (3.2%)	17 (3.2%)	41 (3.1%)	15 (2.0%)	25 (2.9%)	5 (0.6%)	4 (0.8%)	13 (1.0)	10 (1.3%)	9 (1.0%)
Definite	43 (5.1%)	18 (3.4%)	54 (4.0)	30 (4.0%)	43 (4.9%)	35 (4.1%)	16 (3.0%)	43 (3.2%)	41 (5.4%)	64 (7.2%)
Concentration										
Low	16 (1.9%)	12 (2.3%)	29 (2.2%)	20 (2.7%)	35 (4.0%)	8 (0.9%)	2 (0.4%)	17 (1.3%)	35 (4.6%)	67 (7.5%)
Medium	53 (6.3%)	22 (4.1%)	61 (4.5%)	25 (3.3%)	28 (3.2%)	21 (2.5%)	17 (3.2%)	20 (1.5%)	16 (2.1%)	5 (0.6%)
High	1 (0.1%)	1 (0.2%)	5 (0.4%)	0 (0.0%)	5 (0.6%)	11 (1.3%)	1 (0.2%)	19 (1.4%)	0 (0.0%)	1 (0.1%)
Frequency										
<2 hours	29 (3.4%)	13 (2.5%)	28 (2.1%)	23 (3.1%)	27 (3.1%)	11 (1.3%)	6 (1.1%)	21 (1.6%)	11 (1.6%)	19 (2.1%)
2-12 hours	33 (3.9%)	18 (3.4%)	55 (4.1%)	12 (1.6%)	22 (2.5%)	22 (2.6%)	11 (2.1%)	30 (2.2%)	29 (3.8%)	43 (4.8%)
>12 hours	8 (0.9%)	4 (0.8%)	12 (0.9%)	10 (1.3%)	19 (2.2%)	7 (0.8%)	3 (0.6%)	5 (0.4%)	11 (1.5%)	11 (1.2%)
Duration										
< 5 years	13 (1.5%)	9 (1.7%)	28 (2.1%)	14 (1.9%)	19 (2.2%)	12 (1.4%)	8 (1.5%)	13 (1.0%)	16 (2.1%)	27 (3.0%)
5-20 years	29 (3.4%)	13 (2.5%)	38 (2.8%)	23 (3.1%)	29 (3.3%)	16 (1.9%)	8 (1.5%)	17 (1.3%)	25 (3.3%)	23 (2.6%
> 20 years	28 (3.3%)	13 (2.5%)	29 (2.2%)	8 (1.1%)	20 (2.3%)	12 (1.4%)	4 (0.8%)	26 (1.9%)	10 (1.3%)	23 (2.6%)

Column percentages are estimated based on dividing by the total sub-population (i.e., N=857 for cancer cases in Study 1).

5.4 Occupational exposures to the six cleaning related agents, and lung cancer

In Study 1, three sets of controls were considered: population controls, cancer controls and pooled controls. The reference group (ref A) was used in both Study 1 and Study 2 main analyses which comprised individuals unexposed to the agent under analysis.

5.4.1 Occupational exposure to cleaning agents, biocides, and lung cancer in Study 1

Table 5.6 presents the association between exposure to cleaning agents and biocides and lung cancer risk. For exposure to cleaning agents across all three control groups, there was no indication of an association with lung cancer risk. However, using population controls, there was a slight tendency to suggest an inverse association between ever exposed to cleaning agents and lung cancer risk (OR=0.7; 95% CI: 0.5-1.0), though a dose-response pattern is observed when considering those not substantially exposed (OR=0.7; 95% CI: 0.4-1.2) and substantially exposed (OR=0.7; 95% CI: 0.5-1.1) to cleaning agents. With regards to exposure to biocides across all control groups, a suggestive inverse association with ever exposure to biocides with lung cancer risk was found (OR= 0.8; 95 % CI =0.6-1.3 for population controls; OR= 0.8; 95 % CI =0.6-1.1 for cancer controls, and OR = 0.8; 95 % CI =0.6-1.0 for pooled controls). This suggestive inverse association appeared restricted to those not substantially exposed to biocides.

Table 5.6. Odds ratio between occupational exposure to cleaning agents and biocides and lung cancer in Study 1

	Cases/Population controls		Cases/Cancer controls		Cases/Pooled controls	
Agents/exposure metrics	Ncases/Npcons[§]	OR(95% CI)[ǂ]	Ncases/Ncacons[§]	OR(95% CI)[ǂ]	Ncases/Ncontrols[§]	OR(95% CI)[ǂ]
Cleaning Agents						
Never exposed	711/431	1.0	711/1129	1.0	711/1560	1.0
Ever exposed	145/102	0.7 (0.5-1.0)	145/218	0.9 (0.7-1.2)	145/320	0.8 (0.7-1.1)
Non-substantially exposed	51/39	0.7 (0.4-1.2)	51/71	1.1 (0.7-1.6)	51/110	0.9 (0.6-1.3)
Substantially exposed	94/63	0.7 (0.5-1.1)	94/147	0.8 (0.6-1.1)	94/210	0.8 (0.6-1.1)
Biocides						
Never exposed	771/471	1.0	771/1205	1.0	771/1676	1.0
Ever exposed	74/57	0.8 (0.6-1.3)	74/136	0.8 (0.6-1.1)	74/193	0.8 (0.6-1.0)
Non-substantially exposed	38/30	0.9 (0.5-1.6)	38/86	0.6 (0.4-1.0)	38/116	0.7 (0.4-1.0)
Substantially exposed	36/27	0.8 (0.4-1.5)	36/50	1.0 (0.6-1.6)	36/77	0.9 (0.6-1.4)

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
[§]Ncases =Number of cases.
Npcons = Number of population controls.
Ncacons = Number of cancer controls.
Ncontrols = Number of pooled controls.

5.4.2 Occupational exposure to cleaning agents, biocides, and lung cancer in Study 2

Table 5.7 presents the associations between cleaning agents and biocides and lung cancer in Study 2. We observed a null association for ever exposed to cleaning agents and lung cancer risk (OR=0.9; 95% CI: 0.7-1.2). Though a suggestive increased risk of lung cancer was found among subjects with substantial exposure to cleaning agents (OR=1.5; 95% CI: 0.8-2.9)

For ever exposure to biocides, suggestive inverse associations with lung cancer risk were observed (OR=0.8; 95% CI: 0.6-1.1). However, when considering both duration and intensity of exposure to biocides, contrasting those with a substantial exposure versus those never exposed to biocides revealed a suggestive increase risk of lung cancer (OR=1.6; 95% CI: 0.8-3.3).

Table 5.7. Odds ratio between occupational exposures to cleaning agents and biocides and lung cancer in Study 2

Agents/exposure metrics	Ncases/Npopulation controls[§]	OR(95% CI)[ǂ]
Cleaning Agents		
Never exposed	498/570	1.0
Ever exposed	245/312	0.9 (0.7-1.2)
Non-substantially exposed	216/290	0.9 (0.7-1.1)
Substantially exposed	29/22	1.5 (0.8-2.9)
Biocides		
Never exposed	609/679	1.0
Ever exposed	138/188	0.8 (0.6-1.1)
Non-substantially exposed	115/169	0.8 (0.6-1.0)
Substantially exposed	23/19	1.6 (0.8-3.3)

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
[§]Ncases =Number of cases.
Npopulationcontrols = Number of population controls.

5.4.3 Occupational exposure to aliphatic alcohols, ammonia, caustic soda, waxes and polishes, and lung cancer in Studies 1 and 2

Table 5.8 presents the ORs for lung cancer risk associated with occupational exposure to aliphatic alcohols, ammonia, caustic soda, and waxes and polishes in Study 1. For ever exposure to aliphatic alcohols across all three control groups, there was no indication of an association with lung cancer risk. Ever exposure to ammonia was suggestive of an increased risk of lung cancer among population controls (OR= 1.4; 95% CI: 0.9-2.1), cancer controls (OR = 1.2; 95 % CI: 0.9-1.6) and pooled controls (OR = 1.2; 95 % CI: 0.9-1.6). Though no discernible dose-response pattern was observed between not substantial and substantial exposure to ammonia, and lung cancer risk. Similarly, overall, there was no indication of risk associated with ever exposure to caustic soda nor waxes and polishes.

Table 5.9 presents the association between lung cancer risk and occupational exposure to aliphatic alcohols, ammonia, caustic soda, and waxes and polishes in Study 2. Across all agents, the 95% CI were wide and not supportive of any association with lung cancer risk.

Table 5.8. Odds ratio between occupational exposures to aliphatic alcohols, ammonia, caustic soda, and waxes and polishes and lung cancer in Study 1

	Cases/Population controls		Cases/Cancer controls		Cases/Pooled controls	
Agents/exposure metrics	Ncases /Npopcons[§]	OR (95% CI)[ǂ]	Ncases /Ncacons[§]	OR (95% CI)[ǂ]	Ncases /Ncontrols[§]	(95% CI)[ǂ]
Aliphatic alcohols						1.0
Never exposed	768/463	1.0	768/1225	1.0	768/1688	
Ever exposed	85/61	0.9 (0.6-1.3)	85/119	1.1 (0.8-1.5)	85/180	1.0 (0.8-1.4)
Non-substantially exposed	48/33	1.0 (0.6-1.8)	48/60	1.3 (0.8-1.9)	48/99	1.2 (0.8-1.7)
Substantially exposed	37/28	0.8 (0.4-1.3)	37/59	1.0 (0.6-1.5)	37/87	0.9 (0.6-1.4)
Ammonia						
Never exposed	762/473	1.0	762/1200	1.0	762/1673	1.0
Ever exposed	91/55	1.4 (0.9-2.1)	91/140	1.2 (0.9-1.6)	91/195	1.2 (0.9-1.6)
Non-substantially exposed	59/38	1.4 (0.8-2.2)	59/71	1.5 (1.0-2.2)	59/109	1.4 (1.0-2.0)
Substantially exposed	32/17	1.5 (0.7-3.0)	32/69	0.8 (0.5-1.3)	32/86	0.9 (0.6-1.5)
Caustic soda						
Never exposed	777/496	1.0	777/1251	1.0	777/1747	1.0
Ever exposed	70/35	1.5 (0.9-2.4)	70/95	1.1 (0.8-1.6)	70/130	1.2 (0.8-1.6)
Non-substantially exposed	46/25	1.3 (0.7-2.4)	46/62	1.1 (0.7-1.6)	46/87	1.1 (0.8-1.7)
Substantially exposed	24/10	1.9 (0.8-4.5)	24/33	1.2 (0.7-2.2)	24/43	1.2 (0.7-2.2)
Waxes and polishes						
Never exposed	814/512	1.0	814/1291	1.0	814/1803	1.0
Ever exposed	40/20	1.1 (0.6-2.0)	40/56	1.1 (0.7-1.7)	40/76	1.0 (0.7-1.6)
Non-substantially exposed	22/14	1.1(0.5-2.3)	22/36	1.1 (0.6-2.0)	22/50	1.0 (0.6-1.8)
Substantially exposed	18/6	1.2 (0.4-3.1)	18/20	1.0 (0.5-2.1)	18/26	1.1 (0.6-2.1)

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).

[§]Ncases =Number of cases.

Npcons = Number of population controls.

Ncacons = Number of cancer controls; Ncontrols = Number of pooled controls.

Table 5.9. Odds ratio between occupational exposures to aliphatic alcohols, ammonia, caustic soda, and waxes and polishes and lung cancer in Study2

Agents/Exposure metrics	Ncases/Npopulation controls[§]	OR(95% CI)[ǂ]
Aliphatic alcohols		
Never exposed	610/715	1.0
Ever exposed	135/157	1.1 (0.8-1.5)
Non-substantially exposed	119/137	1.1 (0.8-1.6)
Substantially exposed	16/20	1.1 (0.5-2.4)
Ammonia		
Never exposed	572/650	1.0
Ever exposed	169/221	1.1 (0.8-1.4)
Non-substantially exposed	157/188	1.1 (0.9-1.5)
Substantially exposed	12/33	0.6 (0.3-1.2)
Caustic soda		
Never exposed	709/810	1.0
Ever exposed	45/68	0.9 (0.5-1.4)
Non-substantially exposed	38/57	0.9 (0.6-1.5)
Substantially exposed	7/11	0.6 (0.2-1.7)
Waxes and polishes		
Never exposed	709/822	1.0
Ever exposed	51/73	0.8 (0.5-1.3)
Non-substantially exposed	41/71	-
Substantially exposed	10/2	-

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
[§]Ncases =Number of cases.
Npopulationcontrols = Number of population controls.

5.5. Analysis by smoking intensity : Cleaning agents and biocides, and lung cancer in Studies 1 and 2

Table 5.10 presents the association between ever exposure to cleaning agents and biocides, and lung cancer within two strata of smoking intensity: never-low intensity smokers versus medium-heavy intensity smokers in Studies 1 and 2; in Study 1, due to limited power, only an analysis using pooled controls was conducted.

Overall, in both studies, there was no indication that smoking modifies the association between occupational exposure to cleaning agents and biocides, and lung cancer risk; though, some trends emerged. In Study 1, ever exposure to cleaning agents indicated no association with lung cancer risk (OR=1.1; 95% CI: 0.5-2.5) among the never-low intensity smokers. However, among medium-heavy intensity smokers, ever exposure to cleaning was associated with a borderline decrease in lung cancer risk (a protective effect) (OR=0.8; 95% CI: 0.6-1.0; p-value for interaction = 0.27). For biocides, among never-low intensity smokers, no association with lung cancer risk was observed (OR=1.3; 95% CI: 0.5-3.2); while an inverse association with lung cancer risk was similarly observed among medium-heavy intensity smokers (p-value for interaction = 0.23). In Study 2, ever exposure to cleaning agents and biocides demonstrated no association with lung cancer risk among both strata of never-low intensity smokers and medium-heavy intensity smokers.

Table 5.10. Odds ratio between lung cancer and occupational exposures to cleaning agents and biocides stratified by smoking status in Studies 1 and 2

	Study 1					**Study 2**				
	N cases=**857** N population controls=**533** N cancer controls=**1349**					N cases=**762** N population controls=**899**				
Agents/Exposure metrics	**Never-low smokers**		**Medium-heavy smokers**			**Never-low smokers**		**Medium-heavy smokers**		
	Pooled controls		**Pooled controls**		**p-value (inter-action)**	**Cases/Population controls**		**Cases/ Population controls**		**p-value (inter-action)**
	Ncase/ Ncon[§]	OR(95% CI) ǂ	Ncase/ Ncon[§]	OR(95% CI) ǂ		Ncase/ Npcon[§]	OR(95% CI) ǂ	Ncase/ Npcon[§]	OR(95% CI) ǂ	
Cleaning Agents										
Never exposed	43/545	1.0	668/1015	1.0		42/236	1.0	456/334	1.0	
Ever exposed	9/88	1.1 (0.5-2.5)	136/232	0.8 (0.6-1.0)	**0.27**	17/111	0.9 (0.5-1.8)	228/201	0.9 (0.7-1.3)	**0.94**
Biocides										
Never exposed	45/572	1.0	726/1104	1.0		48/279	1.0	561/400	1.0	
Ever exposed	6/56	1.3 (0.5-3.2)	68/137	0.7 (0.5-1.0)	**0.23**	10/62	1.1 (0.5-2.4)	128/126	0.8 (0.6-1.1)	**0.47**

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
[§]Ncase = Number of cases.
Ncon = Number of pooled controls.
Npcon = Number of population controls.

5.6. Analysis by smoking intensity: Aliphatic alcohols, ammonia, waxes, and polishes, and lung cancer in Studies 1 and 2

Table 5.11 illustrates the association between ever exposure to aliphatic alcohols, ammonia, and caustic soda, and lung cancer risk within two strata of smoking intensity: never-low intensity smokers versus medium-heavy intensity smokers in Studies 1 and 2, using pooled controls for Study 1 due to limited power. Interaction between waxes and polishers and smoking intensity was not examined in Studies 1 and 2; similarly, interaction between caustic soda and smoking intensity was not examined in Study 2 due to cell sizes less than 5 for cases and controls.

In Study 1, ever exposure to caustic soda was suggestive of a statistically significant increased risk with lung cancer (OR=3.0; 95% CI: 1.3-7.2) among never-low intensity smokers while no association between caustic soda and lung cancer risk was observed among medium-heavy intensity smoking; a test for interaction on the multiplicative scale revealed that smoking modifies the association between ever exposure to caustic soda and lung cancer risk (p-value of interaction = 0.03). While the remaining interaction analyses did not reveal any associations.

Similarly, in Study 2, the associations between exposure to aliphatic alcohols and ammonia, and lung cancer risk did not differ by smoking status.

Table 5.11. Odds ratio between lung cancer and occupational exposures to aliphatic alcohols, ammonia, caustic soda, and waxes and polishes stratified by smoking status in Studies 1 and 2

	Study 1					**Study 2**				
	N cases=**857**	N population controls=**533**		N cancer controls =**1349**		N cases=**762**	N population controls=**899**			
Agents/Exposure metrics	**Never-low smokers**		**Medium-heavy smokers**			**Never-low smokers**		**Medium-heavy smokers**		
	Pooled controls		**Pooled controls**		**p-value (inter-action)**	**Cases/ Population controls**		**Cases/ Population controls**		**p-value (inter-action)**
	Ncase/ Ncon§	OR(95% CI) ǂ	Ncase/ Ncon§	OR(95% CI) ǂ		Ncase/ Npcon§	OR(95% CI) ǂ	Ncase/ Npcon§	OR(95% CI)ǂ	
Aliphatic alcohols										
Never exposed	45/575	1.0	723/1113	1.0		45/166	1.0	723/297	1.0	
Ever exposed	7/55	1.4 (0.6-3.6)	78/125	1.0 (0.7-1.3)	**0.23**	7/20	0.9 (0.3-2.7)	78/41	0.9 (0.6-1.3)	**0.74**
Ammonia										
Never exposed	43/560	1.0	719/1113	1.0		45/257	1.0	526/393	1.0	
Ever exposed	9/69	1.5 (0.7-3.5)	82/126	1.1 (0.8-1.5)	**0.33**	11/85	0.9 (0.4-1.8)	158/136	1.1 (0.8-1.5)	**0.57**
Caustic soda										
Never exposed	43/598	1.0	734/1149	1.0		54/323	-	655/487	-	
Ever exposed	9/34	3.0 (1.3-7.2)	61/96	1.0 (0.7-1.4)	**0.03**	4/27	-	41/41	-	**-**
Waxes and polishes										
Never exposed	48/612	-	766/1191	-		55/332	-	654/490	-	
Ever exposed	4/21	-	36/55	-	**-**	4/23	-	47/50	-	**-**

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
§Ncase = Number of cases.
Ncon = Number of pooled controls.
Npcon = Number of population controls.

5.7. Analysis by ever had asthma: Cleaning agents and biocides, and lung cancer in Studies 1 and 2

Table 5.12 presents the association between exposure to cleaning agents and biocides and lung cancer within two strata of asthma status: never had asthma and ever had asthma in Studies 1 and 2, using pooled controls for Study 1 due to low power. In Study 1, there were 266 subjects (102 cases, 164 controls) with missing information on asthma status; in Study 2 there were 28 subjects (20 cases, 8 controls) with missing information on asthma status. Interaction analyses were only undertaken if within each stratum there were at least 5 cases and 5 controls. Overall, in both studies, there was no indication that asthma modifies the association between occupational exposure to cleaning agents and biocides, and lung cancer.

Table 5.12. Odds ratio between lung cancer and occupational exposures to cleaning agents and biocides stratified by asthma status in Studies 1 and 2

	Study 1					**Study 2**				
Agents/Exposure	N cases=**857**		N population controls=**533**		N cancer controls =**1349**	N cases=**762**		N population controls=**899**		
metrics	**Never had asthma**		**Ever had asthma**			**Never had asthma**		**Ever had asthma**		
	Pooled controls		**Pooled controls**		**p-value (inter-action)**	**Cases/ Population controls**		**Cases/ Population controls**		**p-value (inter-action)**
	Ncase/ Ncon[§]	OR(95% CI)[ǂ]	Ncase /Ncon[§]	OR(95% CI)[ǂ]		Ncase/ Npcon[§]	OR(95% CI)[ǂ]	Ncase/ Npcon[§]	OR(95% CI)[ǂ]	
Cleaning agents										
Never exposed	591/1358	1.0	36/57	1.0		441/529	1.0	42/36	1.0	
Ever exposed	120/283	0.8 (0.6-1.1)	8/18	0.9 (0.2-3.4)	**0.77**	215/278	1.0 (0.7-1.2)	25/31	0.8 (0.4-2.0)	**0.79**
Biocides										
Never exposed	640/1459	1.0	40/66	1.0		542/630	1.0	53/45	1.0	
Ever exposed	62/173	-	3/9	-	-	130/185	0.9 (0.6-1.2)	15/22	0.7 (0.3-2.0)	**0.84**

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
§ Ncase = Number of cases.
Ncon = Number of pooled controls.
Npcon = Number of population controls.

5.8. Analysis by ever had asthma: Occupational exposures to aliphatic alcohols, ammonia, caustic soda, and waxes and polishes, and lung cancer in Studies 1 and 2

Table 5.13 illustrates the association between exposure to aliphatic alcohols, ammonia, caustic soda, and waxes and polishes and lung cancer within two strata of asthma status in Studies 1 and 2, using pooled controls for Study 1 due to low power. Again, interaction analyses were only undertaken if within each stratum there were at least 5 cases and 5 controls.

In Study 1, there was no indication that asthma status modifies the associations between ever exposure to aliphatic acid and caustic soda, and lung cancer risk. While in Study 2, those who have ever had asthma and were occupationally exposed to aliphatic alcohols experienced a higher risk of lung cancer (OR=4.6; 95% CI: 1.4-4.9; p-value for interaction = 0.04) while no association was observed among those without asthma. While for the ammonia-lung cancer risk association, the opposite trends were observed when stratified by asthma status. Specifically, among those who have never had asthma, a suggestive positive association was observed between exposure to ammonia and lung cancer risk; while an inverse association was found among those who have ever had asthma (p-value for interaction = 0.05)

Table 5.13. Odds ratio between lung cancer and occupational exposures to aliphatic alcohols, ammonia, caustic soda, and waxes and polishes stratified by asthma status in Studies 1 and 2

	Study 1					**Study 2**				
	N cases=**857** N population controls=**533** N cancer controls =**1349**					N cases=**762** N population controls=**899**				
	Never had asthma		**Ever had asthma**			**Never had asthma**		**Ever had asthma**		
Agents/Exposure metrics	**Pooled controls** Ncase/ Ncon§	OR(95% CI)‡	**Pooled controls** Ncase/ Ncon§	OR(95% CI)‡	**p-value (inter-action)**	**Cases/ Population controls** Ncase/ Npcon§	OR(95% CI)‡	**Cases/ Population controls** Ncase/ Npcon§	OR(95% CI)‡	**p-value (inter-action)**
Aliphatic alcohols										
Never exposed	635/1469	1.0	39/68	1.0		546/655	1.0	49/55	1.0	
Ever exposed	76/174	1.0 (0.7-1.4)	5/7	3.5 (0.4-27.2)	**0.55**	112/145	1.0 (0.8-1.4)	18/10	4.6 (1.4-14.9)	**0.04**
Ammonia										
Never exposed	630/1455	-	40/68	-		500/603	1.0	54/40	1.0	
Ever exposed	79/177	-	4/5	-	**-**	153/195	1.2 (0.9-1.6)	14/25	0.5 (0.2-1.3)	**0.05**
Caustic soda										
Never exposed	644/1526	-	40/68	-		628/740	-	62/63	-	
Ever exposed	60/114	-	4/7	-	**-**	38/66	-	6/2	-	**-**
Waxes & polishes										
Never exposed	678/1571	-	43/70	-		629/759	1.0	60/56	1.0	
Ever exposed	32/69	-	1/5	-	**-**	43/62	0.8 (0.5-1.3)	8/10	1.3 (0.3-5.1)	**0.47**

‡ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
§Ncases = Number of cases; Ncont = Number of pooled controls.
Npcon = Number of population controls.

5.9. Analysis by histological types: Cleaning agents, biocides, and lung cancer in Study 1

Table 5.14 presents the association between cleaning agents and biocides, and the histological types of lung cancer in Study 1. We observed no associations for ever exposed to cleaning agents and biocides and the risks of SqCC, SCC and ADC.

Table 5.14. Odds ratio between occupational exposures to cleaning agents and biocides and lung cancer histological types in Study 1

	Study 1 Cleaning agents		Study 1 Biocides	
Lung cancer types	**Ncases/Nplconts[§]**	**OR (95 % CI) ǂ**	**Ncases/Nplconts[§]**	**OR (95 % CI) ǂ**
Squamous cell carcinoma				
Never exposed	300 /1560	1.0 (ref)	320/1676	1.0 (ref)
Ever exposed	58 /320	0.8 (0.6-1.1)	34/193	0.9 (0.6-1.3)
Small cell carcinoma				
Never exposed	129/1560	1.0 (ref)	143/1676	1.0 (ref)
Ever exposed	30/320	1.0 (0.6-1.5)	14/193	0.8 (0.5-1.5)
Adenocarcinoma				
Never exposed	137 /1560	1.0 (ref)	148/1676	1.0 (ref)
Ever exposed	30 /320	0.9 (0.6-1.5)	14/193	0.8 (0.5-1.4)

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
[§]Ncases = Number of cases; Nplconts = Number of pooled controls.

5.10. Analysis by histological types: Cleaning agents and biocides, and lung cancer in Study 2

Table 5.15 presents the association between cleaning agents and biocides, and SqCC, SCC and ADC in Study 2. Similar to Study 1, no association was observed between those ever exposed to cleaning agents and the main histological types of lung cancer. For biocides, a suggestive inverse association was observed between ever exposure to biocides and SqCC (OR=0.7; 95% CI: 0.5-1.0).

Table 5.15. Odds ratio between occupational exposures to cleaning agents and biocides and lung cancer histological types in Study 2

	Study 2 Cleaning agents		Study 2 Biocides	
Lung cancer types	**Ncases/Npopconts[§]**	**OR (95 % CI) ǂ**	**Ncases/Npopconts[§]**	**OR (95 % CI) ǂ**
Squamous cell carcinoma				
Never exposed	158/570	1.0 (ref)	212/679	1.0 (ref)
Ever exposed	97/312	1.1 (0.8-1.5)	43/188	0.7 (0.5-1.0)
Small cell carcinoma				
Never exposed	86 /570	1.0 (ref)	99/679	1.0 (ref)
Ever exposed	38/312	0.8 (0.5-1.3)	26/188	1.0 (0.6-1.7)
Adenocarcinoma				
Never exposed	159/570	1.0 (ref)	188/679	1.0 (ref)
Ever exposed	76/312	0.9 (0.6-1.2)	47/188	0.9 (0.6-1.3)

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
[§]Ncases = Number of cases.
Npopconts = Number of population controls.

5.11. Analysis by histological types: Aliphatic alcohols and ammonia, and lung cancer in Study 1

Table 5.16 illustrates the association between aliphatic alcohols and ammonia, and histological types of lung cancer in Study 1. Generally, there was no indication of a relationship between occupational exposure to aliphatic alcohols and the three histological types of lung cancer. For ever exposure to ammonia, however, there was a suggestive increased risk for SqCC (OR=1.3; 95% CI: 0.9-1.9).

Table 5.16. Odds ratio between occupational exposures to aliphatic alcohols and ammonia and lung cancer histological types in Study 1

	Study 1 Aliphatic alcohols		Study 1 Ammonia	
Lung cancer types	**Ncases/Nplconts[§]**	**OR (95 % CI) ǂ**	**Ncases/Nplconts[§]**	**OR (95 % CI) ǂ**
Squamous cell carcinoma				
Never exposed	320/1688	1.0 (ref)	316/1673	1.0 (ref)
Ever exposed	37/180	1.0 (0.7-1.5)	42/195	1.3 (0.9-1.9)
Small cell carcinoma				
Never exposed	145/1688	1.0 (ref)	143/1673	1.0 (ref)
Ever exposed	14/180	0.8 (0.5-1.5)	15/195	1.1 (0.6-1.9)
Adenocarcinoma				
Never exposed	156/1688	1.0 (ref)	147/1673	1.0 (ref)
Ever exposed	11/180	0.6 (0.3-1.2)	18/195	1.3 (0.7-2.1)

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
[§]Ncases = Number of cases.
Nplconts = Number of pooled controls.

5.12. Analysis by histological types: Aliphatic alcohols, ammonia, and lung cancer in Study 2

Table 5.17 shows the results for the association between aliphatic alcohols and ammonia, and the histological types of lung cancer in Study 2. Occupational exposure to aliphatic alcohols and ammonia were suggestive of increased risk with ADC (OR=1.3; 95% CI: 0.9-2.0 for aliphatic alcohols, and OR=1.2; 95% CI: 0.8-1.7 for ammonia). For SqCC and SCC, no association with aliphatic alcohols and ammonia was observed.

Table 5.17. Odds ratio between occupational exposures to aliphatic alcohols and ammonia and lung cancer histological types in Study 2

	Study 2 Aliphatic alcohols		Study 2 Ammonia	
Lung cancer types	**Ncases/Npopconts[§]**	**OR (95 % CI) ǂ**	**Ncases/Npopconts[§]**	**OR (95 % CI) ǂ**
Squamous cell carcinoma				
Never exposed	211/715	1.0 (ref)	194/650	1.0 (ref)
Ever exposed	46/157	1.1 (0.7-1.6)	63/221	1.1 (0.8-1.6)
Small cell carcinoma				
Never exposed	102/715	1.0 (ref)	97/650	1.0 (ref)
Ever exposed	20/157	1.1 (0.6-1.9)	23/221	0.9 (0.5-1.6)
Adenocarcinoma				
Never exposed	188/715	1.0 (ref)	177/650	1.0 (ref)
Ever exposed	49/157	1.3 (0.9-2.0)	57/221	1.2 (0.8-1.7)

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy) .
[§]Ncases = Number of cases.
Npopconts = Number of population controls.

5.13. Analysis by histological types: Caustic soda and, waxes and polishes, and lung cancer in Study 1

Table 5.18 presents the results for the association between caustic soda, and waxes and polishes, and the histological types of lung cancer in Study 1 . Ever exposed to caustic soda was suggestive of increased risk with SCC (OR=1.3; 95% CI: 0.7-2.3) though the confidence interval was very wide. Similarly, ever exposure to waxes and polishes was suggestive of an increased risk for SqCC (OR=1.3; 95% CI: 0.8-2.1).

Table 5.18. Odds ratio between occupational exposures to caustic soda, and waxes and polishes, and lung cancer histological types in Study 1

	Study 1 Caustic soda		Study 1 Waxes and polishes	
Lung cancer types	**Ncases/Nplconts[§]**	**OR (95 % CI) ǂ**	**Ncases/Nplconts[§]**	**OR (95 % CI) ǂ**
Squamous cell carcinoma				
Never exposed	324/1747	1.0 (ref)	331/1798	1.0 (ref)
Ever exposed	29/130	1.1 (0.7-1.7)	22/79	1.3 (0.8-2.1)
Small cell carcinoma				
Never exposed	142/1747	1.0 (ref)	152/1798	-
Ever exposed	14/130	1.3 (0.7-2.3)	4/79	-
Adenocarcinoma				
Never exposed	155/1747	1.0 (ref)	159/1798	1.0 (ref)
Ever exposed	11/130	0.9 (0.5-1.7)	7/79	0.9 (0.4-2.0)

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
[§]Ncases = Number of cases.
Nplconts = Number of pooled controls.

5.14. Analysis by histological types: Caustic soda and, waxes and polishes, and lung cancer in Study 2

Table 5.19 presents the association between caustic soda, and waxes and polishes, and histological types of lung cancer in Study 2. In general, there was no indication of associations between ever exposed to caustic soda and waxes and polishes, and SqCC, SCC and ADC.

Table 5.19. Odds ratio between occupational exposures to caustic soda, and waxes and polishes, and lung cancer histological types in Study 2

	Study 2 Caustic soda		**Study 2 Waxes and polishes**	
Lung cancer types	**Ncases/Npconts[§]**	**OR (95 % CI) ǂ**	**Ncases/Npconts[§]**	**OR (95 % CI) ǂ**
Squamous cell carcinoma				
Never exposed	237/810	1.0 (ref)	242/822	1.0 (ref)
Ever exposed	20/68	1.0 (0.6-1.8)	18/73	0.8 (0.5-1.5)
Small cell carcinoma				
Never exposed	121/810	1.0 (ref)	116/822	1.0 (ref)
Ever exposed	6/68	0.6 (0.3-1.6)	10/73	1.0 (0.5-2.2)
Adenocarcinoma				
Never exposed	225/810	1.0 (ref)	227/822	1.0 (ref)
Ever exposed	14/68	0.8 (0.4-1.5)	14/73	0.7 (0.4-1.3)

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high), education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
[§]Ncases = Number of cases.
Npconts = Number of population controls.

5.15. Sensitivity analysis using reference group B: Subjects unexposed to any of the cleaning-related agents

Tables 5.20, 5.21, 5.22 and 5.23 present the ORs between occupational exposures to cleaning agents and biocides and lung cancer risk in Study 1, the ORs between occupational exposures to cleaning agents and biocides and lung cancer risk in Study 2, and the ORs between occupational exposures to aliphatic alcohols, ammonia, caustic soda, and waxes and polishes and lung cancer risk in Study 1, and the ORs between occupational exposures to aliphatic alcohols, ammonia, caustic soda, and waxes and polishes and lung cancer risk in 2 respectively, using reference group B (ref B). Ref B comprised subjects unexposed to any of the six cleaning related agents (cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes. Overall, the OR estimates using ref B showed similar trends as in using ref A for the main analyses (See Tables 5.6, 5.7 and 5.8). [Ref A included subjects unexposed to the particular agent under analysis].

Table 5.20. Odds ratio between occupational exposures to cleaning agents and biocides and lung cancer in Study 1 (using reference group B)

	Cases/Population controls§		Cases/Cancer controls§		Cases/Pooled controls§	
Agents/exposure metrics	Ncase/Npcon§	OR(95% CI)ǂ	Ncase/Ncacon§	OR(95% CI)ǂ	Ncases/Ncontrols§	OR(95% CI)ǂ
Cleaning Agents						
Never exposed	583/334	1.0	583/925	1.0	583/1259	1.0
Ever exposed	145/102	0.7 (0.5-1.0)	145/218	0.9 (0.7-1.2)	145/320	0.8 (0.6-1.1)
Non-substantially exposed	51/39	0.7 (0.4-1.1)	51/71	1.1 (0.7-1.6)	51/110	0.9 (0.6-1.3)
Substantially exposed	94/63	0.7 (0.5-1.1)	94/147	0.8 (0.6-1.1)	94/210	0.8 (0.6-1.1)
Biocides						
Never exposed	583/334	1.0	583/925	1.0	583/1259	1.0
Ever exposed	74/57	0.8 (0.5-1.2)	74/136	0.8 (0.5-1.1)	74/193	0.7 (0.5-1.0)
Non-substantially exposed	38/30	0.8 (0.4-1.4)	38/86	0.6 (0.4-1.0)	38/116	0.7 (0.4-1.0)
Substantially exposed	36/27	0.7 (0.4-1.4)	36/50	1.0 (0.6-1.6)	336/77	0.9 (0.6-1.4)

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
§Ncases =Number of cases.
Npcons = Number of population controls.
Ncacons = Number of cancer controls.
Ncontrols = Number of pooled controls.

Table 5.21. Odds ratio between occupational exposures to cleaning agents and biocides and lung cancer in Study 2 (using reference group B)

Agents/exposure metrics	Ncases/Npopulation controls[§]	OR(95% CI)[ǂ]
Cleaning Agents		
Never exposed	342/381	1.0
Ever exposed	245/312	0.9 (0.7-1.2)
Non-substantially exposed	216/290	0.9 (0.7-1.2)
Substantially exposed	29/22	1.5 (0.8-3.0)
Biocides		
Never exposed	342/381	1.0
Ever exposed	138/188	0.9 (0.7-1.3)
Non-substantially exposed	115/169	0.8 (0.6-1.2)
Substantially exposed	23/19	1.7 (0.8-3.7)

[ǂ] ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
[§] Ncases =Number of cases.
Npopulation controls = Number of population controls.

Table 5.22. Odds ratio between occupational exposures to aliphatic alcohols, ammonia, caustic soda, and waxes and polishes and lung cancer in Study 1 (Using reference group B)

	Cases/Population controls		Cases/Cancer controls		Cases/Pooled controls	
Agents/exposure metrics	Ncases /Npopcons[§]	OR (95% CI)[ǂ]	Ncases /Ncacons[§]	OR (95% CI)[ǂ]	Ncases /Ncontrols[§]	(95% CI)[ǂ]
Aliphatic alcohols						1.0
Never exposed	583/334	1.0	583/925	1.0	583/1259	
Ever exposed	85/61	0.9 (0.6-1.3)	85/119	1.1 (0.8-1.5)	85/180	1.0 (0.7-1.3)
Non-substantially exposed	48/33	1.0 (0.6-1.7)	48/60	1.2 (0.8-1.9)	48/93	1.1 (0.8-1.7)
Substantially exposed	37/28	0.7 (0.4-1.3)	37/59	0.9 (0.6-1.5)	37/87	0.9 (0.6-1.3)
Ammonia						
Never exposed	583/334	1.0	583/925	1.0	583/1259	1.0
Ever exposed	91/55	1.3 (0.8-2.0)	91/140	1.1 (0.8-1.6)	91/195	1.1 (0.8-1.5)
Non-substantially exposed	59/38	1.2 (0.7-2.0)	59/71	1.5 (1.0-2.2)	59/109	1.4 (0.9-2.0)
Substantially exposed	32/17	1.4 (0.7-2.9)	32/69	0.8 (0.5-1.3)	32/86	0.9 (0.5-1.4)
Caustic soda						
Never exposed	583/334	1.0	583/925	1.0	583/1259	1.0
Ever exposed	70/35	1.3 (0.8-2.2)	70/95	1.1 (0.7-1.6)	70/130	1.1 (0.8-1.5)
Non-substantially exposed	46/25	1.2 (0.7-2.2)	46/62	1.0 (0.7-1.6)	46/87	1.1 (0.7-1.6)
Substantially exposed	24/10	1.7 (0.7-4.1)	24/33	1.2 (0.7-2.2)	24/43	1.2 (0.7-2.1)
Waxes and polishes						
Never exposed	583/334	1.0	583/925	1.0	583/1259	1.0
Ever exposed	40/20	1.0 (0.5-1.8)	40/56	1.1 (0.7-1.7)	40/76	1.0 (0.6-1.5)
Non-substantially exposed	22/14	1.0 (0.4-2.1)	22/36	1.1 (0.6-2.1)	22/50	1.0 (0.6-1.7)
Substantially exposed	18/6	1.0 (0.4-2.8)	18/20	1.0 (0.5-2.0)	18/26	1.0 (0.5-2.0)

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
[§]Ncases =Number of cases; Npcons = Number of population controls; Ncacons = Number of cancer controls; Ncontrols = Number of pooled controls.

Table 5.23. Odds ratio between occupational exposures to aliphatic alcohols, ammonia, caustic soda, and waxes and polishes and lung cancer in Study 2 (using reference group B)

Agents/Exposure metrics	Ncases/Npopulation controls[§]	OR(95% CI)[ǂ]
Aliphatic alcohols		
Never exposed	342/381	1.0
Ever exposed	135/157	1.1 (0.8-1.6)
Non-substantially exposed	119/137	1.1 (0.8-1.6)
Substantially exposed	16/20	1.1 (0.5-2.5)
Ammonia		
Never exposed	342/381	1.0
Ever exposed	169/221	1.0 (0.8-1.4)
Non-substantially exposed	157/188	1.1 (0.8-1.5)
Substantially exposed	12/33	0.6 (0.3-1.2)
Caustic soda		
Never exposed	342/381	1.0
Ever exposed	45/68	0.9 (0.6-1.5)
Non-substantially exposed	38/57	1.0 (0.6-1.7)
Substantially exposed	7/11	0.6 (0.2-1.8)
Waxes and polishes		
Never exposed	342/381	1.0
Ever exposed	51/73	0.9 (0.6-1.4)
Non-substantially exposed	41/71	-
Substantially exposed	10/2	-

ǂ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy).
[§]Ncases =Number of cases.
Npopulationcontrols = Number of population controls.

5.16 Selection of main occupations exposed to cleaning related agents

In addition to our analysis focusing on occupational exposures to cleaning-related agents in lung cancer etiology, we contrasted lung cancer risk among cleaning-related occupations and the duration in years spent in such occupations. The top 10 occupations exposed to cleaning agents and biocides and their distributions in Studies 1 and 2 are presented in Table 5.24. The occupational groups selected were: (1) Janitors, Charworkers and Cleaners; (2) Chefs and Cooks; (3) Labourers, Services; (4) Fire Fighting Occupations; (5) Supervisors, Food and Beverage Preparations and Related Occupations (SFBPRO); (6) Supervisors: Sales and Occupations, Commodities; (7) Barbers, Hairdressers and Related Occupations; (8) Laundering Occupations; (9) Service Station Attendants and (10) Farm Workers. We then retained the top five occupational groups for analysis in relation to lung cancer risk.

Table 5.24. Distribution of ten main occupations exposed to cleaning agents and biocides in Studies 1 and 2

	Study 1						Study 2				
					Cleaning agents	Biocides				Cleaning agents	Biocides
Occupational groups	N*	**Cancer Cases**	**Population Controls**	**Cancer Controls**	**n*(%)**	**n*(%)**	N*	**Cancer Cases**	**Population Controls**	**n*(%)**	**n*(%)**
Janitors, Charworkers and Cleaners	**203**	80	41	82	163 (80%)	99 (49%)	**169**	72	97	152 (90%)	99 (59%)
Chefs and Cooks	**115**	34	58	23	58 (50%)	19 ((17%)	**84**	38	46	62 (74%)	2 (2%)
Labourers, Services	**61**	21	16	24	47 (77%)	18 (30%)	**59**	29	30	41 (69%)	1 (2%)
Fire Fighting Occupations	**27**	10	2	15	25 (93%)	14 (52%)	**15**	11	4	10 (67%)	18 (120%)
Supervisors, Food and Beverage Preparations and Related Occupations	**80**	20	19	41	21 (26%)	12 (15%)	**26**	9	17	8 (31%)	2 (8%)
Supervisors: Sales Occupations, Commodities	**260**	61	51	148	17 (7%)	11 (4%)	**114**	43	71	20 (18%)	0 (0%)
Barbers, Hairdressers and related Occupations	**21**	3	4	14	17 (81%)	9 (43%)	**18**	7	11	18 (100%)	19 (106%)
Laundering Occupations	**15**	5	3	7	15 (100%)	8 (53%)	**5**	2	3	5 (100%)	0 (0%)
Service Stations Attendants	**42**	15	8	19	14 (33%)	8 (19%)	**23**	12	11	3 (13%)	0 (0%)
Farm Workers	**201**	59	35	107	12 (6%)	8 (4%)	**94**	34	60	56 (60%)	14 (15%)

N** =Total number of person-jobs in an occupational group exposed to the chemical agent.: **n = Number of person-jobs in an occupational group exposed to the chemical agent. E.g., for cleaning agents in Study 1, 80 % [i.e. n divided by N (163/203)] of jobs classified as Janitors, Charworkers and Cleaners were exposed to cleaning agents.

5.17. Analysis between lung cancer and ever having been employed in main occupations and durations in those occupations

Table 5.25 shows the five most prevalent cleaning-related occupations selected from Studies 1 and 2, and their ORs for lung cancer risk associated with ever having been employed in such occupations and the durations (in years) spent in such occupations, using pooled controls in Study 1.

In Study 1, ever having held one of our five most prevalent cleaning-related occupations was not significantly associated with lung cancer risk. There were no discernible dose-response trends related to duration of employment in these jobs and lung cancer risk. Similar trends were observed in Study 2, except a suggestive increase in risk for lung cancer associated with ever having been employed as Labourers, Services (OR=1.4; 95% CI: 0.7-3.0) and having held this position for a period of 10 years (OR=1.6; 95% CI: 0.7-3), which were associated with increased lung cancer risks.

Table 5.25. Odds ratio between lung cancer and ever having been employed and durations in such occupations as Janitors, Charworkers and Cleaners, Labourers, Services, Supervisors Food and Beverage Preparations and Related Occupations (*SFBPRO), and Service Stations Attendants in Studies 1 and 2

	Study 1		Study 2	
Occupational groups exposures	Ncase/Ncon	OR(95% CI)‡	Ncase/Npopcon	OR(95% CI)‡
Never as Janitors, Charworkers and Cleaners	65/147	1.0	64/67	1.0
Ever as Janitors, Charworkers Cleaners	72/110	1.2 (0.8-2.0)	62/76	0.8 (0.4-1.5)
Duration in occupation				
0 year (unexposed)	65/147	1.0	64/67	1.0
> 0 to ≤ 10 years	49/71	1.3 (0.7-2.2)	41/46	0.9 (0.5-1.8)
> 10 years	23/39	1.1 (0.6-2.1)	21/30	0.6 (0.3-1.4)
Never as Chefs and Cooks	106/194	1.0	99/111	1.0
Ever as Chefs and Cooks	31/63	0.9 (0.5-1.5)	27/32	0.9 (0.5-1.9)
Duration in occupation				
0 year (unexposed)	106/194	1.0	99/111	1.0
> 0 to ≤ 10 years	27/37	1.2 (0.6-2.1)	14/15	0.9 (0.3-2.2)
> 10 years	4/26	0.4 (0.1-1.1)	13/17	1.1 (0.4-2.9)
Never as Labourers, Services	118/218	1.0	101/116	1.0
Ever as Labourers, Services	19/39	1.1 (0.6-2.2)	25/27	1.4 (0.7-3.0)
Duration in occupation				
0 year (unexposed)	118/218	1.0	101/116	1.0
> 0 to ≤ 10 years	15/26	1.5 (0.7-3.2)	18/20	1.6 (0.7-3.8)
> 10 years	4/13	0.5 (0.2-1.9)	7/7	1.0 (0.3-3.6)
Never as *SFBPRO	120/207	1.0	117/128	1.0
Ever as *SFBPRO	17/50	0.7 (0.4-1.4)	9/15	0.8 (0.3-2.3)
Duration in occupation				
0 year (unexposed)	120/207	1.0	117/128	1.0
> 0 to ≤ 10 years	9/30	0.7 (0.3-1.7)	5/7	0.7 (0.1-2.8)
> 10 years	8/20	0.7 (0.3-1.8)	4/8	1.0 (0.2 - 4.2)
Never as Service Station Attendants	123/231	1.0	116/132	1.0
Ever as Service Station Attendants	14/26	0.9 (0.4-2.0)	10/11	0.6 (0.2-1.7)
Duration in occupation				
0 year (unexposed)	123/231	1.0	116/132	1.0
> 0 to ≤ 10 years	10/22	-	8/11	-
> 10 years	4/4	-	2/0	-

*SFBPRO = Supervisors, Food and Beverage Preparations and Related Occupations.‡ ORs adjusted for age, comprehensive smoking index, income (low, medium, high) , education in years (0-7, 8-12, ≥ 13), ethnicity (French Canadian, English Canadian, other) and respondent status (self, proxy). Ncase = Number of cases. Ncon = Number of pooled controls. Npopcon = Number of population controls.

6 DISCUSSION

The primary objective of this thesis was to examine the associations between occupational exposure to cleaning agents and biocides (main exposures of interest) and their related agents namely aliphatic alcohols, ammonia, caustic soda, and waxes and polishes. In addition, the associations between these six cleaning-related agents and lung cancer risk were investigated within strata of smoking intensity and asthma status, and in relation to the main histological types of lung cancer. Finally, employment in certain cleaning-related occupations and duration in that occupation in relation to lung cancer risk was explored. Using data from two large case-control studies conducted in Monteal in the province of Quebec, Canada from 1979-1986 (Study 1) and 1996-2001 (Study 2), occupational exposure to cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes were defined using several exposure metrics to better understand the associations between these agents and the risk of lung cancer. This chapter will present a summary of our results in comparison with previous studies, followed by the methodological considerations (i.e. strengths and limitations of the methodology used for this study), and conclude with suggestions for future studies.

6.1 Summary of key findings

6.1.1 Main analysis: Cleaning agents, biocides and other cleaning-related agents, and lung cancer risk in Studies 1 and 2

Taken together, the results of Studies 1 and 2 do not support the hypothesis that occupational exposure to cleaning agents, biocides, and other cleaning-related agents play a role in lung cancer etiology

6.1.2 Secondary analysis: Smoking intensity: Cleaning agents, biocides, and other cleaning-related agents, and lung cancer risk in Studies 1 and 2

As tobacco smoking is the strongest risk factor in the development of lung cancer, we examined the potential that smoking would modify the association between occupational exposure to cleaning-related agents and lung cancer. Nevertheless, the associations generally did not differ appreciably among the two smoking-strata, except in Study 1, where smoking intensity appeared to modify the association between ever exposure to caustic soda and lung cancer risk.

6.1.3 Secondary analysis: Asthma status: Cleaning agents, biocides, and other cleaning-related agents, and lung cancer risk in Studies 1 and 2

We explored effect modification by asthma status on the association between workplace exposure to cleaning-related agents and lung cancer. In Study 1, we were limited in power to explore effect modification by asthma status for the associations between ammonia, caustic soda and waxes and polishes, and lung cancer risk. Generally, the results of the analyses did not indicate any effect modification by asthma on the association between cleaning-related agents and lung cancer except in Study 2, where those occupationally exposed to aliphatic alcohols and who have ever had asthma experienced a four-fold increase in lung cancer risk in comparison to a null association observed among those who have never had asthma.

6.1.4 Secondary analysis: Histological types of lung cancer: Cleaning agents, biocides, and other cleaning-related agents, and lung cancer risk in Studies 1 and 2

Different histological types of lung cancer are known to have different etiologies, warranting the investigation of the association between occupational exposure to cleaning-related agents and lung cancer with respect to the major histological types of lung cancer for this present research. In Study 1 ever exposure to cleaning agents, biocides, caustic soda, and waxes and polishes did not reveal any risk with the main histological types of lung cancer (namely, SqCC, SCC and ADC). Nevertheless, ever exposure to ammonia suggested an increased risk for SqCC. Similarly, in Study 2 ever exposure to cleaning agents, biocides, caustic soda and waxes and polishes was not associated with the main histological types of lung cancer. While occupational exposure to aliphatic alcohols and ammonia were suggestive of an increased risk with ADC.

6.1.5 Secondary analysis: Employment and durations in cleaning-related occupations in Studies 1 and 2

In addition to our analysis focusing on occupational exposures to cleaning-related agents in lung cancer etiology, we estimated lung cancer risk among cleaning-related occupations by the duration in years spent in such occupations. In Study 1 ever having held one of our five most prevalent cleaning-related occupations was not significantly associated with lung cancer risk. There were no discernible dose-response trends related to duration of employment in these jobs and lung cancer risk. Results were similar in Study 2 except a suggestive increase in lung cancer

risk associated with ever having been employed as Labourers, Services for a period of 10 years or more.

6.1.6 Comparison with previous studies

There have been few studies that have investigated the association between occupational exposures to cleaning-related agents and the risk of lung cancer. A summary of the literature has been presented earlier in the Literature Review Section 2.7 of this thesis. Briefly, most previous studies used job-titles as a proxy for exposure to cleaning agents and employed a case-control design;[96-102] the results of which have supported an increased risk of lung cancer among cleaners, building care takers, charworkers, hairdressers and barders, and waitresses, bartenders and related work. Among the two studies that focussed on exposure to specific cleaning-related agents, one retrospective cohort study among workers in three automobile manufacturing plants in Michigan, USA, revealed a decreased risk of lung cancer risk associated with exposure to synthetic MWF which may contain biocides[127], while no association between cleaning-related agents and lung cancer risk was found in a Montreal case-control study (Study 2) conducted only among women.[103] One of the limitations of the previous studies was the use of self-reported exposures of the past that might have contributed to recall/information bias. The studies also likely suffer from the presence of various confounders that were not controlled for including: socioeconomic factors, diet, air pollution, differences in ethnicity and genetic background. Simlarly, though smoking status was usually controlled for in the analysis, the parameterization of smoking was often rudimentary and could lead to residual confouding. Moreover, even though studies have indicated that different histological types of lung cancer have different etiologies,[23-26] these studies did not assess the associations between the cleaning-related agents in relation to lung cancer histological types, resulting in further gaps in knowledge.

In this present work, globally, there was very little indication that occupational exposure to cleaning-related agents was associated with lung cancer risk in either study which is relatively consistent with the limited literature on this topic. In our job title-based analysis, generally, there was no discernible dose-response trend related to duration of employment in cleaning-related jobs and lung cancer risk except a suggestive increased risk observed in Study 2 for Labourers. However, it is difficult to discern whether this association is related to exposure to cleaning-related agents as Labourers may be exposed to a variety of different occupational agents.

Though there were some suggestive associations in Studies 1 and 2 that the cleaning-related agents-lung cancer risk association may be modified by smoking intensity (i.e., Study 1 results for caustic soda) and asthma status (Study 2 results for aliphatic alcohols), we cannot rule out the possibility of a chance finding. Globally, the null associations observed between cleaning-related agents and lung cancer risk overall did not differ by histological type. To date, no study has examined whether occupational exposure to cleaning-related agents and lung cancer risk differ by smoking intensity, asthma status and histological type of lung cancer. Consequently, limiting the comparison of our results to the literature.

6.2 Methodological considerations

Some biases, limitations and strengths associated with this study are discussed in the next sections.

6.2.1 Impact of over 20 years cleaning-related agents-lung cancer data

The data for this study is over 20 years old and cleaning products are constantly changing in composition in response to ecological, economic and consumer demands.[78] For example, recent consumer demands have led to the development of "green products" as they are marketed as less hazardous and more environmentally sustainable, as compared to synthetic cleaners.[128] Thus, cleaning products used two decades ago may not be the same ones being used today. This is a potential limitation of our study; nevertheless, findings from this present work may be still useful as studies associating occupational exposures to cleaning-related agents and lung cancer risk are scarce and exposure to cleaning-related agents in the workplace is widespread. We encourage the pursuit of further studies on occupational exposures to cleaning products particularly in comparing the application of "green cleaning products" vs "non-green cleaning products" to better evaluate whether their exposure contributes to lung cancer risk.

6.2.2 Selection bias

Selection bias in case control studies arises when the study population does not represent the true distribution of exposure status for cases and controls in the source population.[129] In this research, the following response rates were observed in Study 1 (79% for cases and 72% for population controls) and Study 2 (86% for cases and 69% for controls); among cases, responses

rates are relatively high but notably lower among controls. Thus, it is possible that participating controls do not reflect the exposure distribution among the source population in which the cases arose, therefore, as in most case-control studies, it is difficult to rule out the possibility of selection bias.

6.2.3 Selection and pooling of control groups – Study 1

The choice of a control group is a primary challenge in the design of case-control studies. Controls should be representatives of persons, who, if they had become ill with the disease under study should have been included in the study as cases. At the same time, we want to ensure the collection of data of equivalent quality from our controls as from our cases.[130] [11] For this thesis, contrasts in occupational exposures were made between lung cancer cases and two control groups in Study 1: population controls and cancer controls. While a population control group may be more representative of the source population, cancer controls are often less susceptible to non-participation and information bias.[11] However, one cannot affirm that one control group is necessarily better than the other as each type of control group has its own advantages and disadvantages.[131] Generally in Study 1, results from contrasts of lung cancer cases versus population and cancer controls were fairly homogeneous and thus, the controls were pooled to increase sample size and power.

6.2.4 Information bias

In this study, using case-control data on occupational exposures collected retrospectively, the quality of the data depends largely on the ability of the subject to remember past exposures accurately. This raises the concern whether information provided on exposures to cleaning-related agents differed between cases and controls. In this thesis, the implications of measurement error are considered separately from the moment of interview and expert assessment of occupational exposure. At the time of interview, it is true the cases may have over reported information if they wished to attribute their disease to occupational exposures to what they perceived as hazardous chemicals used in their cleaning duties. Controls, on the other hand, may not have recalled important information to the same extent as cases. This difference in recall might have introduced recall bias and thus, a bias of the true estimates of the association between occupational exposures to cleaning-related agents and lung cancer risk. However, it is important to note that the

interviewers were trained, and thus, this might have mitigated recall bias, to an extent in that the interviewers sought to elicit the same quality of information from both cases and controls. Moreover, the information provided by the subjects during the interview was then reviewed by experts, comprising a team of chemists and industrial hygienists, who assigned occupational exposures to many substances including cleaning agents, biocides, aliphatic alcohols, ammonia, caustic soda, and waxes and polishes. These experts were blinded to the disease status of the subject and thus, any imprecision (misclassification) in assigning exposure would have been random among cases and controls, resulting in non-differential misclassification. Studies have shown that this expert-based assessment is reliable[132, 133] and valid.[134] Nevertheless, the exposure assessment protocol was based on expert opinion (a semi-quantitative measurement) rather than direct quantitative measurements. This imprecision would most likely lead to the attenuation of risk estimates towards the null value.

6.2.5 Proxy respondents

There was a significant disparity in the proportion of proxy respondents used for cases than controls, which might have introduced information error and even bias if proxy respondents systematically over or under-estimated occupational exposures. Given the different distribution in the use of proxy respondents among cases and controls, this might have contributed to differential misclassification of exposures. However, the respondent status was included in the *a priori* statistical model as a covariate to adjust for this potential misclassification.

6.2.6 Interaction and mediation effects

For this thesis, secondary analyses were performed to examine whether smoking intensity modified the association between the occupational exposures to cleaning-related agents and lung cancer risk. It would have been more appropriate to explore interaction by smoking among never-smokers versus smokers. However, as the number of non-smokers among lung cancer cases was very low, we had to combine never-smokers with low-intensity smokers to ensure adequate statistical power. The pooling of low-intensity smokers and never-smokers might have introduced misclassification, reducing the ability of our study to detect an interaction if it truly exists.

Effect modification by asthma status was performed for Studies 1 and 2 using the multivariate logistic regression models on the association between occupational exposures to the cleaning-related agents and lung cancer risks. Studies have shown that asthma, characterized by chronic inflammation of the lungs, may predispose individuals to lung cancer and thus, we hypothesized that the cleaning-agents-lung cancer association could differ among those with and without asthma.[18-20] Indeed, in Study 2, those occupationally exposed to aliphatic alcohols and who have ever had asthma experienced a four-fold increase in lung cancer risk in comparison to a null association observed among those who have never had asthma. However, the opposite trend was observed in the ammonia-lung cancer risk association when stratified by asthma status, though this interaction was of borderline statistical significance.

Asthma could also lie in the causal pathway between occupational exposure to cleaning-related agents and lung cancer development, and act as a mediator. Conventionally, mediation analyses are performed by regressing the outcome on the exposure with and without the mediator(s).[135 136] The unadjusted estimate is referred to as the total effect of the exposure on the outcome. The effect of the exposure that is explained by a given set of mediators is known as the indirect effect and the effect of the exposure unexplained by those same mediators is known as the direct effect. Thus, the indirect effect is the difference between the total effect and the direct effect. In this thesis, no mediation analysis was conducted as we did not have information on the timing of the asthma diagnosis. Thus, in addition to the possibility of a chance finding, we were unable to clearly tease out the role of asthma status on the associations between cleaning related-agents and lung cancer risk

6.2.7 Confounding

Confounding can be thought as a mixing of the effects of the exposure being studied with the effects of other factors (confounders) on risk of the health outcome of interest. If not adequately controlled in the study design or analysis, a confounder may bias the exposure-disease association, making it either closer to or farther from the null than the true effect. Confounding may even reverse the apparent direction of an effect in extreme situations.[129]

Our confounders selection approach consisted of considering the following:

(1) Adjusting for six *a priori* confounders including smoking (measured by the CSI) age, ethnicity, income, education, and respondent status.

(2) Considering three additional potential confounders namely: (i) residential fire-cooking after 20 years of age (ii) residential fire-heating after 20 years of age and (iii) total duration of occupational exposures to asbestos, diesel exhaust, silica, cadmium, chromium, and nickel.

To assess the impact of the three additional confounders on the association between occupational exposures to cleaning agents and biocides and lung cancer, a CIE procedure was performed and a threshold of 10% was used to define a meaningful change. None of the three confounders were retained based on this cut-off point and only the six *a priori* confounders were selected and included in models for adjustments.

Residual confounding occurs when distortion remains even after controlling for confounders during the design and/or analysis of a study, resulting in an imperfect adjustment.[137] For this thesis, even though the six *a priori* confounders including smoking were adjusted for using multivariate logistic regression models, there remains the possibility of residual confounding by cigarette smoking (being the strongest risk factor for lung cancer).[121] The investigation of the association between cleaning-related agents and lung cancer risk among never smokers would remove the confounding effects of smoking. In our smoking-stratified analysis, we attempted to examine our main associations of interest within strata of smoking intensity. However, given the limited number of never smokers among our lung cancer cases, we had to re-group never smokers with low intensity smokers; this limited our ability to assess the associations of interest while restricting to never smokers.

6.2.8 External validity

Internal validity refers to the extent to which the observed results represent the truth in the population we are studying and, thus, are not due to methodological errors. [138] External validity is the extent to which the results of one population can be generalized or extrapolated to others. [139, 140] Once the internal validity of the study is established, the researcher can proceed to make a judgment regarding its external validity by asking whether the study results apply to similar patients in a different setting or not.[138] In this study, the main systematic errors namely, selection bias, information bias and confounding and their impact on the internal validity of our study were discussed above.

It is quite difficult to compare the results of the previous studies that examined occupational exposures to cleaning-related agents and lung cancer risk to the present investigation due to differences in exposure assessment, covariates used, sample size, among others. For example, the

majority of former studies employed job-title based assessment, while our study employed expert-based approach for exposure assessment. In addition, the previous studies reported increased risks of lung cancer associated with occupational exposures to cleaning-related substances whereas in this present research, no increased risk was observed between occupational exposures to cleaning-related agents and lung cancer. Due to the inconsistent results for the occupational exposures to cleaning-related agents and lung cancer risk, more studies are warranted to support the findings of this current research.

It was found in this study that cleaning-related agents are not associated with the risk of lung cancer. The study used occupational exposure data from two population-based case-control studies conducted among men in Montreal area, in the province of Quebec, Canada, where exposure assessment was performed by the local experts in Montreal. As the present research employed data from one geographic location i.e., the Montreal work environment, expert assessment of occupational exposures, among others, the conclusions drawn from it cannot be generalized to other populations (men and women) that might have different work environment, exposure assessment, etc. (other than that of this present study carried out in Montreal, Quebec). Therefore, external validity for this research could be established if the results are replicated in different populations, places, and time periods [141, 142], among men and women.

7 CONCLUSION

The use of cleaning-related substances is widespread in the occupational setting and in the general population. Few studies have examined the association between the exposures to cleaning-related agents and the risk of lung cancer. Most of these studies were based on job titles that indicated that workers in such occupations incurred excess lung cancer risk. These studies, however, have limitations including residual confounding by smoking.

This present study investigated the associations between occupational exposures to cleaning agents, biocides and other cleaning-related agents, and the risk of lung cancer among men. Overall, the results of this study do not support the hypothesis that occupational exposure to cleaning agents, biocides, and other cleaning-related agents play a role in lung cancer etiology. Expert assessment of occupational exposures was used in this study which greatly improved upon the previous estimates of lung cancer risk by job titles only. Nevertheless, future studies should explore prospective exposure assessment strategies that better quantifies level and duration of exposure while adjusting for established risk factors for lung cancer.

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APPENDICES

Appendix A. Ethics approval of Studies 1 and 2

Figure A1.1. Ethics approval letter for the case-control study of occupational risk factors for lung cancer

McGill | Faculty of Medicine and Health Sciences | Faculté de médecine et des sciences de la santé

3655 Sir William Osler #633, Montreal, Quebec H3G 1Y6 | 3655, Promenade Sir William Osler #633, Montréal (Québec) H3G 1Y6 | Tél/Tel: (514) 398-3124

December 15, 2020

Dr. Jack Siemiatycki
CHUM - Pavillon S
850, rue St-Denis, Bureau S03-448
Montreal (Québec) H2X 0A9

RE: IRB Study Number A12-E06-99
Case-Control Study of Occupational Risk Factors for Lung Cancer

Dear Dr. Siemiatycki,

Thank you for submitting an application for Continuing Ethics Review for the above-referenced study.

The study progress report underwent review, and full Board re-approval was provided on December 14, 2020. The ethics certification renewal is valid from **December 7, 2020 to December 6, 2021.**

The Investigator is reminded of the requirement to report all IRB approved protocol and consent form modifications to the Research Ethics Offices (REOs) for the participating study sites, when applicable. Please contact the individual research ethics offices for instructions on how to proceed. Research funds may be withheld, and/or the study's data may be revoked for failing to comply with this requirement.

Please promptly notify the IRB office of any study modifications or unanticipated events that may occur to the study prior to the next annual renewal. Study modifications cannot be implemented prior to an ethics review and approval by the Board.

Regards,

[redacted]

Roberta M. Palmour, PhD
Chair
Institutional Review Board

cc: Natasha Graham
SMH-REB
A12-E06-99A

Appendix B. Questionnaire for data collection

Figure B1.1. Excerpt of questionnaire used for janitors to obtain cleaning-related information

Mat: _____ Job: ____ Family Name: _____ Given Name: _____

JANITORS

1. What type of building(s) or vehicle(s) were you working in?

Office buildings	θ	Dry cleaners	θ
Apartment buildings	θ	Freight cars	θ
Department stores	θ	Other vehicles	θ
Hospitals	θ	Laboratory	θ
Hotel	θ	Subway	θ
Industrial plant	θ		

→ **If Yes:** What type of plant was it? _____

Did you clean the office area? Yes θ No θ

Did you clean the plant area? Yes θ No θ

Did you clean any other area?
(specify: e.g., warehouse, stockroom) _____

Garage/service station θ

→ **If Yes:** specify (ex. general or specialized - radiators, mufflers, brakes)

_____

Other type of building or area (specify) _____

2.

a) Which of the following materials did you use?			During how many weeks of the year did you use them?	For how many hours per week?
Soap (bar, flake, liquid, granular)	No θ	Yes θ	_____	_____
Abrasive cleaner - e.g., ajax (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Detergents (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Oven cleaner (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Carpet shampoo (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Glass cleaner - e.g., windex (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Caustic (lye)	No θ	Yes θ	_____	_____

Janitors page 1

2. continued

Which of the following materials did you use?			During how many weeks of the year did you use them?	For how many hours per week?
Toilet cleaner (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Liquid drain opener (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Granular drain opener (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Ammonia (powder, solution)	No θ	Yes θ	_____	_____
Wax stripper (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Javex, javel water	No θ	Yes θ	_____	_____
Deodorants (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Hydrochloric acid (muriatic acid)	No θ	Yes θ	_____	_____
Disinfectants (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Insecticides (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Furniture polish (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Metal polish - e.g., chrome, brass, silver (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Waxes (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Petroleum solvents (specify trade names, if possible) _____	No θ	Yes θ	_____	_____
Carbon tetrachloride	No θ	Yes θ	_____	_____

Appendix C. Confounder assessment

Table C1.1. Crude ORs between the *a priori* covariates and lung cancer, and change in estimate for cleaning agents and biocides exposures associated with lung cancer in Study 1

Covariate	Crude OR (95% CI) for lung cancer	P-value		OR for cleaning agents	Change in estimate for cleaning agents	P-value		OR for biocides	Change in estimate for biocides	P-value
Age	1.0 (1.0 - 1.0)	0.5093		0.868	0.0%	0.3216		0.847	0.0%	0.3476
CSI	3.6 (3.0-4.2)	< 0.0001		0.811	6.6%	0.1902		0.946	-11.7%	0.785
Income	0.8 (0.7-0.9)	0.0002		0.814	6.2%	0.1548		0.810	4.4%	0.2374
Education	0.6 (0.5-0.7)	< 0.0001		0.736	15.2%	0.0375		0.757	10.6%	0.1237
Ethnicity	0.9 (0.8-1.0)	0.0342		0.876	-0.9%	0.3557		0.839	0.9%	0.3198
Respondent	2.9 (2.2 - 3.9)	< 0.0001		0.892	-2.8%	0.4339		0.881	-4.0%	0.4791
			Cleaning agents OR				**Biocides OR**			
			0.868				**0.847**			

Table C1.2. Crude ORs between the *a priori* covariates and lung cancer, and change in estimate for cleaning agents and biocides exposures associated with lung cancer in Study 2

Covariate	Crude OR (95% CI) for lung cancer	P-value		OR for cleaning agents	Change in estimate for cleaning agents	P-value		OR for biocides	Change in estimate for biocides	P-value
Age	1.0 (1.0-1.0)	0.0311		0.920	-0.1%	0.4189		0.773	0.3%	0.0312
CSI	3.4 (2.9-3.9)	<0.0001		0.858	6.6%	0.1885		0.749	3.4%	0.0311
Income	0.8 (0.7-0.9)	0.0004		0.881	4.1%	0.2212		0.740	4.5%	0.0123
Education	0.7 (0.7-0.8)	<0.0001		0.808	12.1%	0.0457		0.721	7.0%	0.0068
Ethnicity	0.7 (0.6-0.8)	<0.0001		0.939	-2.2%	0.5439		0.746	3.7%	0.0152
Respondent	6.0 (4.6-7.9)	<0.0001		1.050	-14.3%	0.6573		0.903	-16.5%	0.4164
			Cleaning agents				**Biocides**			
			OR				**OR**			
			0.919				**0.775**			

Table C1.3. Change-in-estimate approach for cleaning agents and biocides exposures associated with lung cancer in Study 1

Cleaning agents								Biocides							
Model 1 Variables	**Model 1 OR**	**Model 2 variables**	**Model 2 OR**	**Model 3 variables**	**Model 3 OR**	**Model 4 variables**	**Model 4 OR**	**Model 1 variables**	**Model 1 OR**	**Model 2 variables**	**Model 2 OR**	**Model 3 variables**	**Model 3 OR**	**Model 4 variables**	**Model 4 OR**
Age		Age		Age		Age		Age		Age		Age		Age	
Income		Income		Income		Income		Income		Income		Income		Income	
Education		Education		Education		Education		Education		Education		Education		Education	
Respondent		Respondent		Respondent		Respondent		Respondent		Respondent		Respondent		Respondent	
Ethnicity		Ethnicity		Ethnicity		Ethnicity		Ethnicity		Ethnicity		Ethnicity		Ethnicity	
CSI		CSI		CSI		CSI		CSI		CSI		CSI		CSI	
		Asbs+Dies + § Silc+Cadm+ Chrm+Nick		**Fire-cook**		**Fire-heat**				**Asbs+Dies +§ Silc+Cadm+ Chrm+Nick**		**Fire-cook**		**Fire-heat**	
Cleaning Agents	**0.737**	Cleaning agents	**0.742**	Cleaning agents	**0.756**	Cleaning Agents	**0.752**	Biocides	**0.926**	Biocides	**0.915**	Biocides	**0.938**	Biocides	**0.937**
% change			-0.7%		-2.6%		-2.0%	**% change**			1.2%		-1.3%		-1.2%

§ Asbs = Asbestos ; Dies = Diesel enginie exhaust; Silc = Silicon; Cadm = Cadmium; Chrm = Chromium; Nick = Nickel.

Table C1.4. Change-in-estimate approach for cleaning agents and biocides exposures associated with lung cancer in Study 2

Cleaning agents								Biocides							
Model 1 Variables	**Model 1 OR**	**Model 2 variables**	**Model 2 OR**	**Model 3 Variables**	**Model 3 OR**	**Model 4 variables**	**Model 4 OR**	**Model 1 variables**	**Model 1 OR**	**Model 2 variables**	**Model 2 OR**	**Model 3 variables**	**Model 3 OR**	**Model 4 variables**	**Model 4 OR**
Age		Age		Age		Age		Age		Age		Age		Age	
Income		Income		Income		Income		Income		Income		Income		Income	
Education		Education		Education		Education		Education		Education		Education		Education	
Respondent		Respondent		Respondent		Respondent		Respondent		Respondent		Respondent		Respondent	
Ethnicity		Ethnicity		Ethnicity		Ethnicity		Ethnicity		Ethnicity		Ethnicity		Ethnicity	
CSI		CSI		CSI		CSI		CSI		CSI		CSI		CSI	
		Asbs+Dies + § Silc+Cadm+ Chrm+Nick		**Fire-cook**		**Fire-heat**				**Asbs+Dies +§ Silc+Cadm+ Chrm+Nick**		**Fire-cook**		**Fire-heat**	
Cleaning Agents	**0.946**	Cleaning agents	**0.950**	Cleaning Agents	**0.948**	Cleaning Agents	**0.972**	Biocides	**0.804**	Biocides	**0.803**	Biocides	**0.806**	Biocides	**0.835**
% change			-0.4%		-0.2%		-2.7%	**% change**			0.1%		-0.2%		-3.9.%

§ Asbs = Asbestos ; **Dies** = Diesel enginie exhaust; **Silc** = Silicon; **Cadm** = Cadmium; **Chrm** = Chromium; **Nick** = Nickel.