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Occupational Risk Factors for Pancreatic Cancer in Montreal

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RÉSUMÉ

Problématique. L'étiologie du cancer pancréatique est encore peu caractérisée, notamment quant au rôle des expositions environnementales modifiables. L'objectif de cette étude est d'examiner si les expositions chimiques dans les milieux de travail sont des facteurs de risques pour ce cancer le plus souvent mortel.

Méthodes. Une étude cas-témoin populationnelle à Montréal incluant 19 types de cancer a été réalisée entre 1979 et 1985. Pour chaque participant, un historique de travail détaillé a été obtenu ainsi que des données sur des variables sociodémographiques et des habitudes de vie. Les antécédents de travail ont été examinés par des chimistes et hygiénistes de travail afin de déterminer le statut d'exposition de chaque participant pour environ 300 substances d'intérêt. Pour ce rapport, les 116 cas participants de cancer pancréatique ont été comparés avec les autres cas de cancers et des témoins populationnelles. Des analyses préliminaires ont été effectuées pour repérer les substances qui démontraient des indices d'association avec le cancer du pancréas. Celles-ci, en plus des substances qui sont réputées être associées avec le cancer du pancréas dans la littérature, ont été retenues pour des analyses statistiques plus approfondies. Pour chaque substance, deux catégories d'exposition ont été établies : « exposé » et « substantiellement exposé ». Les ratios de cotes entre le cancer pancréatique et chaque substance ont été estimés par régression logistique tout en contrôlant pour des facteurs de confusion possibles. Des analyses semblables ont été réalisées pour des catégories industrielles et occupationnelles.

Résultats. Parmi toutes les expositions étudiées, la majorité d'entre eux n'ont pas démontré une association avec le cancer du pancréas. Cependant, des associations positives ont été repérées pour quelques substances, notamment pour les produits de combustion du charbon (RC 2,6, IC 95 % [1,3-5,3]), la suie (RC 3,4, IC 95 % [1,3-8,6]), les cires et agents de polissage (RC 2,7, 95 % [1,1-4,1]), les produits de nettoyage (RC 1,9, IC 95 % [1,1-3,2]) et pour la catégorie des concierges et nettoyeurs (RC 2,8, IC 95 % [1,5-5,1]).

Conclusion. Malgré que plusieurs des associations observées dans cette étude ne sont pas suffisamment appuyées directement par la littérature existante, nos résultats représentent une ressource utile pour diriger les futurs projets de recherche et notamment pour les éventuelles méta-analyses.

Mots-clés : Cancer du pancréas, facteurs de risques, travail, étude cas-témoin, épidémiologie

ABSTRACT

Background. Pancreatic cancer is a fatal disease in most cases. Unfortunately, little is known about the etiology of pancreatic cancer and whether modifiable environmental chemical exposures may play an important role. The purpose of this study is to explore whether chemical exposures in the workplace may be risk factors for pancreatic cancer.

Methods. A population-based case-control study including 19 types of cancer was conducted in Montreal between 1979 and 1985. Detailed occupational histories were obtained from all subjects as well as information on several socio-demographic and lifestyle variables. Occupational histories were assessed by industrial hygienists and chemists to determine whether exposure had occurred to any of nearly 300 substances from a checklist. For this report, the participating 116 pancreatic cancer cases were compared with other cancer controls and population controls. Preliminary analyses were conducted to identify agents from the checklist showing evidence of an association with pancreatic cancer. These were selected for more in-depth statistical analyses together with agents reported in the literature as being potentially associated with pancreatic cancer. For each agent, "any" and "substantial" exposure metrics were defined. Unconditional logistic regression methods were used to estimate odds ratios between pancreatic cancer and each of the selected exposures while controlling for potential confounders. Similar analyses were conducted for occupation and industry groups.

Results. Of all the exposures assessed, the majority did not reveal an association with pancreatic cancer. However, suggestive positive associations were found for several agents including coal combustion products (OR 2.6, 95% CI [1.3-5.3]), soot (OR 3.4, 95% [1.3-8.6]), waxes and polishes (OR 2.7, 95% [1.1-4.1]), cleaning agents (OR 1.9, 95% [1.1-3.2]) and for the occupational category "janitors and cleaners" (OR 2.8, 95% CI [1.5-5.1]).

Conclusion. For most of the agents revealing an association with pancreatic cancer in our study, there is a paucity of direct evidence published by other authors to corroborate our findings. However, parallels can be made with previously observed excesses in occupational groups making our findings useful for guiding future research efforts, notably for meta-analyses, to uncover the specific chemical exposures that may account for these excesses.

Keywords: Pancreatic cancer, risk factors, occupation, case-control study, epidemiology

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CHC: Chlorinated hydrocarbons

CI: Confidence interval

DDT: Dichlorodiphenyltrichloroethane

HPV: Human papilloma virus

IARC: International Agency of Research on Cancer

MRR: Meta-risk ratio

NSAIDS: Non-steroidal anti-inflammatory drugs

OR: Odds ratio

PAH: Polycyclic aromatic hydrocarbons

PCB: Polychlorinated biphenyl

RR: Relative risk

SMR: Standardized mortality ratio

US: United States

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1. INTRODUCTION

A diagnosis of pancreatic cancer is a devastating one. The 5-year survival for this cancer is only 8%, one of the lowest of all types of cancer (1). Such a low survival is in large part due to the advanced stage of disease when clinical symptoms typically manifest. In fact, fewer than 10% of pancreatic malignancies are at a localized stage of disease at the time of diagnosis (2). Thus, only a small proportion of cases are eligible for surgical resection which is the only treatment option currently offering the possibility of a definitive cure.

Fortunately, pancreatic cancer is relatively rare accounting for approximately 2.5% of new cancer cases per year in Canada (1). Incidence rates for pancreatic cancer vary by sex, race and geographic distribution. Men have slightly higher rates than women, blacks have two-to threefold higher rates than whites (3) and, internationally, the annual age-adjusted incidence rates range from 4.3 (Granada, Spain) to 14.7 (USA, Missouri, blacks) per 100,000 males and 2.7 (Catanzaro, Italy) to 13.0 (USA, Nebraska, blacks) per 100,000 females (4). In Canada, the overall incidence of pancreatic cancer was 9.3 per 100,000 in 2015 and it has been stable in recent years (1).

Because pancreatic cancer is a disease with low incidence and of short duration owing to its high case fatality, the prevalence of this cancer in the population is low rendering screening efforts ineffective. Moreover, at the present time, there is no screening test reasonably capable of detecting the presence of a tumour or precursor lesion in the pancreas (2). Therefore, given the unlikely prospect of large scale screening to detect early stage pancreatic cancer, and given the fact that primary prevention of cancer is always preferable to treatment no matter the

likelihood of its success, the main hope in reducing the burden of pancreatic cancer is to identify modifiable risk factors leading to prevention.

Pancreatic carcinogenesis, as for other types of cancer, is believed to follow a multi-stage process of tumour initiation, promotion and progression involving an accumulation of genetic mutations and epigenetic changes which can be inherited and/or acquired (i.e. induced by exposure to exogenous toxins and chemicals) (5). The BRCA2 gene mutation is one example of an inherited factor. This mutation is well known for having an association with hereditary breast and ovarian cancers, but it is also associated with an up to 10 fold increased relative risk of pancreatic cancer (5). Several other germline mutations related to hereditary cancer syndromes (e.g. Peutz-Jeghers and Multiple Endocrine Neoplasia type 1) have also been linked to significantly increased risks of pancreatic cancer (5). Not including these syndromes, a family history of pancreatic cancer, in general, is associated with an approximate twofold increased risk (6). However, recognized inherited risk factors only account for an estimated 10% of pancreatic cancer cases (5). Thus, it is reasonable to explore the extent to which modifiable environmental and lifestyle factors may play an important role for this cancer.

The discussion that follows presents a review of the recent literature on the risk factors for pancreatic cancer with an emphasis on those related to work environments. To retrieve articles on this topic, a search of the PubMed and Web of Science databases was carried out using the search strategy outlined in figure 1 (appendix 1). This search yielded a total of 123 relevant articles.

2. LITERATURE REVIEW

2.1 NON-OCCUPATIONAL RISK FACTORS

A recently published comprehensive review of pooled studies and meta-analyses examining risk factors for pancreatic cancer provided a good summary of several non-occupational exposures and their associations with this malignancy (6). In this article, Maisonneuve and colleagues reviewed the evidence from 86 meta-analyses and 31 pooled studies and calculated a summary risk estimate for each type of exposure which they classified as low (RR 1.0-1.4), moderate (RR 1.5-1.9) or high (RR ≥ 2.0). They also rated the quality of the evidence for each risk factor as poor, moderate or strong[1]. This publication served as the main reference for the following discussion which aims to summarize the current knowledge of non-occupational pancreatic cancer risk factors. An overview of these factors categorized by the direction and magnitude of the association and the quality of the supporting evidence is presented in table 1 (see Appendix 2).

2.1.1 Tobacco and alcohol

Tobacco smoking is the most firmly established modifiable risk factor for pancreatic cancer based on the consistent replication of research findings. The presence of a dose-response

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[1] The authors defined "strong" evidence as based on more than one meta-analysis and confirmed in cohort studies or pooled studies; "moderate" evidence as based on either more than one meta-analysis or a single meta-analysis of cohort studies; and "poor" as evidence based on a single meta-analysis that was not exclusively based on cohort studies or if the results were discordant.

relationship has also been observed. Indeed, Maisonneuve and colleagues concluded that smoking is a moderate risk factor for pancreatic cancer based on strong evidence. Summary risk estimates for smoking related to pancreatic cancer range between 1.2 for former smokers and light smokers to 3.0 for heavier smokers (6). Among former smokers, the elevated risk appears to return to baseline after approximately 20 years of smoking cessation (3, 7). Tobacco specific nitrosamines, in particular 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N′-nitrosonornicotine (NNN), are the putative pancreatic carcinogens in tobacco smoke. These compounds have been shown to induce pancreatic tumours in animal models and are classified as definite (group 1) human carcinogens by the International Agency for Research on Cancer (IARC) (8). As with most smoking-derived carcinogens, these compounds are also present in environmental tobacco smoke, albeit in different concentrations (8). However, there are too few sufficiently powered studies on the association between environmental tobacco smoke and pancreatic cancer to draw any inferences about this potential risk factor as the present time (6). For alcohol, Maisonneuve et al. found that moderate to heavy consumption (i.e. >30 g of alcohol or >3 standard drinks per day) is a moderate risk factor for pancreatic cancer based on strong evidence.

The evidence supporting cigarette smoking and alcohol consumption as risk factors for pancreatic cancer is important not only from a preventative perspective, but also because it demonstrates the "proof of principle" that extrinsic chemical exposures are involved in the pathogenesis of pancreatic cancer. It thereby adds to the relevance of investigating the possible role of other extrinsic chemical agents in pancreatic cancer etiology.

2.1.2 Coffee and tea

Concern over a possible link between coffee consumption and pancreatic cancer was first raised in 1981 following the publication of a hospital-based case-control study conducted by McMahon and colleagues (9). This study was subsequently found to be flawed because of an important selection bias. Based on numerous studies published since, Maisonneuve et al. concluded that there is no discernable association between coffee or tea consumption and pancreatic cancer. In support of this, a recent prospective study involving 4 155 256 person-years of follow-up over which 1541 incident cases of pancreatic cancer occurred, did not find an association between coffee intake and the occurrence of pancreatic cancer: HR 1.01, 95% CI [0.80-1.27] for 4-5 cups of coffee per day and HR 1.26, 95% CI [0.94-1.69] for 6 or more cups per day (10).

2.1.3 Diet

Dietary factors can exert either a protective or causal role in the development of cancer. Consequently, nutrition is an area of keen interest in cancer research, especially for cancers of the gastrointestinal tract which includes the pancreas. A diet high in sugar may be pro carcinogenic through complex metabolic and hormonal pathways involving hyperinsulinemia and its downstream effects on cellular regulation (11). Although the evidence is rather thin, studies looking at sugar intake seem to indicate a slight increased risk of pancreatic cancer for those with an elevated intake (6). In contrast, studies examining soft drink consumption and

glycemic index generally indicate a lack of association for which the evidence base is strong to moderate (6).

A high consumption of red and processed meat has been consistently linked with an increased risk of colorectal cancer, possibly through exposure to heterocyclic amines, polycyclic aromatic hydrocarbons, heme iron or bovine infectious factors (12). For pancreatic cancer, there is only poor evidence of a low-level risk from these dietary exposures based on the studies reviewed by Maisonneuve and colleagues. A more recently published study of the National Institutes of Health-American Association of Retired Persons (NIH-AARP) diet and health cohort reported significant but small positive associations for intakes of red meat (HR 1.22, 95% CI [1.01-1.48], p-trend = 0.02) and heme iron from red meat (Q4 vs. Q1: HR 1.21, 95% CI [1.01-1.45], p-trend = 0.04) (13). Regarding protective factors, there is poor to moderate evidence that high intakes of vegetables, fruits and folate is associated with a slightly decreased risk of pancreatic cancer (6). The flavonoid class of bioactive compounds present in various foods and beverages (for example berries, citrus fruits and teas) have been shown to exert anti-carcinogenic effects for the pancreas in *in vitro* and *in vivo* studies (14). However, epidemiological studies have not yet convincingly corroborated this association (14). Finally, a relationship between fish or vitamin D intake and the occurrence of pancreatic cancer has not been demonstrated (6).

2.1.4   Body habitus and physical activity

Obesity is characterized by hormonal and metabolic dysregulations and a pro-inflammatory state which are the main proposed pathophysiological changes explaining the increased

incidence of certain cancers in overweight and obese individuals (15). Regarding pancreatic cancer, Maisonneuve and colleagues found strong evidence of a low-grade risk increase with higher BMI and a higher waist-to-hip ratio. A recent umbrella review of systematic reviews and meta-analyses also concluded that there was strong evidence to support an association between BMI and pancreatic cancer (16). Considering this, exercise may be expected to exert a protective effect for pancreatic cancer by opposing overweight and obesity. The relationship between physical activity and pancreatic cancer was summarized in a meta-analysis of 30 studies by Behrens and colleagues (17). In this study, the authors calculated several summary risk estimates for different intensities and timing in life of physical activity. Although most risk estimates were nonsignificant or only weakly inversely associated with pancreatic cancer, consistent physical activity over the life course appeared to confer a reduction in risk: meta-risk ratio (MRR) 0.86 (95% CI: 0.76-0.97) for cohort studies and 0.74 (95% CI: 0.61-0.90) for case-control studies.

2.1.5   Medical history

In the past, the observed relationship between diabetes and pancreatic cancer was clouded by the issue of reverse causality because pancreatic neoplasms destroy islet cells thereby impairing the normal production of insulin. However, it is now fairly clear based on strong evidence that long-standing diabetes is associated with a moderately increased risk of pancreatic cancer (6). In addition, chronic pancreatitis, independently of alcohol consumption, increases the risk of developing a malignant tumour in the pancreas by 6 to 12 fold (6, 18). This observation is unsurprising given that many other cancers arise in chronically inflamed tissues. In fact, a causal link between inflammation and cancer is generally accepted (19). Consistent with this, chronic

infection with *Helicobacter pylori* and hepatitis B virus emerged as moderate risk factors for pancreatic cancer in the review by Maisonneuve and colleagues based on moderate and strong evidence respectively. However, for infection with hepatitis C virus, the evidence is poor. With regards to medications, fortunately the use of common medications, including NSAIDS and statins do not appear to be associated with the development of pancreatic cancers. Long-term use (> 5 years) of aspirin may in fact be protective based on a pooled analysis of eight randomized controlled trials (summary RR 0.25, 95% CI [0.07-0.92]) (20). Finally, a history of allergies appears to confer a low level of protection against pancreatic cancer.

2.1.6 *Environmental exposures*

Besides individual level risk factors, environmental exposures may also play a role as a causal component for pancreatic cancers as suggested by the disparities in incidence rates between different countries and geographic regions. For example, incidence rates tend to be lower near the equator compared to regions situated at the antipodes (3). The reasons for these variations remain largely unexplained. Some studies conducted in the general population have examined levels of trace elements in biological specimens and exposure to pesticides and the risk of pancreatic cancer (see Table 2, Appendix 3). Further evidence regarding possible associations between exposure to these trace elements and to pesticides and pancreatic cancer can be derived from occupational studies which are discussed in more detail in sections 2.2.3 *Metals* and 2.2.5 *Pesticides* of this review.

2.2   OCCUPATIONAL RISK FACTORS

For carcinogenesis to occur, the sustained presence or repeated exposure to a carcinogenic agent is often required. Therefore exposures to different substances in the workplace are important to consider in cancer research because of the dose, frequency and chronology of exposure. Workers, especially in industrial environments, are exposed to various chemicals at much higher doses than the general population and this exposure occurs often daily and over long periods of time.

Another reason to be concerned about occupation-related cancers is that they are mostly preventable through the application of workplace safety measures and regulations intended to protect against hazardous exposures. Moreover, whereas most cases of some malignancies can be accounted for by a single or very few etiological factors (e.g. smoking and lung cancer or HPV and cervical cancer), others, including pancreatic cancer, appear to be more multifactorial in nature. Over 30 substances present in work environments have been identified as carcinogens (21) and it has been estimated that 6% of incident cancer cases in the province of Quebec could be attributed to exposure to these substances (22). For pancreatic cancer, some authors have claimed that approximately 10% of cases could result from workplace exposures (23).

In the next sections of this literature review, the principal suspected occupational risk factors for pancreatic cancer will be presented by substance or substance category. Associations with specific occupations or industries are discussed in the most relevant substance section. The review is based on a synthesis of occupational studies of pancreatic cancer published since 1998 as well as three meta-analyses published by Ojajärvi and colleagues covering most of such

studies published prior to this date and going back to 1969. For expediency, the measures of effect are not stated in the text, but can be found in table 3 (see Appendix 4) where the main characteristics of all reviewed studies are summarized. Occasionally, effect estimates from studies not included in the table but referenced in the text are specified.

2.2.1 Biological agents

It has been hypothesized that poultry oncogenic viruses, which are capable of infecting human cells *in vitro*, may play a role in causing cancer in humans (24). Several occupational epidemiologic studies of pancreatic cancer have addressed this hypothesis by estimating the risk of disease among workers in close contact with poultry. While one such study found no excess mortality from pancreatic cancer in one cohort of workers performing the slaughtering of chickens (24), the same task in a second study was significantly associated with the occurrence of pancreatic neoplasms in a different cohort of workers (25).

2.2.2 Dusts

Given the strong association between asbestos and lung cancer, several studies have considered this substance as a potential etiologic agent for other cancer sites including the pancreas. One meta-analysis based on 24 populations did not find an increased risk of this disease with exposure to asbestos (26). In contrast, two hospital-based case-control studies published more

recently have reported significantly increased odds of pancreatic cancer with asbestos exposure (27, 28).

Studies of pancreatic cancer referring to exposure to silica and other dusts are more limited. In a meta-analysis published by Ojajärvi and colleagues there was no indication of an increased risk for exposure to silica dust, man-made vitreous fibres (e.g. fibreglass), wood dust or flour dust (26). More recently however, an increased standardized mortality ratio (SMR) among men was detected in a cohort study of German porcelain workers potentially exposed to crystalline silica (29).

2.2.3   Metals

Several metal elements have been studied with respect to pancreatic cancer risk including cadmium, chromium, lead and nickel. Cadmium is of considerable interest because it has been recognized as a human lung carcinogen (30) and because there is mechanistic data to support the biological plausibility of this element as a pancreatic carcinogen (31). For example, in *in vitro* studies, chronic exposure of human pancreatic ductal epithelial cells to cadmium induced the acquisition of tumour cell characteristics (32). The meta-analysis findings of occupational studies by Ojajärvi et al. found an excess risk only for nickel (26). However, it was later determined that two studies of nickel and pancreatic cancer with null findings were not included in the analysis (23). Subsequent studies have suggested an increased risk for occupational exposures to chromium and lead (33, 34) and non-occupational studies conducted in the general population have reported significant positive associations for exposure to arsenic, lead and

cadmium (see Table 2, Appendix 3) (31, 35-37). Although pancreatic cancer risk was not increased among those occupationally exposed to cadmium in a population-based case-control study in South Louisiana, the risk increased among occupations exposed to metal fumes (plumbers, pipe fitters and welders) in the same study (38). Ji et al. also found an increased risk among plumbers and welders (39). Other metal-related jobs (40), and, more specifically, work in metal plating (41) and in the printing industry (39, 42) have also been linked to higher risks of pancreatic cancer. However, exposures in these occupations are multiple including to polycyclic aromatic hydrocarbons and to chlorinated hydrocarbon compounds (23).

2.2.4   *Polycyclic aromatic hydrocarbons*

Polycyclic aromatic hydrocarbons (PAHs) comprise a large group of organic compounds formed by the combustion of organic matter and found in soot, carbon black, coal tar and pitch, bitumen, asphalt and mineral oils (43). Experimentally, they are well-established carcinogens and several have been classified by IARC as definite, probable or possible human carcinogens (44, 45). For pancreatic cancer, there is some evidence from epidemiologic studies that occupational exposure to PAHs presents an increased risk. These studies have mostly examined occupation and industry groups with significant exposure to PAHs including the aluminum production and asphalt industries and those exposed to diesel exhaust (e.g. motor vehicle drivers and railroad workers). Workers in the aluminum production industry have been well studied and several different cohort studies conducted in Norway, Italy and Canada have pointed to an increased risk of pancreatic cancer incidence and mortality in this group (46-50), with some providing evidence of an exposure-response gradient (46, 47). However, these results should be

evaluated cautiously given that these workers were exposed to a variety of other agents in aluminum reduction potrooms including alumina, carbon oxides, carbon dusts, fluorides, metals and electromagnetic fields (51).

With exposure to bitumen increased mortality from pancreatic cancer was found in a cohort of Finnish Road pavers (52). In addition, two record-linkage studies in Sweden found excess risks of pancreatic cancer among "drivers," although only among women drivers (40, 53), while a case-control study in Iowa revealed that male railroad workers had an elevated risk of this cancer (54). Finally, the meta-analysis by Ojajärvi et al. reported nonsignificant excess risks of pancreatic cancer for exposure to PAHs but no excess was found for diesel exhaust (26). In agreement with this, a recent systematic review of the epidemiologic data on exposure to diesel exhaust and risk of pancreatic cancer revealed an overall lack of association in the literature (55).

2.2.5   *Pesticides*

"Pesticide" is an umbrella term referring to hundreds of different chemical compounds that are used to repel pests which pose a threat to human health or to agricultural crops. Pesticides may be classified by the type of pest that they target. For example, "herbicides" are designed for weeds, "insecticides" for insects and "fungicides" for fungi. Several epidemiological studies have investigated whether exposure to these families of pesticides or to pesticides in general is linked to the occurrence of pancreatic cancer. The findings of some of these studies support the existence of an association between occupational pesticide use and risk of pancreatic cancer.

For example, two studies conducted in the US [one case cohort (56) and one case control (57)] reported increased risks for exposure to any type of pesticide in the highest exposures categories with one study showing a trend for increased odds of pancreatic cancer with increasing levels of exposure (57). In addition, two hospital-based case control studies, one in Spain (58) and one in Egypt (59) reported increased odds of pancreatic cancer for any exposure to pesticides. Finally, a more recent hospital-based case-control study in the US found self-reported pesticide use to be associated with increased odds of pancreatic cancer (28). Conversely, other studies have provided evidence against an association between pesticide use and risk of pancreatic cancer. Most notably, the meta-analysis conducted by Ojajärvi et al. found no association for herbicides, fungicides or insecticides (26). Additionally, two case-control studies, one hospital-based (27) and one population-based (60) found no increased risk for exposure to any pesticide.

Such inconsistent findings may partly be explained by the heterogeneity of exposures in these studies because they considered broad groups of pesticides encompassing substances of distinct chemical composition. One study which examined specific pesticides individually found increased odds of pancreatic cancer among high users of pendimethalin and ethyl-dipropylthiocarbamate (EPTC) (61). In the US Agricultural Health Study Cohort, a non-significant excess risk for exposure to the herbicide acetochlor was detected (62). Other studies have focused on chemical classes of pesticides such as organochlorines which includes the well-known pesticide DDT (63-65). A review of these studies observed that while earlier reports indicated the existence of a strong relationship between organochlorine pesticide exposure and pancreatic cancer, more recent studies have described weaker associations, possibly because exposure to these types of pesticides has decreased since their banning in many countries (22).

Evidence of pancreatic cancer risk from pesticide exposure may also be gathered from studies focused on farming occupations. In two mortality studies of farmers conducted in the United States, increased proportionate mortality was found in one study among male farmers over 65 years of age (66) and in the other among livestock farmers but not among crop farmers (67). In addition, a hospital-based case-control study in Egypt reported that farming was associated with an increased odds of pancreatic cancer (37). On the other hand, the meta-analysis by Ojajärvi and colleagues did not detect this risk among farmers (MRR 0.88, 95% CI [0.77-1.01]) (41).

2.2.6 Physical agents

Ionizing radiation consists of higher frequency electromagnetic waves capable of damaging mammalian cells and tissues at the molecular level, including to DNA, ultimately leading to tumorigenesis. Exposure to ionizing radiation has been shown to cause cancer in humans at many different sites (68). None of the large occupational cohort studies of exposure to ionizing radiation has demonstrated significant positive associations for cancers of the pancreas (69-72) with the exception of a subgroup analysis of males in one of the Canadian cohorts (69). A couple of non-occupational studies reviewed by IARC reported excess risks although one of these was based on a very small number of cases (68).

The association between lower frequency electromagnetic waves or non-ionization radiation and cancer is more ambiguous. Although there is some evidence from epidemiologic studies to suggest a link between exposure to radio frequency radiation and certain cancers (glioma and acoustic neuromas), the possible mechanisms whereby electromagnetic waves may cause cancer

are at present unclear (73). For pancreatic cancer in occupational settings, a meta-analysis of five studies did not find an excess risk (26), while one case-control study and one cohort study published after this analysis suggested elevated risks among workers exposed at higher intensities (33, 39).

2.2.7 Solvents

Chlorinated hydrocarbons

Chlorinated hydrocarbons (CHC) are a class of organic solvents omnipresent in many industrial settings because they have properties which make them useful agents for cleaning, degreasing and in extraction processes. Many of these compounds have been classified as group 2A (probably carcinogenic to humans) or 2B (possibly carcinogenic to humans) by IARC (44). Because of their widespread use, the carcinogenic risk to humans has been the subject of numerous studies. Three meta-analyses by Ojajärvi et al. consolidated the available epidemiological data from 1969 to 1998 on the relationship between CHC compounds and pancreatic cancer (26, 41, 74). In the first published meta-analysis, they reported that CHC compounds were associated with a slight increased risk based on 20 populations (26). Two subsequent publications from hospital-based case control studies in Spain and in the United States reported increased odds of pancreatic cancer with exposure to CHC solvents (27). In the Spanish study, the magnitude of the association was even greater when the analysis was restricted to cases of ductal adenocarcinoma (the most common histologic subtype) compared to all subtypes combined.

In the second meta-study by Ojajärvi et al., they considered the risk associated with individual CHC solvents and found small but nonsignificant excesses for trichloroethylene, tetrachloroethylene, methylene chloride, vinyl chloride, carbon tetrachloride and polychlorinated biphenyls (PCBs) (74). Another meta-analysis published by a different group also found no increased risk of pancreatic cancer in relation to occupational exposure to methylene chloride (75). In the last published meta-analysis by Ojajärvi et al., they estimated the risk of pancreatic cancer for different occupations using job-title data and found excess risks for laundry/dry cleaners and metal-plating workers (41), two occupations in which CHC solvents are heavily used. Other studies conducted in the dry-cleaning industry are consistent with the findings by agent. In a cohort of dry cleaners in the United States, excess mortality was detected for those workers exposed to tetrachloroethylene plus other dry-cleaning solvents but not for those exposed to tetrachloroethylene alone (76). Similarly, a case cohort in four European countries found no excess risk for dry cleaners exposed mostly to tetrachloroethylene (77), and a review of the epidemiologic literature on occupational exposure to tetrachloroethylene concluded that an association with cancer of the pancreas was unlikely (78).

Formaldehyde

Formaldehyde is a gaseous substance used in the manufacture of wood, plastic and textile products. It is also used in aqueous solution as a disinfectant and tissue preservative. The latest monograph on formaldehyde published by IARC classified this compound as a group 1 (definite) carcinogen based on sufficient evidence for nasopharyngeal cancer in humans (79). With respect to pancreatic cancer, one meta-analysis found a slight increased risk for

occupational exposure to formaldehyde which was mainly accounted for by excesses among embalmers and pathologists/anatomists, whereas the association did not attain statistical significance among industrial workers (80). Because the latter group are exposed to significantly greater peak and average doses of formaldehyde than embalmers and pathologists/anatomists, the authors surmised that the observed excess risk was likely the result of confounding or diagnostic bias. Consistent with the absence of an association between occupational exposure to formaldehyde and cancer of the pancreas, risk estimates not different than unity were reported in the meta-analysis by Ojajärvi et al. (26) and in several cohort studies of industrial workers exposed to formaldehyde (79, 81, 82). Moreover, if we consider biological plausibility, formaldehyde would be an improbable pancreatic carcinogen as laboratory experiments have shown the rapid degradation of this substance in the respiratory tract of animals (79). As a result, it is unlikely to be absorbed and distributed in the organism to exert toxic effects on the pancreas and other downstream organs.

Styrene

Styrene is an organic solvent used in the manufacture of various polymers including plastics, rubbers and resins. Styrene and its principal metabolite in humans (styrene-7, 8 oxide) are classified respectively as possible and probable human carcinogens by IARC (83). Several cohorts of industrial workers exposed to styrene in the United States and in Europe have been followed to study cancer mortality. Based on a review of these studies (83) and more recently published updates of the cohorts (84-86), there does not appear to be an association between exposure to styrene and mortality from pancreatic cancer.

Metalworking fluids

Metalworking fluids are a highly heterogeneous group of fluids used, as the name would suggest, in metalworking processes to lubricate, clean and cool metal parts. A range of formulations exist with some containing mineral oils (derived from crude petroleum), which are themselves diverse mixtures. Such substances are very difficult to study from a cancer epidemiology perspective and, unsurprisingly, some studies indicate a link between exposure to metalworking fluids and pancreatic cancer (87-89) while others do not (87, 90-93). Even within studies where significant positive associations were revealed, inconsistencies were apparent such as lack of dose-response associations, associations only among white men or only among black men (87, 88).

2.2.8 Other work-related factors

Apart from exposure to different biological, chemical and physical elements in the workplace, other factors pertaining to work life have been investigated as potential causes of cancer. In particular, physical activity related to work and exposure to light at night as would occur during night work or shift work are areas of increasing interest in occupational cancer research. The participants who are the focus of the study presented in this report have already been the subject of analyses in both of these areas. In the first, Parent et al. found no association between higher lifelong occupational physical activity level and pancreatic cancer (94). However, in the meta-analysis by Maisonneuve and colleagues, intense occupational physical activity appeared to reduce the risk of pancreatic cancer (OR 0.75, 95% CI [0.58-0.96]) (6). In addition, a more

recent meta-analysis by Behrens et al. found a slight inverse association for occupational physical activity among cohort studies but not among case-control studies (17).

The sleep hormone, melatonin, is purported to have oncostatic effects. In theory then, the disruption of the circadian rhythm and of regular melatonin secretion resulting from sleep interruption could ostensibly promote the development of cancer. Parent et al. found a significantly positive association between a history of night work and the occurrence of pancreatic cancer (95). The only other retrieved study that addressed this question found no such association (96).

2.3   METHODOLOGICAL LIMITATIONS OF REVIEWED STUDIES

The principal methodological limitation in occupational cancer research relates to the difficulties of accurately ascertaining exposures retrospectively. For reasons of practicality and cost-saving, few studies measure individual-level exposures in absolute concentration terms. Exposures are usually inferred based on job title or industry/occupation categories, sometimes using a job-exposure matrix[2]. In some cases, investigators rely on evaluations conducted by experts in industrial hygiene who can translate occupational histories into possible exposures. This method is considered one of the more valid approaches of assessing workplace exposures (97). More often though, the sources of exposure information are administrative in nature, extracted from death certificates or cancer registries. These types of data often contain information on most recent job or industry titles but lack detailed occupational exposure information and information on potential confounders. Where pancreatic cancer is concerned, proxy sources of information are also frequently used because of the rapidly fatal nature of this disease and case ascertainment may not be well-timed. When sufficient occupational information is collected, estimations of exposure doses can be inferred from the duration of employment and/or from details on the workers performed tasks. Finally the variety of exposures, both within a job and between workers with the same job title, is an added complication when inferring exposures in occupational environments.

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[2] Job-exposure matrices are constructed by listing jobs on one axis and exposures on the other axis. The cells of the matrix indicate whether exposure to a specific substance occurs in the corresponding job and may also indicate measures of probability, frequency and/or intensity of exposure.

The difficulty of both obtaining reliable data on specific past exposures and the complex exposure patterns in occupational settings can induce the misclassification of exposures. Such misclassification occurs most likely randomly and thus non-differentially between diseased and healthy groups, resulting in an attenuation of the relative risk of disease. Similarly, misclassification of pancreatic cancer cases may occur at a higher rate because case ascertainment often relies on data from death certificates rather than on more accurate sources such as medical or pathology records. Again, this leads to bias most likely toward the null value thus attenuating the estimated relative risk of the exposure under study.

Another limitation affecting studies of occupation and pancreatic cancer is the under adjustment for confounding factors. This occurs for two main reasons. First, few such factors (i.e. risk factors for pancreatic cancer) are scientifically well established and, second, industrial cohorts do not habitually collect information on even those that are well-known, such as smoking. Moreover, given that exposures in industrial environments are often multiple and complex and cannot all be reasonably measured and adjusted for, unmeasured confounding is a clear possibility.

2.4   SUMMARY AND RESEARCH OBJECTIVE

Epidemiological studies conducted in recent decades have helped to clarify some of the modifiable risk factors for pancreatic cancer. Most of the identified risk and protective factors relate to diet, lifestyle and medical history (summarized in table 1, Appendix 2). In addition to tobacco smoking, which has long been the only recognized risk factor for cancer of the pancreas, there is now much more evidence to support a causal relationship between this cancer and obesity, diabetes, heavy alcohol consumption, chronic pancreatitis and chronic infection with hepatitis B. The main identified occupational risk factor is exposure to chlorinated hydrocarbon compounds and possibly exposure to PAHs and employment in the aluminum production industry. However, as demonstrated in table 4 (page 25), for most of the investigated workplace exposures the findings are too inconsistent to draw any definitive conclusions. Such inconsistency is probably due to the combination of the statistical imprecision resulting from small studies and the small number of studies that have been conducted on occupational risk factors for pancreatic cancer.

In the 1980s, a large population-based case control study was conducted in Montreal, Canada (the Montreal Multisite cancer study) with the purpose of identifying occupational risk factors for many different types of cancer using a set of methods intended to allow more accurate and valid inferences to be made. The study's design included rapid ascertainment of nearly all incident cancer cases among males ages 35 to 70 in the catchment area and period, with diagnosis based on pathology and occupational exposures attributed case by case by a team of experts. The study population was restricted to men because at the time of the study (and even today) the industrial workforce and therefore most occupational studies were male dominated.

Cases in younger and older age groups were excluded because it was reasoned that these cases were more likely to be associated with genetic and age-related factors.

The present analysis of the Montreal Multisite cancer study will focus on the series of pancreatic cancer cases with the main objective of identifying which, among the most common industrial exposures in Montreal at the time of the study, are associated with an increased risk of disease. A secondary objective is to assess the relationship between pancreatic cancer in the Montreal Multisite cancer study and the non-occupational risk factors suggested by the literature.

Table IV. Summary of the associations between occupational exposures and pancreatic cancer.

Direction of the association	Evidence level	Exposures	
		Agents	**Occupations or industries**
Positive (risk factor)	Satisfactory	CHC solvents	Aluminum production industry
	Weak	PAHs	
No association	Satisfactory	Flour dust Glass dust Wood dust Formaldehyde Styrene	
Negative (protective factor)	Satisfactory	Occupational physical activity	
Inconclusive [1]	N/A	Asbestos Arsenic Benzene Bitumen Cadmium Chromium Diesel exhaust Dyes/inks Electromagnetic fields Ionizing radiation Lead Metal-working fluids Nickel Pesticides Poultry/poultry viruses Silica	Asphalt industry Construction work Drivers Farming Hairdressers/barbers Laundry/dry cleaning Leather tanning Machinery/electrical workers Metal work/Metal-plating Painting Pipefitting/plumbing/welding Printing industry Pulp and paper industry Radiological technicians Railroad workers Rubber industry Sedentary work

CHC, chlorinated hydrocarbon; PAHs, polycyclic aromatic hydrocarbons
[1] This category includes those exposures for which there are conflicting and/or insufficient evidence.

3. METHODS

The design and data collection methods of the Montreal Multisite cancer study have been extensively described elsewhere (98). In summary, males between the ages of 35 and 70 with a new diagnosis of cancer among 19 possible types during the period of 1979 to 1985 were recruited from the largest hospitals in Montreal. To be eligible, participants had to be residents of the Montreal Metropolitan area with a histologically confirmed diagnosis of a cancer type included in the study. Case ascertainment was accomplished through reporting by designated personnel in the pathology department of each hospital. To encourage reporting, a small stipend was paid to informants for each notified case. A member of the research staff also carried out regular checks of all pathology reports to pick up omitted cases. Eligible cases were first contacted by mail or in person if in hospital. They received an information package containing a letter describing the study and an initial self-administered questionnaire. Subsequently, attempts were made to obtain in-person interviews with participants (82%), but in some cases interviews were conducted by telephone (10%) or using a self-administered questionnaire (8%). Of the total number of eligible cancer cases (4576), exposure information was collected for 3730 (82%), either directly from the participant in over 82%, or from a proxy informant for the remainder. At the time of the study, the 20 largest hospitals in the region of Montreal reported approximately 97% of all cancer diagnoses in the area to the Quebec Tumour Registry and all but one of the smaller hospitals participated in the study. Thus nearly all cases of cancer occurring in the base population were likely captured during the Montreal Multisite cancer study term. For each patient, the cancer diagnosis was classified by topography and morphology in accordance with the 9th revision of the International Classification of Diseases (WHO, 1977).

3.1   Exposure assessment

Determination of exposure status in this study was completed by expert assessment. Specifically, trained interviewers collected detailed information on every participant's job history including but not limited to tasks performed, products and personal protective equipment used and characteristics of the company and work site for each job held over their lifetime. Based on the information obtained in these occupational histories, a group of technical experts comprised of industrial chemists, hygienists and engineers derived a list of potential exposures for each subject using a checklist of 294 different agents. These agents were chosen because they represented the most common workplace exposures in Montreal at the time. For each attributed exposure, the expert coders evaluated three aspects: their degree of confidence that the exposure had occurred (possible, probable or definite); the frequency of exposure during a normal work week (<5%, 5–30% or >30%); and the likely concentration of the substance in the work environment (low, medium or high). In addition, each job for each subject was coded per occupation and industry groups defined in the *Canadian Classification and Dictionary of Occupations 1971* (Department of Manpower and Immigration, 1974) and the *Standard Industrial Classification Manual* (Dominion Bureau of Statistics, 1970) respectively. In a second part of the participant interviews, a structured questionnaire was administered to collect information on several non-occupational variables or possible confounders, including sociodemographic characteristics (e.g. ethnic group, residence, income, education), lifestyle practices (e.g. smoking, alcohol use, hobbies) and past medical history.

3.2   *Pancreatic cancer case series*

To identify newly diagnosed cases of pancreatic cancer, a system of rapid case ascertainment through hospital pathology departments was used in conjunction with subsequent cross-checking of patients' medical charts and tumour registries. A total of 164 cases of pancreatic cancer were ascertained during the study period and information was obtained regarding 116 participating cases, corresponding to a 71% response rate.

3.3   *Control series*

Two different control groups were available for the analysis of risk factors for pancreatic cancer; a population control group and a cancer control group. Population controls, frequency-matched to the case group for age, were selected from the general male population in Montreal over the study period by either random digit dialling or the use of electoral lists. The latter sampling strategy was initially used, however, two years into the study issues arose with contacting controls who had since moved because electoral lists were only updated about every four years. The method of sampling controls was therefore changed to random digit dialling for the year 1983. Because this strategy proved to be quite costly, it was abandoned for the final leg of the study and the initial strategy was readopted after electoral lists were updated in 1984. Overall, a total of 533 population control subjects (375 from electoral lists) were successfully interviewed corresponding to a 72% response rate.

The cancer-control group was formed from a subset of other cancer cases participating in the study excluding those of lung origin (n = 851) to guard against residual confounding related to smoking; and of gallbladder (n = 30), liver (n = 47) and peritoneal (n = 6) origins as they represent anatomically and perhaps etiologically related sites. In addition, no single cancer site was permitted to make up more than 20% of the control group. The cancer control group totalling 2448 cases was constituted as follows: bladder (478), colon (237), esophageal (97), Hodgkin's lymphoma (54), kidney (174), non-Hodgkin's lymphoma (213), melanoma (120), multiple myeloma (23), penile (10), prostate (437), recto sigmoid (154), rectal (127), sarcoma (16), small bowel (20), gastric (247), testicular (25) and other cancers (8). A pooled control group was also formed by combining the population and cancer control groups and by equally weighting these two sets. All analyses were performed with the two original control groups and with the pooled control group.

3.4 *Occupational circumstances selected for analysis*

This report presents an in-depth analysis of the association between pancreatic cancer and a subset of the 469 occupational circumstances (i.e. 294 agents, 98 occupations and 77 industries) explored in the original study (98). A complete listing of these exposures can be consulted in appendices 5-7. The subset of exposures evaluated in the analysis presented here was determined by using two approaches: 1) by selecting those exposures reported as potential risk factors for pancreatic cancer in the literature (*a priori* exposures); and 2) by performing a screen of the data to flag possible risk factors (data-driven exposures).

Three agents and one industry were selected based on a comprehensive review of the literature presented in section 2.2 and summarized in table 4 (page 25). The *a priori* agents are chlorinated alkanes, chlorinated alkenes and PAHs from any source. Although exposure information was available for several individual chlorinated hydrocarbon compounds in our dataset, there were too few exposed pancreatic cancer cases to permit analysis of these agents separately. The *a priori* selected industry is "Non-ferrous metal smelting and refining" which includes the primary production of aluminum and of other non-ferrous metals (*Standard Industrial Classification Manual*, Dominion Bureau of Statistics, 1970). The "Aluminum, copper and other alloys industries" category did not contain any exposed cases and was therefore excluded.

To constitute a list of data-driven exposures, screening analyses were carried out in which an occupational circumstance was selected for more advanced study if exposure was associated with the outcome of interest with an OR of at least 1.3 and a two-sided probability value less than 0.1 when compared to at least one of the two control groups in at least one of the exposure categories (any or substantial). In addition, the screening analyses were carried out only for those exposures with at least 5 exposed cases for agents and 10 exposed cases for occupations and industries. By applying these criteria, 16 agents, 2 industries and 2 occupations were identified. An organized and complete listing of the exposures selected for analysis is shown in table 5 (page 33) and their definitions can be found in appendix 8.

3.5   Statistical analysis

Unconditional logistic regression methods were used to estimate odds ratios between pancreatic cancer and selected non-occupational variables in addition to each of the selected occupational exposures while controlling for potential confounders. Odds ratios for each agent were calculated for two exposure levels ("any" and "substantial") for each control group. Those considered substantially exposed were participants whom the technical experts were confident had been exposed (confidence levels "probable" or "definite") and who had accumulated more than 5 years of exposure at a medium or high concentration and frequency (see table 6, page 34 for exposure group classifications). Those whose exposure was merely possible (versus probable or definite) or occurred only recently (i.e. less than five years before the interview) were categorized as "uncertain exposure" and were not included in the present analyses [3]. Occupation and industry groupings were similarly analyzed comparing those never employed to those ever employed, employed for less than 10 years and employed for 10 years or more.

In the screening analyses, the following non-occupational covariates designated *a priori* were included in the regression models: age (continuous), ethnic group (French/other), self-reported income (continuous), years of education (continuous), composite scores for alcohol and cigarette consumption (continuous) and proxy status (binary). Age was included as a covariate to control for any residual confounding. For the analyses by agent, selected exposures were subsequently examined in regression models further adjusted for mutual confounding by other workplace exposures. These confounders were identified among the list of selected agents using the change in estimate method (99). An agent was retained as a confounding variable if it changed the estimated disease-exposure odds ratio of the agent under analysis by more than

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[3] The proportion of subjects with "uncertain" exposures were fewer than 1% for the control groups and ranged from less than 1% to 3.5% for the pancreatic cancer case group.

10%[4] when inserted into the models for both control groups. Sets of occupational confounders were established separately for each agent.

All statistical analyses were run using IBM SPSS Statistics version 24.0.

Ethics approval was obtained for the original Multisite cancer study from each participating hospital. For this sub-analysis, approval was obtained from the ethics board of the Université de Montréal.

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[4] Confounding determined if $|(OR_{adjusted} - OR_{unadjusted})/OR_{unadjusted}| + 1 > 1.10$

Table V. Occupational circumstances [a] selected for analysis of an association with pancreatic cancer, Montreal Multisite cancer study (1979–1985).

Selected from the literature (*a priori* exposures)

AGENTS

    Chlorinated alkanes

    Chlorinated alkenes

    PAHs from any source

INDUSTRIES

    Metal smelting and refining

Selected from the screening analyses (data-driven exposures)

AGENTS

Antimony	Cleaning agents
Brass dust	Hypochlorites
Nickel	Javel water
Tin fumes	Coal combustion products
Fluorides	Soot
Hydrogen fluoride	Plastic dust
Nitric acid	Synthetic adhesives
Sulfuric acid	Waxes/polishes

INDUSTRIES

    Railway transport

    Education and related services

OCCUPATIONS

    Other service occupations

    Janitors charworkers and cleaners

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[a] Exposure definitions are listed in appendix 8.

Table VI. Classification of exposure groups based on different indices of exposure, Montreal Multisite cancer study (1979–1985).

Exposure group	Confidence level	Time since first exposure (years)	Frequency x Concentration[a]	Duration of exposure (years)
Unexposed	Never exposed			
Uncertain	Any	≤ 5	Any	Any
Uncertain	Possible	Any	Any	Any
Any exposure	Probable or definite	> 5	Any	Any
Substantial exposure [b]	Probable or definite	> 5	≥ 4	> 5

[a] Frequency and concentration were scored as follows: 1=low, 2=medium and 3= high.
[b] The "substantial" exposure group is a subset of the "any" exposure group.

4. RESULTS

Table 7 (page 40) shows the distribution of several socio-demographic and other non-occupational variables of interest among the pancreatic cancer cases and control groups. These groups were similar in terms of mean age (due to frequency matching on this variable) and income. Compared to population controls, a smaller proportion of cancer cases (both pancreatic and cancer controls) were of French ethnicity. When compared to both control groups, pancreatic cancer cases tended to have accumulated slightly fewer years of education and were more likely to have ever smoked and to be heavy drinkers. Pancreatic cancer cases also had a more significant history of smoking than controls. Unsurprisingly, there were far more proxy respondents in the case group because of the rapidly fatal progression of pancreatic cancer. Although a greater proportion of cases reported a history of diabetes, it was not possible to distinguish those diagnoses which could have been caused by the underlying pancreatic malignancy. While there was no difference in the proportion of self-reported hepatitis among groups, pancreatic cancer cases were less afflicted by certain allergic diseases than the other cancer cases and population controls.

4.1 Non-occupational variables

We investigated the relationship of selected non-occupational variables with pancreatic cancer in univariate and multivariate logistic regression models; the odds ratios are shown in table 8 (page 41). A higher level of education was significantly associated with an estimated 30% decreased risk of pancreatic cancer compared to both control groups even after accounting for

potential confounders. Compared to population controls, being an ever smoker (OR 1.3, 95% CI [0.6-2.6]) or heavy drinker (OR 1.3, 95% CI [0.7-2.3]) was associated with a small excess risk of pancreatic cancer once adjusted for confounding. No association was apparent between premorbid BMI or history of hepatitis and the cancer outcome in this study. For atopic diseases estimated odds ratios ranged from 0.4 to 0.9 but these did not attain statistical significance.

4.2   Agents

All analyses of agents and pancreatic cancer risk were performed with the population and cancer control group and with the pooled and weighted set of controls. Because the results using the pooled group were very similar to those using cancer controls, only the results obtained using the two original control groups are presented here.

Three agents were selected for analysis based on prior evidence and 16 were identified from the screening analyses performed for the 294 different agents (complete list in appendix 5). The lifetime exposure prevalence to these selected 19 agents for the subjects in the pancreatic case-control series is shown in table 9 (page 42). The other 275 agents were dropped from the analysis either because they had too few exposed subjects or because the results were not distinguishable from the null.

Table 10 (page 45) shows that the following 15 occupational exposures were significantly associated with pancreatic cancer risk based on the estimates obtained in regression models adjusted for non-occupational covariates using the cancer control group comparison: antimony, brass dust, nickel, tin fumes, fluorides, hydrogen fluoride, nitric acid, sulfuric acid, cleaning

products, hypochlorites, javel water, coal combustion products, soot, synthetic adhesives and waxes/polishes. Two of these agents (nitric acid and waxes/polishes) showed significant associations in both ever exposed and substantially exposed workers, while exposure to sulfuric acid, cleaning products, soot and synthetic adhesives demonstrated significant positive associations only in the substantially exposed group.

For the population control group comparison, estimated odds ratios for the studied substances were generally comparable in magnitude or slightly lower than those estimated using the cancer controls. However, most of these excesses did not achieve statistical significance apart from any exposure to antimony, nitric acid and hypochlorites, and substantial exposure to waxes/polishes.

Among those agents selected on the basis of prior knowledge (i.e. chlorinated alkanes, chlorinated alkenes and PAHs) only chlorinated alkanes demonstrated weak evidence of excess risk of pancreatic cancer in the group with substantial exposure for the cancer control comparison (OR 1.6, 95% CI [0.7-3.7]).

Table 11 (page 46) shows the estimated odds ratios obtained for the 19 selected agents when other occupational covariates were included in the regression models. Overall, inclusion of these additional covariates tended to attenuate risk estimates and resulted in a loss of statistical significance. Only waxes/polishes (OR 3.6, 95% CI [1.1-12.0] retained its significantly positive result in the substantially exposed group.

4.3   Occupations and industries

As for the agents, the results presented here are for the two original control groups because those obtained with pooled controls approximated the results from the cancer control comparison.

One industry group was selected for analysis based on existing evidence in the literature and two groups were selected each from the occupation and industry categories as data-driven exposures. The lifetime exposure prevalence to these 5 occupations/industries for the subjects in the pancreatic case-control series is shown in table 12 (page 47). The complete list of industries and occupations that were available for analysis can be consulted in appendices 6 and 7. Many of these categories contained few exposed cases excluding them from the analysis based on the previously established minimal criteria for empirically identifying possible associations. For most of the industry and occupation categories with sufficiently exposed cases (at least 10), the odds ratios were not significantly different from the null value.

Table 13 (page 48) lists the industries and occupations which showed suggestive associations with the cancer outcome in this study in at least one of the multivariate analyses. Among the different industries, only "Railway transport" was associated with a statistically significant increased risk of pancreatic cancer in ever-employed workers and those employed for 10 or more years. Results from both control groups were consistent in this finding. A second industry group, "Education and related services," was associated with a non-significant elevated risk in most analyses except for those employed for less than 10 years in the cancer control comparison where the result was statistically significant. Among the various occupation groups, the general category "Other service occupations" revealed a statistically significant increased risk of pancreatic cancer among those ever employed (OR 2.1, 95% CI [1.2-3.7]) and also in those

employed for 10 years or more (OR 2.6, 95% CI [1.2-5.4]), which could be entirely accounted for by the excess among the subgroup of "Janitors and cleaners." This excess risk was also evident using population controls although it did not reach statistical significance.

Regarding the industry selected because of a demonstrated suggestive association in the literature (i.e. metal smelting and refining), two to threefold excess risks were found across the board with the exception of the group employed less than 10 years in the cancer control comparison.

Table VII. Distribution of selected non-occupational characteristics among pancreatic cancer cases and controls in the Montreal Multisite cancer study (1979–1985).

Characteristic	Pancreatic cancer cases (*n* = 116)	Cancer controls (*n* = 2448)	Population controls (*n* = 533)
Age, in years [mean (SD)] [a]	59.1 (7.6)	58.7 (8.4)	59.6 (7.9)
Ethnicity (%)			
French	57.8	58.2	64.2
Other	42.2	41.8	35.8
Income index [b]	1.15	1.14	1.19
Education, in years [mean (SD)]	8.8 (4.1)	9.8 (4.5)	10.1 (4.6)
Respondent status (%)			
Self	49.1	82.5	87.4
Proxy	50.9	17.5	12.6
Smoking history (%)			
Never	12.1	16.3	19.7
Ever	87.9	83.7	80.3
Smoking index, in pack-years [c] [mean (SD)]	50 (38)	44 (38)	40 (35)
Alcohol index, in drink-years [d] (%)			
<120	71.6	74.9	82.9
≥ 120	28.4	25.1	17.1
BMI, in kg/m^3 (%)			
<25	38.0	36.6	33.2
25–29	48.9	49.9	51.7
≥ 30	13.0	13.5	15.1
History of diabetes [e] (%)	12.9	7.8	7.9
History of hepatitis [e] (%)	3.4	3.6	3.4
History of atopic [e] disease (%)			
Asthma	1.7	4.2	5.1
Eczema	2.6	3.3	4.3
Both asthma & eczema	0	0.3	1.1

[a] Population controls were frequency matched for age to the cancer case group.
[b] The income index is based on the median household income in the census tract in which the subject lived, using data from the federal census of 1986. Rather than reporting the absolute dollar amount as it was at the time, we create an index by dividing the subject's census tract value by the average in all of Quebec at the time.
[c] Pack-years = (average daily number of cigarettes/20 cigarettes per pack) x number of years of smoking.
[d] Drink-years = average daily number of drinks x number of years of drinking.
[e] Self-reported medical history.

Table VIII. Odds ratios for the association between pancreatic cancer and selected non-occupational characteristics in the Montreal Multisite cancer study (1979–1985).

Characteristic	Cancer controls		Population controls	
	OR_1 (95% CI)[a]	OR_2 (95% CI)[b]	OR_1 (95% CI)	OR_2 (95% CI)
Ethnicity				
French	Ref	Ref	Ref	Ref
Other	1.0 (0.7-1.5)	1.1 (0.7-1.7)	1.3 (0.9-2.0)	1.6 (1.0-2.7)
Income, in CAD$				
<25 000	Ref	Ref	Ref	Ref
> 25 000	1.1 (0.8-1.6)	1.3 (0.8-2.0)	0.8 (0.5-1.1)	0.9 (0.5-1.5)
Education, per 5 years	**0.8 (0.6-1.0)**	**0.7 (0.5-0.9)**	**0.7 (0.6-0.9)**	**0.7 (0.5-1.0)**
Smoking history				
Never	Ref	Ref	Ref	Ref
Ever	1.4 (0.8-2.5)	1.2 (0.6-2.3)	1.8 (1.0-3.3)	1.3 (0.6-2.6)
Smoking index, per 20 pack-years [c]	1.1 (1.0-1.2)	1.0 (0.9-1.2)	1.2 (1.0-1.3)	1.1 (1.0-1.3)
Alcohol use, drink-years [d]				
<120	Ref	Ref	Ref	Ref
≥ 120	1.2 (0.8-1.8)	1.0 (0.6-1.7)	**1.9 (1.2-3.1)**	1.3 (0.7-2.3)
BMI, per 5 kg/m^3	0.9 (0.7-1.3)	1.0 (0.8-1.4)	1.0 (0.8-1.4)	0.9 (0.6-1.3)
History of hepatitis [e]	1.1 (0.4-3.0)	1.2 (0.4-3.4)	1.2 (0.4-3.7)	1.1 (0.3-3.8)
History of atopic [e] disease				
Asthma	0.5 (0.1-1.9)	0.4 (0.1-1.8)	0.4 (0.1-1.6)	0.5 (0.1-2.4)
Eczema	0.9 (0.3-2.8)	0.9 (0.3-3.0)	0.7 (0.2-2.4)	0.5 (0.1-2.0)

[a] Odds ratios and 95% confidence intervals obtained in univariate logistic regression models.
[b] Odds ratios and 95% confidence intervals obtained in multivariate logistic regression models including age, respondent status and all other non-occupational variables listed in the table.
[c] Pack-years = (average daily number of cigarettes/20 cigarettes per pack) x number of years of smoking.
[d] Drink-years = average daily number of drinks x number of years of drinking.
[e] Self-reported medical history.

Table IX. Lifetime prevalence of exposure to the 19 selected agents among all study subjects (pancreatic cases and controls combined, n=3097) and occupation and industry groups with the highest exposure prevalence to these agents in the study subsample.

Agent	Prevalence [n (%)]		Occupations and industries in which the agent is most commonly found [a]	
	Any exposure	Substantial exposure	Occupations	Industries
Antimony	58 (1.9)	13 (0.4)	Printing and related occupations Stationary engine and utilities equipment operating and related occupations Water transport operating occupations	Commercial Printing and Publishing Industries Smelting and Refining Shoe Repair Shops
Brass dust	62 (2.0)	27 (0.9)	Metal processing and related occupations Metal machining occupations Other machining and related occupations	Aluminum, copper and other alloys industries Metal fabricating and machinery industries Services incidental to mining
Nickel	210 (6.8)	30 (1.0)	Metal processing and related occupations Metal machining occupations Metal shaping and forming occupations except machining	Aluminum, Copper and Other Alloys Industries Aircraft and Aircraft Parts Manufacturing Industries Metal Fabricating and Machinery Industries
Tin fumes	124 (4.0)	26 (0.8)	Metal processing and related occupations Metal shaping and forming occupations except machining Other construction trades occupations	Aluminum, Copper and Other Alloys Industries Services Incidental to Mining Transportation Equipment Industries (Except Aircraft)
Fluorides	94 (3.0)	9 (0.3)	Fabricating and assembling occupations metal products Mineral ore treating occupations Metal shaping and forming occupations except machining	Services Incidental to Mining Smelting and Refining Transportation Equipment Industries (Except Aircraft)
Hydrogen fluoride	84 (2.8)	5 (0.2)	Fabricating and assembling occupations metal products Mineral ore treating occupations Metal shaping and forming occupations except machining	Services Incidental to Mining Smelting and Refining Transportation Equipment Industries (Except Aircraft)
Nitric acid	40 (1.3)	19 (0.6)	Metal processing and related occupations Occupations in medicine and health Printing and related occupations	Aluminum, Copper and Other Alloys Industries Commercial Printing and Publishing Industries Miscellaneous Manuf. Industries

| Agent | Prevalence [n (%)] | | Occupations and industries in which the agent is most commonly found [a] | |
	Any exposure	Substantial exposure	Occupations	Industries
Sulfuric acid	283 (9.1)	53 (1.7)	Metal processing and related occupations Mechanics and repairmen Other crafts and equipment operating occupations	Aluminum, Copper and Other Alloys Industries Leather Tanneries Smelting and Refining
Cleaning agents	489 (15.8)	286 (9.2)	Apparel and furnishings service occupations Other service occupations Personal service occupations	Barber and Beauty Shops Laundries, Cleaners and Pressers Veneer and Plywood Mills
Hypochlorites	172 (5.6)	82 (2.6)	Apparel and furnishings service occupations Other service occupations Other crafts and equipment operating occupations	Fishing and Trapping Shoe Repair Shops Veneer and Plywood Mills
Javel water	165 (5.4)	80 (2.6)	Apparel and furnishings service occupations Other service occupations Other crafts and equipment operating occupations	Fishing and Trapping Laundries, Cleaners and Pressers Shoe Repair Shops
Chlorinated alkanes	326 (10.5)	132 (4.3)	Chemicals petroleum rubber plastic processing occupations Fabricating and assembling occupations (electrical and related equipment) Other crafts and equipment operating occupations	Aircraft and Aircraft Parts Manufacturing Industries Air Transport Chemical and Chemical Products Industries (Except Paint and Varnish)
Chlorinated alkenes	143 (4.6)	60 (1.9)	Apparel and furnishings service occupations Metal machining occupations Fabricating and assembling occupations (electrical and related equipment)	Aircraft and Aircraft Parts Manufacturing Industries Air Transport Laundries, Cleaners and Pressers
Coal combustion products	141 (4.6)	61 (2.0)	Railway transport operating occupations Stationary engine and utilities equipment operating and related occupations Water transport operating occupations	Asphalt Roofing Manuf. Industries Railway Transport Services Incidental to Mining
Soot	260 (8.4)	50 (1.6)	Mechanics and repairmen Stationary engine and utilities equipment operating and related occupations Water transport operating occupations	Air Transport Leather Tanneries Shoe Repair Shops
PAHs	1985 (64.1)	125 (4.0)	Mining quarrying and gas field occupations Metal machining occupations	Asphalt Roofing Manuf. Industries Quarries, Sand Pits and Other Non-metal Mines

Agent	Prevalence [n (%)]		Occupations and industries in which the agent is most commonly found [a]	
	Any exposure	Substantial exposure	Occupations	Industries
Plastic dust	163 (5.3)	41 (1.3)	Motor transport operating occupations Clay glass stone and related materials machining Fabricating assembling and repairing occupation: rubber plastic and related products Other crafts and equipment operating occupations	Veneer and Plywood Mills Miscellaneous manufacturing industries Plastic product industries Shoe repair shops
Synthetic adhesives	453 (14.6)	206 (6.7)	Rubber plastic fabricating assembling and repairing occupations Wood products fabricating assembling and repairing occupations Wood machining occupations	Air Transport Leather Goods Manufacturing Veneer and Plywood Mills
Waxes/polishes	166 (5.4)	44 (1.4)	Occupations in sports and recreation Other service occupations Pulp and papermaking and related occupations	Asphalt Roofing Manufacturing Industries Leather Goods Manufacturing Shoe Repair Shops

[a] Occupations and industries are presented in no particular order.
PAHs, polycyclic aromatic hydrocarbons.

Table X. Odds ratios for the association between pancreatic cancer and selected occupational agents in the Montreal Multisite cancer study (1979–1985): results obtained from models including non-occupational covariates only.

Agents	Cancer controls				Population controls			
	Any exposure [a]		Substantial exposure		Any exposure		Substantial exposure	
	n[b]	OR (95% CI) [c]	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
METALS								
Antimony	7	**3.8 (1.6-9.1)**	2	4.4 (1.0-20.3)	7	**3.5 (1.2-10.3)**	2	9.5 (0.9-106.2)
Brass dust	5	**3.7 (1.4-9.9)**	3	3.4 (1.0-11.7)	5	1.7 (0.6-5.5)	3	2.8 (0.7-11.9)
Nickel	12	**2.1 (1.1-3.9)**	2	2.1 (0.5-9.0)	12	1.3 (0.7-2.8)	2	1.3 (0.3-6.5)
Tin fumes	8	**2.3 (1.1-4.9)**	2	2.4 (0.6-10.6)	8	1.9 (0.8-4.7)	2	1.6 (0.3-7.9)
INORGANIC SOLVENTS AND ACIDS								
Fluorides	7	**2.8 (1.2-6.4)**	0	NC [d]	7	1.9 (0.7-5.0)	0	NC [d]
Hydrogen fluoride	6	**2.7 (1.1-6.4)**	0	NC [d]	6	1.5 (0.6-4.3)	0	NC [d]
Nitric acid	5	**4.9 (1.8-13.4)**	4	**5.8 (1.9-17.8)**	5	**7.8 (1.5-40.3)**	4	NC [d]
Sulfuric acid	12	1.1 (0.6-2.1)	5	**2.9 (1.1-7.7)**	12	1.0 (0.5-2.2)	5	1.8 (0.3-11.6)
Cleaning agents	24	1.5 (0.9-2.5)	17	**1.9 (1.1-3.2)**	24	1.1 (0.6-1.9)	17	1.4 (0.8-2.6)
Hypochlorites	12	**2.1 (1.1-4.1)**	5	1.7 (0.7-4.3)	12	**2.3 (1.0-5.1)**	5	2.8 (0.9-8.4)
Javel water	11	**2.0 (1.0-3.9)**	4	1.4 (0.5-3.8)	11	2.0 (0.9-4.5)	4	2.2 (0.6-7.2)
ORGANIC AND OTHER COMPOUNDS								
Chlorinated alkanes	8	0.8 (0.4-1.6)	6	1.6 (0.7-3.7)	8	0.5 (0.2-1.2)	6	0.9 (0.3-2.4)
Chlorinated alkenes	3	0.7 (0.2-2.3)	0	NC [d]	3	0.8 (0.2-3.0)	0	NC [d]
Coal combustion products	10	**2.6 (1.3-5.3)**	5	1.9 (1.0-6.6)	10	2.1 (0.9-4.7)	5	1.8 (0.6-5.2)
PAHs [e] from any source	76	1.1 (0.7-1.8)	5	1.1 (0.4-2.9)	76	0.9 (0.6-1.5)	5	1.2 (0.4-3.7)
Soot	11	1.2 (0.6-2.3)	6	**3.4 (1.3-8.6)**	11	0.9 (0.4-1.9)	6	3.0 (1.0-9.3)
Plastic dust	10	1.8 (0.9-2.4)	3	2.2 (0.7-7.3)	10	1.6 (0.7-3.8)	3	1.8 (0.5-6.9)
Synthetic adhesives	18	1.3 (0.8-2.2)	14	**2.1 (1.1-3.8)**	18	0.8 (0.5-1.5)	14	1.6 (0.7-3.4)
Waxes/polishes	11	**2.7 (1.1-4.1)**	5	**3.3 (1.3-8.5)**	11	1.6 (0.7-3.7)	5	**6.2 (1.6-23.6)**

[a] The reference category for any and substantial exposure was non-exposure.
[b] Number of exposed cases.
[c] Odds ratios and 95% confidence intervals adjusted for non-occupational variables (age, ethnicity [French/other], income, years of education, respondent status, cigarette index and alcohol index).
[d] ORs not calculable because there were no exposed cases or controls.
[e] PAHs, polycyclic aromatic hydrocarbons

Table XI. Odds ratios for the association between pancreatic cancer and selected occupational agents in the Montreal Multisite cancer study (1979–1985): results obtained from models including occupational covariates.

Agents	Cancer controls				Population controls			
	Any exposure [a]		Substantial exposure		Any exposure		Substantial exposure	
	n[b]	OR (95% CI) [c]	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
METALS								
Antimony	7	2.5 (1.0-6.4)	2	1.2 (0.1-10.4)	7	2.5 (0.7-8.1)	2	6.0 (0.3-104.1)
Brass dust	5	NC [e]	3	NC [e]	5	NC [e]	3	NC [e]
Nickel	12	1.5 (0.7-3.1)	2	1.1 (0.1-9.0)	12	1.0 (0.4-2.4)	2	0.2 (0.02-2.4)
Tin fumes	8	1.8 (0.8-4.0)	2	2.9 (0.6-13.6)	8	1.5 (0.5-4.0)	2	2.1 (0.4-12.5)
INORGANIC SOLVENTS AND ACIDS								
Fluorides	7	1.9 (0.7-4.8)	0	NC [d]	7	1.3 (0.4-4.0)	0	NC [d]
Hydrogen fluoride	6	1.7 (0.6-4.7)	0	NC [d]	6	1.0 (0.3-3.3)	0	NC [d]
Nitric acid	5	NC [e]	4	NC [e]	5	NC [e]	4	NC [e]
Sulfuric acid	12	0.8 (0.4-1.7)	5	1.3 (0.3-5.0)	12	0.7 (0.3-1.6)	5	4.0 (0.9-18.0)
Cleaning agents	24	1.2 (0.7-2.2)	17	1.7 (0.9-3.3)	24	0.7 (0.4-1.5)	17	1.1 (0.5-2.3)
Hypochlorites	12	1.7 (0.8-3.7)	5	1.0 (0.3-3.2)	12	2.0 (0.8-5.0)	5	2.7 (0.7-5.9)
Javel water	11	1.4 (0.6-3.3)	4	0.5 (0.1-2.0)	11	1.9 (0.6-5.6)	4	1.7 (0.3-8.3)
ORGANIC AND OTHER COMPOUNDS								
Chlorinated alkanes	8	0.8 (0.4-1.6)	6	1.6 (0.7-3.7)	8	0.5 (0.2-1.2)	6	0.9 (0.3-2.4)
Chlorinated alkenes	3	0.5 (0.1-2.0)	0	NC [d]	3	0.6 (0.1-2.8)	0	NC [d]
Coal combustion products	10	NC [f]	5	NC [f]	10	NC [f]	5	NC [f]
PAHs [g] from any source	76	NC [f]	5	NC [f]	76	NC [f]	5	NC [f]
Soot	11	0.8 (0.4-1.7)	6	2.4 (0.8-7.1)	11	0.6 (0.2-1.3)	6	1.6 (0.4-6.9)
Plastic dust	10	1.6 (0.8-3.3)	3	2.0 (0.6-6.7)	10	1.4 (0.6-3.3)	3	2.5 (0.6-11.1)
Synthetic adhesives	18	NC [f]	14	NC [f]	18	NC [f]	14	NC [f]
Waxes/polishes	11	1.8 (0.8-3.8)	5	**3.6 (1.1-12.0)**	11	1.3 (0.5-3.4)	5	3.4 (0.7-17.6)

[a] The reference category for any and substantial exposure was non-exposure.
[b] Number of exposed cases.
[c] Odds ratios and 95% confidence intervals adjusted for non-occupational variables and occupational confounders indicated in parentheses as follows: antimony (coal combustion products, tin fumes); nickel (cleaning products, fluorides); tin fumes (plastic dust); fluorides (cleaning products, nitric acid, tin fumes); hydrogen fluoride (tin fumes, nitric acid); sulfuric acid (nitric acid); cleaning products (javel*); hypochlorites (waxes/polishes); javel water (cleaning products, waxes/polishes); chlorinated alkanes (none); chlorinated alkenes (PAHs); soot (coal combustion products, waxes/polishes); plastic dust (waxes/polishes); waxes/polishes (javel*).* Two combinations of agents (fluorides and hydrogen fluorides and javel and hypochlorites) could not be entered in the models simultaneously due to high correlations between them. Since estimates obtained with either agent in the model were virtually identical, only one is printed.
[d-f] ORs could not be estimated either because d) there were no exposed cases or controls, e) more occupational confounders were identified than permitted by the model given the number of cases or f) no occupational confounders were identified. [g] PAHs, polycyclic aromatic hydrocarbons

Table XII. Lifetime prevalence of exposure to the selected occupations and industries among all study subjects (pancreatic cases and controls combined, n=3097).

Occupations and Industries	Prevalence [n (%)]		
	Any exposure	Exposed <10 years	Exposed ≥ 10 years
Industry			
Railway transport	272 (8.9)	111 (3.6)	161 (5.2)
Education and related services	203 (6.6)	75 (2.4)	128 (4.1)
Metal smelting and refining	40 (1.3)	25 (0.8)	15 (0.5)
Occupation			
Other service occupations	262 (8.5)	151 (4.9)	111 (3.6)
Janitors and cleaners	173 (5.6)	99 (3.2)	74 (2.4)

Table XIII. Odds ratios for the association between pancreatic cancer and selected industries and occupations in the Montreal Multisite cancer study (1979–1985).

	Cancer controls						Population controls					
	Any exposure [a]		Exposed <10 years		Exposed ≥ 10 years		Any exposure		Exposed <10 years		Exposed ≥ 10 years	
	n^b	OR (95% CI) [c]	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Industry												
Railway transport	17	**2.0 (1.1-3.4)**	3	0.8 (0.2-2.5)	14	**3.0 (1.6-5.5)**	17	**2.2 (1.2-4.3)**	3	1.0 (0.3-3.7)	14	**3.0 (1.4-6.3)**
Education and related services	10	1.9 (0.9-3.8)	5	**3.0 (1.1-8.1)**	5	1.4 (0.5-3.6)	10	1.3 (0.6-2.9)	5	1.7 (0.5-5.3)	4	1.0 (0.4-3.0)
Metal smelting and refining	3	1.9 (0.5-6.5)	1	1.1 (0.1-8.2)	2	3.1 (0.6-15.8)	3	2.5 (0.6-10.9)	1	2.0 (0.2-19.3)	2	3.0 (0.4-20.5)
Occupation												
Other service occupations	18	**2.1 (1.2-3.7)**	8	1.7 (0.8-3.8)	10	**2.6 (1.2-5.4)**	18	1.3 (0.7-2.6)	8	1.0 (0.4-2.3)	18	2.0 (0.8-5.2)
Janitors and cleaners	15	**2.8 (1.5-5.1)**	7	**2.4 (1.4-7.2)**	8	**3.2 (1.4-7.2)**	15	1.7 (0.8-3.5)	7	1.2 (0.5-3.2)	15	2.7 (0.9-8.3)

[a] The reference category for any exposure, exposed <or ≥ 10 years was non-exposure.
[b] Number of exposed cases.
[c] Odds ratios and 95% confidence intervals adjusted for non-occupational variables (age, ethnicity [French/other], income, years of education, respondent status, cigarette index and alcohol index).

5.   DISCUSSION

The overarching purpose of the Montreal Multisite cancer (MMC) study was to identify occupational circumstances associated with an increased risk of developing some of the most common types of cancer. Although conducted over 30 years ago, the study and the results derived from it are nevertheless currently relevant since many of the substances and suspected carcinogens that were evaluated are still frequent exposures in many workplaces. In terms of the occupation and industry titles used as indicators of exposure, even though the tasks performed in some of these jobs may be very different today, the results obtained from these analyses are complementary to those from the substance exposures and can also yield important clues regarding occupational risk factors. Furthermore, their use can often facilitate the comparison of findings between studies. Although the MMC study is older, its design and the epidemiological methods used are certainly not considered outdated. An additional justification for performing these analyses now is that in the intervening years there have not been many studies reporting results on possible associations between occupational chemical exposures and pancreatic cancer.

In the sub-analysis of the Montreal Multisite cancer study reported here, the main objective was to identify risk factors for one cancer site in particular, that of pancreatic cancer, among the hundreds of occupational circumstances for which exposure information was collected. The analytical process therefore involved performing numerous tests of statistical significance in order to uncover possible associations, a scenario in which some authors suggest adjusting for multiple comparisons (100). When performing multiple comparisons, one might expect that

with a larger number of associations tested, there is a greater probability of finding a statistically

significant result and thus more potentially spurious associations could be identified. However,

no matter the *number* of statistical significance tests performed, the probability of committing a

type I error (rejecting the null hypothesis when it is true) is nonetheless equivalent to the

predetermined value of alpha (5% in most studies). An adjustment for multiple analyses usually

involves lowering the value of alpha (101). The trade-off, however, is a decrease in the statistical

power of the test thus increasing the chance of committing a type II error; that is rejecting the

alternative hypothesis when it is in fact true. Committing such an error would entail overlooking

real associations which is not a desirable outcome in hypothesis generating studies such as this

one. Therefore, adjustments for multiple comparisons were not carried out. Indeed, some

authors contend that "adjustments for multiple comparisons are not needed" and that doing so

diminishes the value of the information contained in large sets of data (101). Moreover, a subset

of our analysis was based on substantive literature-based hypotheses in which case such

adjustments are certainly not warranted.

One of the premier challenges in conducting case-control studies is the selection of an

appropriate control group. In this selection process, the aim is to recruit control subjects from

the same population base from which the cases originated such that the two groups are

comparable. There are two main methods of assembling control groups: one is to select

"healthy" controls from the general population, the other to select other patients as controls from

the same clinical setting as the cases but who lack the disease of interest. Both approaches were

used in the Montreal Multisite cancer study, and, while there are pros and cons for each method,

the cancer control group in this study is considered the superior control group yielding more

valid estimates of risk for several reasons. First, because it was impossible to blind the interviewers to disease status, the comparison of pancreatic cancer cases with other cancer cases is less likely to be affected by interviewer bias than the comparison with healthy populations controls. Second, diseased subjects may have better recollection of past exposures than healthy subjects thus reducing the bias from differential recall between case and control groups. Third, given that there are more subjects available as controls from the other cancer cases compared to the number of subjects recruited as population controls, the power to detect an association, if it exists, between the various exposures and pancreatic cancer is greater. Indeed, when comparing the overall results obtained with cancer controls and population controls, the majority of the excess risks were detected using the cancer control group. However, it is important to consider that the pancreatic cancer cases and other cancer cases used as controls may share some occupational etiologic factors which could mask associations. Therefore, comparisons were also made with the population control group to avoid missing any risk factors.

In all epidemiological studies, one must evaluate the validity of the results obtained. To accomplish this, both bias and confounding must be considered as alternative explanations to the observed associations. In case-control studies, important biases can be introduced if there are systematic differences in the way case and control subjects are selected or in how the information regarding exposure and/or disease is collected in these groups. Bias is thus broadly divided into two categories based on these main sources, *selection* bias and *information* bias.

Selection bias in case-control studies occurs when the selection of cases and controls does not occur independently of exposure status. One strength in the design of the Montreal Multisite

cancer study which is likely to minimize this particular bias is its population-based design as opposed to the use of convenience samples for selecting cases and controls, in which case the groups are more likely to be non-comparable at the outset. However, differential response rates in case and control groups according to exposure status can also result in a form of selection bias, nonresponse bias. In an earlier analysis of data from the MMC study, responders and non-responders among all cancer cases ascertained were compared on several socio-demographic characteristics available in medical records. Few differences were observed and it was determined, based on a comparison of odds ratios derived from all eligible subjects and from respondents only that any bias resulting from non-response would be unlikely to cause significant distortion of odds ratios (102). In addition, the cancer-control group comparison lessens the chance of non-response bias because non-responders among cases of pancreatic cancer are less likely to differ from non-responders among the other cases of cancer than from healthy controls.

Information bias in observational studies arises primarily from errors in the classification of disease and/or exposure status. One aspect of the MMC study that operated to minimize misclassification of disease status is the use of histological diagnosis to identify cases of pancreatic cancer. This method is considerably more accurate than that of assigning case or control status based on information contained only in vital and administrative records, a common practice in other occupational studies. Information bias resulting from errors in the attribution of exposure status is more of a concern in case-control studies because exposures are determined retrospectively. In order to limit the possibility of information bias, the MMC study relied on personnel with an expertise in industrial hygiene to objectively assign exposures to the

study participants while being blinded to their disease status. Therefore any exposure misclassification at this stage should have occurred without regard to disease status resulting in an attenuation of the risk estimates. However, as previously mentioned, blinding to disease status was not possible with the participant interviews offering an opportunity for information bias to arise at this stage. Moreover, the proportion of proxy respondents for the pancreatic cancer case group was noticeably greater as compared to the control groups because of the rapid progression and high case fatality of this cancer. Therefore, a lesser quality of information obtained from pancreatic cancer cases is a concern and some evidence of this is apparent in the higher proportion of exposures categorized as "uncertain" by the expert coders for this group. This justified the inclusion of the variable "respondent status" in the regression models.

The precision of the exposure assessment method in this study was evaluated in several trials of inter-coder agreement. The percent agreement was found to be between 93% and 98% and the kappa statistic between 0.52 to 0.67 indicating moderate to substantial agreement of assigned exposures (98). While the validity of the method was not directly evaluated in this study, others have estimated the sensitivity and specificity of expert assessment of exposures to be between 0.21 and 0.79 and 0.91 and 0.98 respectively (97).

Another strength of the MMC study is the availability of information on several relevant potential confounders. In this analysis, not only were important non-occupational variables accounted for, but adjustment was also made for other occupational variables which few other studies of pancreatic cancer have done. However, this adjustment could not be carried out completely for two reasons. Firstly, for some agents (e.g. nitric acid), too many potential

confounders were identified than could be allowed in the model owing to the limited number of pancreatic cancer cases. Secondly, some highly correlated substances, namely javel water and hypochlorites and fluorides and hydrogen fluoride, could not be included simultaneously in the models due to multicollinearity problems. Although the statistical adjustment for confounding is an important step in calculating valid estimates of risk, one concern is the possibility of distorting the estimate if over-adjustment occurs (103). Moreover, adjustment for variables identified as confounders based on "internal" or data-based evidence rather than "external" or *a priori* evidence may introduce bias rather than eliminate it (104). Therefore, in this study the true estimates may in fact be in between the odds ratios partially adjusted for *a priori* non-occupational confounders and the odds ratios additionally adjusted for the internally identified occupational confounders.

As far as other study limitations, the principal one relevant to this analysis is the relatively low number of pancreatic cancer cases and exposed subjects for several different occupational circumstances and, consequently, a low statistical power to detect risks. Despite the small numbers and low power, this analysis nevertheless constitutes one of the largest case-control studies of occupational exposures and pancreatic cancer serving at the very least as a valuable contribution to potential future meta-analyses.

An additional limitation for the pancreatic cancer arm of the MMC study is the potential effect of incidence-prevalence bias, a form of selection bias which can arise when a group of survivors is selected. Because of the aggressive nature of pancreatic cancer, this study would have missed those cases which progressed so quickly that formal histopathological diagnosis was not

performed. To obtain an estimate of the proportion of pancreatic cases captured by the study, since incidence of the disease approximates mortality, one could look at the number of deaths among the eligible population attributed to pancreatic cancer during the period of the study or with a slight lag corresponding to median survival time.

Before discussing the findings for the occupational agents, it is useful to consider our findings regarding non-occupational exposures and pancreatic cancer. In keeping with what has been reported in numerous other publications (6), both smoking and alcohol use were associated with an increased risk of pancreatic cancer in this study. As was expected, the increases in risk related to smoking and alcohol were attenuated when pancreatic cancer cases were compared with the other cancer cases, presumably because several tumour sites included in the latter group are also related to tobacco and heavy alcohol consumption. Among the other non-occupational factors for which there is good evidence of an association with pancreatic cancer (table 1, appendix 2), a history of allergic disease appeared to offer a protective effect in this study population as has also been observed in others (6).

In the analysis of occupational agents overall, increased risks of pancreatic cancer were found for exposure to several categories of occupational substances including metals (antimony, brass dust, nickel and tin fumes), other inorganic compounds including acids (nitric acid, sulfuric acid, fluorides, cleaning agents, javel water and hypochlorites) and organic compounds including chlorinated alkanes, synthetic adhesives, coal combustion products, soot and waxes/polishes.

Among the metal compounds flagged in this study, only nickel, an IARC classified group 1 carcinogen, has been flagged by some (26, 28) but not all studies of pancreatic cancer risk (23). Antimony, brass and tin as risk factors were not specifically mentioned in the reviewed studies, however, some occupations exposed to these substances have occasionally been found to be associated with pancreatic cancer. These occupations include machinists (27), plumbers, pipefitters and welders (38, 39), toolmakers (39), metal platers (41), printers (42) and other metal jobs (58). Two other substances earmarked in this analysis, nitric acid and sulfuric acid, are also widely used in these occupations for cleaning and degreasing of metal parts but have not themselves been implicated in the literature as pancreatic carcinogens.

Near threefold excess risks for pancreatic cancer were found for exposure to fluorides and to hydrogen fluoride in this analysis. Fluorides are used in many occupations, but in this study population, use was most commonly observed in metal working occupations, mining and smelting (see table 9, page 42). Although fluorides have not so far been associated with pancreatic cancer in other studies, the aforementioned occupations have. Excess risks have been observed among miners (27), metal platers (41), plumbers (38, 39), welders (38, 39) and metal degreasers (74). Interestingly, employment in the aluminum production industry for which there is a stronger suggestion of an association with pancreatic cancer based on the replication of findings (46-50), involves exposure to both fluorides and hydrogen fluoride (51). In accordance with these studies, while based on a very small number of cases, we found twofold excess risks in those ever employed in metal smelting and refining with threefold excesses in those employed for 10 or more years.

A recent review of cancer risks in primary aluminum production workers observed that while there have been several reports of increased risks of pancreatic cancer in this industry, there is currently insufficient evidence to indicate a relationship with a specific exposure in aluminum reduction potrooms (51). A likely candidate for such an effect among worker cohorts in aluminum production is PAHs, because these compounds are established carcinogens for other tumour sites, most notably the lung and bladder (44, 45). We therefore tested this hypothesis in the MMC study population but did not observe an increase in risk of pancreatic cancer with exposure to PAHs from any source. This finding is in agreement with some other studies which considered the same research question (26, 55). However, these studies mainly examined PAHs derived from diesel exhaust. In fact, PAHs form a large group of hundreds of different compounds and the profile of PAHs to which one is exposed depends on the source material (98). In aluminum reduction potrooms, PAHs are primarily derived from the coal tar used in the production process (51). The compounds emitted from the heating and combustion of this material may contain the putative pancreatic carcinogens. Such a hypothesis would be supported by the finding of an increased risk of pancreatic cancer with exposure to coal combustion products in our analysis. The latter exposure includes a mixture of particulates (carbon, silica, alumina, and iron oxides) and gases (aldehydes, carbon monoxide, nitrogen oxides, sulfur oxides and hydrocarbons) (98). Furthermore, we found twofold excess risks of pancreatic cancer among those substantially exposed to soot, a black substance formed by the combustion of carbon compounds including coal.

Other than aluminum production, coal tar exposure can also occur in roofing and paving occupations (105) and excesses in pancreatic cancer incidence and mortality have previously

been observed among road pavers (52). Exposure to coal-tar creosote, a related substance containing many of the same PAHs as coal tar, can occur in rail road work (106). In this analysis, extended employment in railway transport was significantly associated with a three times increased risk of pancreatic cancer. Another study published by Zhang and colleagues also found an elevated risk among railroad transport workers and operators employed for over 10 years (OR 5.1, 95% CI [2.3-11.5]) (54).

Taken together, our findings and those of previous similar studies suggest that exposure to coal and closely related compounds including the group of PAHs derived from them may increase the risk of pancreatic cancer. It is possible that the small excess risk detected in the meta-analysis by Ojajärvi and colleagues of pancreatic cancer and exposure to PAHs (26) represents a signal from this particular profile of PAH exposure.

Three related chemicals used for cleaning (cleaning agents excluding organic solvents, javel water and hypochlorites) were flagged as possible risk factors for the cancer outcome in the present study based on roughly twofold excess risks. Another category of substances, waxes/polishes was also associated with pancreatic cancer in our study population with a strong and statistically significant measure of association, particularly in those substantially exposed. Inorganic cleaning agents and waxes and polishes have not been specifically identified as pancreatic carcinogens. However, excess cases of pancreatic cancer have been observed in some occupational groups heavily exposed to these substances such as cleaners (41, 74, 76, 77), hair dressers (107) and leather tanners (108). Consistent with this observation, our study uncovered a significantly positive association among janitors and cleaners with a suggestion of a dose-

response trend according to duration of exposure. The substance that is hypothesized to account for the increased risk of pancreatic cancer among these occupational groups is the family of CHCs for which there is accumulating evidence of an association with pancreatic cancer (23). In this analysis, the group of chlorinated alkanes (methylene chloride, chloroform, carbon tetrachloride) but not chlorinated alkenes (trichloroethylene, tetrachloroethylene, vinyl chloride) demonstrated a weak association with pancreatic cancer, however only a small number of exposed cases were available to conduct these analyses.

Exposure to synthetic adhesives in our study was associated with a significantly elevated risk of pancreatic cancer. This substance group includes synthetic resins and rubbers comprising, among others, formaldehyde resins and epoxy resins (98). They are widely used in various industries but particularly in wood, furniture, rubber and shoe industries and occupations. Other authors have reported increases in several related occupational groups such as carpentry (27), furniture sales (54), the textile industry (109, 110), the rubber industry (111) and the paint and varnish industry (112).

Finally, an association was observed for employment in the industry group "Education and related services" which encompasses the usual educational institutions (e.g. schools) and other institutions such as libraries and museums, although the strongest estimate was for the lower exposure category (i.e. less than 10 years of employment). To our knowledge, this association has not been reported in other studies and would merit further attention in prospective studies particularly those including females insofar as this group traditionally represents a more substantial proportion of workers in the education industry.

6.   CONCLUSION

Of the hundreds of different occupational circumstances evaluated in this study for evidence of an association with pancreatic cancer risk, most revealed no association. However, many exposures could not be properly assessed due to the small number of cases of pancreatic cancer.

We endeavored to study a short list of exposures for which the existing evidence base indicates that there is a possible link with pancreatic cancer. For chlorinated hydrocarbon compounds, we found only a small excess risk for the subgroup of chlorinated alkanes. For polycyclic aromatic hydrocarbons, an excess risk was not observed in this study, although some other exposures which contain these recognized carcinogens (soot and products of coal combustion) were flagged in our analysis. In total, 16 agents "screened positive" for an association with pancreatic cancer. For many of these substances, there is no direct evidence published by other authors to corroborate our findings. However, indirect associations can be made with studies which have uncovered excesses of pancreatic cancer in occupations and industries in which exposure to these substances is likely. Our findings could therefore be useful for guiding future research efforts to uncover the specific chemical exposures that account for these excesses and importantly for potential prospective meta-analyses.

The most significant challenges faced in epidemiologic studies of pancreatic cancer are of assembling sufficient numbers of cases and of accurately assigning exposures to be able to discern clear associations. Methodological improvements in the classification of occupational

exposures as well as studies involving larger case groups, such as multi-centre and pooled studies, are greatly needed.

REFERENCES

1.   Canadian Cancer Society's Advisory Committee on Cancer Statistics: Canadian Cancer Statistics 2015. Toronto, ON.
2.   Li K, Ahuja N. Early detection of pancreatic cancer. Chin J Cancer Res. 2015;27(4):321-31.
3.   Yadav D, Lowenfels AB. The Epidemiology of Pancreatitis and Pancreatic Cancer. Gastroenterology. 2013;144(6):1252-61.
4.   Forman D, Bray F, Brewster DH, Mbalawa CG, Kohler B, Piñeros M, et al. Cancer Incidence in Five Continents Vol. X IARC Scientific Publications No 164. Lyon FR; 2014.
5.   Dobrila-Dintinjana R, Vanis N, Dintinjana M, Radi M. Etiology and Oncogenesis of Pancreatic Carcinoma. Coll Antropol. 2012;36(3):1063-67.
6.   Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. International journal of epidemiology. 2015;44(1):186-98.
7.   Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Annals of Oncology 2012;23:1880-8.
8.   International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 100E. Personal habits and indoor combustions. Lyon, France; 2012.
9.   MacMahon B, Yen S, Trichopoulos D, Warren K, Nardi G. Coffee and Cancer of the Pancreas. New England Journal of Medicine. 1981;304(11):630-3.
10.   Guertin KA, Freedman ND, Loftfield E, Stolzenberg-Solomon RZ, Graubard BI, Sinha R. A prospective study of coffee intake and pancreatic cancer: results from the NIH-AARP Diet and Health Study. British Journal of Cancer. 2015;113(7):1081-5.
11.   Li D. Diabetes and Pancreatic Cancer. Molecular carcinogenesis. 2012;51:64-74.
12.   Carr PR, Walter V, Brenner H, Hoffmeister M. Meat subtypes and their association with colorectal cancer: Systematic review and meta-analysis. International journal of cancer. 2016;138:293-302.
13.   Taunk P, Hecht E, Stolzenberg-Solomon R. Are meat and heme iron intake associated with pancreatic cancer? Results from the NIH-AARP diet and health cohort. International journal of cancer. 2016;138(9):2172-89.
14.   Molina-Montes E, Sanchez MJ, Zamora-Ros R, Bueno-de-Mesquita HB, Wark PA, Obon-Santacana M. Flavonoid and lignan intake and pancreatic cancer risk in the European prospective investigation into cancer and nutrition cohort. Int J Cancer. 2016;139:1480-92.
15.   Osório-Costa F, Rocha GZ, Dias MM, Carvalheira JBC. Epidemiological and molecular mechanisms aspects linking obesity and cancer. Arq Bras Endocrinol Metab. 2009;53(2):213-26.
16.   Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E GH, Martin-Hirsch P, Tsilidis KK. Adiposity and cancer at major anatomical sites: umbrella review of the literature. The British Medical Journal. 2017;356(477).
17.   Behrens G, Jochem C, Schmid D, Keimling M, Ricci C, Leitzmann MF. Physical activity and risk of pancreatic cancer: a systematic review and meta-analysis. European journal of epidemiology. 2015;30(4):279-98.

18.   Hart AR, Kennedy H, Harvey I. Pancreatic cancer: a review of the evidence on causation. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2008;6(3):275-82.

19.   Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860-7.

20.   Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet (London, England). 2011;377(9759):31-41.

21.   Siemiatycki J, Richardson L, Straif K, Latreille B, Lakhani R, Campbell S, et al. Listing Occupational Carcinogens. Environmental health perspectives. 2004;112(15):1147-59.

22.   Labreche F, Duguay P, Boucher A, Arcand R. But other than mesothelioma? An estimate of the proportion of work-related cancers in Quebec. Current oncology (Toronto, Ont). 2016;23(2):e144-9.

23.   Andreotti G, Silverman DT. Occupational risk factors and pancreatic cancer: a review of recent findings. Molecular carcinogenesis. 2012;51(1):98-108.

24.   Johnson ES, Ndetan H, Lo KM. Cancer mortality in poultry slaughtering/processing plant workers belonging to a union pension fund. Environmental Research. 2010;110(6):588-94.

25.   Felini M, Johnson E, Preacely N, Sarda V, Ndetan H, Bangara S. A pilot case-cohort study of liver and pancreatic cancers in poultry workers. Annals of epidemiology. 2011;21(10):755-66.

26.   Ojajarvi IA, Partanen TJ, Ahlbom A, Boffetta P, Hakulinen T, Jourenkova N, et al. Occupational exposures and pancreatic cancer: a meta-analysis. Occupational and environmental medicine. 2000;57(5):316-24.

27.   Santibanez M, Vioque J, Alguacil J, de la Hera MG, Moreno-Osset E, Carrato A, et al. Occupational exposures and risk of pancreatic cancer. European journal of epidemiology. 2010;25(10):721-30.

28.   Antwi SO, Eckert EC, Sabaque CV, Leof ER, Hawthorne KM, Bamlet WR, et al. Exposure to environmental chemicals and heavy metals, and risk of pancreatic cancer. Cancer causes & control : CCC. 2015;26(11):1583-91.

29.   Birk T, Mundt KA, Guldner K, Parsons W, Luippold RS. Mortality in the German Porcelain Industry 1985-2005: First Results of an Epidemiological Cohort Study. Journal of Occupational and Environmental Medicine. 2009;51(3):373-85.

30.   International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 100C. Arsenic, Metals, Fibres and Dusts. Lyon, France; 2012.

31.   Chen C, Xun P, Nishijo M, Sekikawa A, He K. Cadmium exposure and risk of pancreatic cancer: A meta- analysis of prospective cohort studies and case-control studies among individuals without occupational exposure history. Environ Sci Pollut Res Int 2015; 22(22):17465–74. .

32.   Qu W, Tokar EJ, Kim AJ, Bell MW, Waalkes MP. Chronic cadmium exposure in vitro causes acquisition of multiple tumor cell characteristics in human pancreatic epithelial cells. Environmental health perspectives. 2012;120(9):1265-71.

33.   Weiderpass E, Vainio H, Kauppinen T, Vasama-Neuvonen K, Partanen T, Pukkala E. Occupational exposures and gastrointestinal cancers among Finnish women. Journal of Occupational and Environmental Medicine. 2003;45(3):305-15.

34.   Ilychova SA, Zaridze DG. Cancer mortality among female and male workers occupationally exposed to inorganic lead in the printing industry. Occupational and environmental medicine. 2012;69(2):87-92.

35.   Amaral AFS, Porta M, Silverman DT, Milne RL, Kogevinas M, Rothman N, et al. Pancreatic cancer risk and levels of trace elements. Gut. 2012;61(11):1583-8.

36.   Garcia-Esquinas E, Pollan M, Umans JG, Francesconi KA, Goessler W, Guallar E, et al. Arsenic Exposure and Cancer Mortality in a US-Based Prospective Cohort: The Strong Heart Study. Cancer Epidemiology Biomarkers & Prevention. 2013;22(11):1944-53.

37.   Kriegel AM, Soliman AS, Zhang Q, El-Ghawalby N, Ezzat F, Soultan A, et al. Serum cadmium levels in pancreatic cancer patients from the East Nile Delta region of Egypt. Environmental health perspectives. 2006;114(1):113-9.

38.   Luckett BG, Su LJ, Rood JC, Fontham ET. Cadmium exposure and pancreatic cancer in south Louisiana. J Environ Public Health. 2012;2012:180186.

39.   Ji BT, Silverman DT, Dosemeci M, Dai Q, Gao YT, Blair A. Occupation and pancreatic cancer risk in Shanghai, China. American journal of industrial medicine. 1999;35(1):76-81.

40.   Alguacil J, Pollan M, Gustavsson P. Occupations with increased risk of pancreatic cancer in the Swedish population. Occupational and environmental medicine. 2003;60(8):570-6.

41.   Ojajärvi A, Partanen T, Ahlbom A, Hakulinen T, Kauppinen T, Weiderpass E, et al. Estimating the relative risk of pancreatic cancer associated with exposure agents in job title data in a hierarchical Bayesian meta-analysis. Scandinavian journal of work, environment & health. 2007;33(5):325-35.

42.   Kvam BMN, Romundstad PR, Boffetta P, Andersen A. Cancer in the Norwegian printing industry. Scandinavian Journal of Work Environment & Health. 2005;31(1):36-43.

43.   Ladou J, Harrison J. Chemicals. Occupational and environmental medicine. 4 ed: McGraw-Hill; 2006.

44.   International Agency for Research on Cancer. Agents Classified by the IARC Monographs, Volumes 1–112 [updated April 7, 2015. Available from: http://monographs.iarc.fr/ENG/Classification/ClassificationsAlphaOrder.pdf.

45.   International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 92. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. Lyon, France; 2010.

46.   Romundstad P, Haldorsen T, Andersen A. Cancer incidence and cause specific mortality among workers in two Norwegian aluminum reduction plants. American journal of industrial medicine. 2000;37(2):175-83.

47.   Romundstad P, Andersen S, Haldorsen T. Cancer incidence among workers in six Norwegian aluminum plants. Scandinavian journal of work, environment & health. 2000(6):461-9.

48.   Carta P, Aru G, Cadeddu C, Gigli G, Papi G, Carta F, et al. Mortality for pancreatic cancer among aluminium smelter workers in Sardinia, Italy. Giornale italiano di medicina del lavoro ed ergonomia. 2004;26(2):83-9.

49.   Gibbs GW, Armstrong B, Sevigny M. Mortality and cancer experience of Quebec aluminum reduction plant workers, part 2: Mortality of three cohorts hired on or before January 1, 1951. Journal of Occupational and Environmental Medicine. 2007;49(10):1105-23.

50.   Gibbs GW, Sevigny M. Mortality and cancer experience of Quebec aluminum reduction plant workers, part 4: Cancer incidence. Journal of Occupational and Environmental Medicine. 2007;49(12):1351-66.

51.   Gibbs GW, Labreche F. Cancer Risks in Aluminum Reduction Plant Workers A Review. Journal of Occupational and Environmental Medicine. 2014;56(5):S40-S59.

52.   Kauppinen T, Heikkila P, Partanen T, Virtanen SV, Pukkala E, Ylostalo P, et al. Mortality and cancer incidence of workers in Finnish road paving companies. American journal of industrial medicine. 2003;43(1):49-57.

53.   Ji J, Hemminki K. Socioeconomic and occupational risk factors for pancreatic cancer: a cohort study in Sweden. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine. 2006;48(3):283-8.

54.   Zhang Y, Cantor KP, Lynch CF, Zhu Y, Zheng T. Occupation and risk of pancreatic cancer: a population-based case-control study in Iowa. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine. 2005;47(4):392-8.

55.   Boffetta P. Lack of association between occupational exposure to diesel exhaust and risk of pancreatic cancer: a systematic evaluation of available data. International archives of occupational and environmental health. 2014;87(5):455-62.

56.   Cantor KP, Silberman W. Mortality among aerial pesticide applicators and flight instructors: Follow-up from 1965-1988. American journal of industrial medicine. 1999;36(2):239-47.

57.   Ji BT, Silverman DT, Stewart PA, Blair A, Swanson GM, Baris D, et al. Occupational Exposure to Pesticides and Pancreatic Cancer. American journal of industrial medicine. 2001;39:92-9.

58.   Alguacil J, Kauppinen T, Porta M, Partanen T, Malats N, Kogevinas M, et al. Risk of pancreatic cancer and occupational exposures in Spain. PANKRAS II Study Group. The Annals of occupational hygiene. 2000;44(5):391-403.

59.   Lo AC, Soliman AS, El-Ghawalby N, Abdel-Wahab M, Fathy O, Khaled HM, et al. Lifestyle, occupational, and reproductive factors in relation to pancreatic cancer risk. Pancreas. 2007;35(2):120-9.

60.   Fritschi L, Benke G, Risch HA, Schulte A, Webb PM, Whiteman DC, et al. Occupational exposure to N-nitrosamines and pesticides and risk of pancreatic cancer. Occupational and environmental medicine. 2015;72(9):678-83.

61.   Andreotti G, Freeman LE, Hou L, Coble J, Rusiecki J, Hoppin JA, et al. Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort. International journal of cancer. 2009;124(10):2495-500.

62.   Lerro CC, Koutros S, Andreotti G, Hines CJ, Blair A, Lubin J, et al. Use of acetochlor and cancer incidence in the Agricultural Health Study. International journal of cancer. 2015;137(5):1167-75.

63.   Hoppin JA, Tolbert PE, Holly EA, Brock JW, Korrick SA, Altshul LM, et al. Pancreatic cancer and serum organochlorine levels. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2000;9(2):199-205.

64.   Beard J, Sladden T, Morgan G, Berry G, Brooks L, McMichael A. Health impacts of pesticide exposure in a cohort of outdoor workers. Environmental health perspectives. 2003;111(5):724-30.

65.   Cocco P, Fadda D, Billai B, D'Atri M, Melis M, Blair A. Cancer Mortality among Men Occupationally Exposed to Dichlorodiphenyltrichloroethane. Cancer Research. 2005;65(20):9588-94.

66.   Cerhan JR, Cantor KP, Williamson K, Lynch CF, Torner JC, Burmeister LF. Cancer mortality among Iowa farmers: Recent results, time trends, and lifestyle factors (United States). Cancer Causes & Control. 1998;9(3):311-9.

67.   Lee E, Burnett CA, Lalich N, Cameron LL, Sestito JP. Proportionate mortality of crop and livestock farmers in the United States, 1984-1993. American journal of industrial medicine. 2002;42(5):410-20.

68.   International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 100D. Radiation. Lyon, France; 2012.

69.   Sont WN, Zielinski JM, Ashmore JP, Jiang H, Krewski D, Fair ME, et al. First analysis of cancer incidence and occupational radiation exposure based on the National Dose Registry of Canada. American journal of epidemiology. 2001;153(4):309-18.

70.   Zielinski JM, Garner MJ, Krewski D, Ashmore JP, Band PR, Fair ME, et al. Decreases in Occupational Exposure to Ionizing Radiation among Canadian Dental Workers. J Can Dent Assoc 2005;71(1):29-33.

71.   Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Estimates of Radiation-Related Cancer Risks. Radiat Res. 2007;167(4):396-416.

72.   Rogel A, Joly K, Metz-Flamant C, Laurent O, Tirmarche M, Hubert D, et al. Mortality in nuclear workers of the French electricity company: Period 1968-2003. Revue D Epidemiologie Et De Sante Publique. 2009;57(4):257-65.

73.   International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol 102. Non-Ionizing Radiation, Part 2: Radiofrequency Electromagnetic Fields. Lyon, France; 2013.

74.   Ojajarvi A, Partanen T, Ahlbom A, Boffetta P, Hakulinen T, Jourenkova N, et al. Risk of pancreatic cancer in workers exposed to chlorinated hydrocarbon solvents and related compounds: A meta-analysis. American journal of epidemiology. 2001;153(9):841-50.

75.   Liu T, Xu QE, Zhang CH, Zhang P. Occupational exposure to methylene chloride and risk of cancer: a meta-analysis. Cancer Causes & Control. 2013;24(12):2037-49.

76.   Ruder AM, Ward EM, Brown DP. Mortality in dry-cleaning workers: An update. American journal of industrial medicine. 2001;39(2):121-32.

77.   Lynge E, Andersen A, Rylander L, Tinnerberg H, Lindbohm ML, Pukkala E, et al. Cancer in persons working in dry cleaning in the Nordic countries. Environmental health perspectives. 2006;114(2):213-9.

78.   Mundt KA, Birk T, Burch MT. Critical review of the epidemiological literature on occupational exposure to perchloroethylene and cancer. International archives of occupational and environmental health. 2003;76(7):473-91.

79.   Bosetti C, McLaughlin JK, Tarone RE, Pira E, LaVecchia C. Formaldehyde and cancer risk: a quantitative review of cohort studies through 2006. Annals of Oncology. 2008;19:29-42.

80.   Collins JJ, Esmen NA, Hall TA. A review and meta-analysis of formaldehyde exposure and pancreatic cancer. American journal of industrial medicine. 2001;39(3):336-45.

81.   Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair A. Mortality from solid cancers among workers in formaldehyde industries. American journal of epidemiology. 2004;159(12):1117-30.

82.   Pira E, Romano C, Verga F, La Vecchia C. Mortality from lymphohematopoietic neoplasms and other causes in a cohort of laminated plastic workers exposed to formaldehyde. Cancer causes & control : CCC. 2014;25(10):1343-9.

83.   Boffetta P, Adami HO, Cole P, Trichopoulos D, Mandel JS. Epidemiologic Studies of Styrene and Cancer: A Review of the Literature. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine. 2009;51:1275-87.

84.   Collins JJ, Bodner KM, Bus JS. Cancer mortality of workers exposed to styrene in the U.S. Reinforced plastics and composite industry. Epidemiology (Cambridge, Mass). 2013;24(2):195-203.

85.   Coggon D, Ntani G, Harris EC, Palmer KT. Risk of cancer in workers exposed to styrene at eight British companies making glass-reinforced plastics. Occupational and environmental medicine. 2015;72(3):165-70.

86.   Ruder AM, Meyers AR, Bertke SJ. Mortality among styrene-exposed workers in the reinforced plastic boatbuilding industry. Occupational and environmental medicine. 2016;73(2):97-102.

87.   Calvert GM, Ward E, Schnorr TM, Fine LJ. Cancer risks among workers exposed to metalworking fluids: a systematic review. American journal of industrial medicine. 1998;33(3):282-92.

88.   Eisen EA, Bardin J, Gore R, Woskie SR, Hallock MF, Monson RR. Exposure-response models based on extended follow-up of a cohort mortality study in the automobile industry. Scandinavian journal of work, environment & health. 2001(4):240-9.

89.   Yassi A, Tate RB, Routledge M. Cancer incidence and mortality in workers employed at a transformer manufacturing plant: update to a cohort study. American journal of industrial medicine. 2003;44(1):58-62.

90.   Ritz B. Cancer mortality among workers exposed to chemicals during uranium processing. Journal of Occupational and Environmental Medicine. 1999;41(7):556-66.

91.   Kazerouni N, Thomas TL, Petralia SA, Hayes RB. Mortality Among Workers Exposed to Cutting Oil Mist: Update of Previous Reports. American journal of industrial medicine. 2000;38:410-6.

92.   Friesen MC, Betenia N, Costello S, Eisen EA. Metalworking fluid exposure and cancer risk in a retrospective cohort of female autoworkers. Cancer Causes & Control. 2012;23(7):1075-82.

93.   Zhao Y, Kennedy N, Morgenstern H, Ritz B. Estimated Effects of Solvents and Mineral Oils on Cancer Incidence and Mortality in a Cohort of Aerospace Workers. American journal of industrial medicine. 2005;48:249-58.

94.   Parent ME, Rousseau MC, El-Zein M, Latreille B, Desy M, Siemiatycki J. Occupational and recreational physical activity during adult life and the risk of cancer among men. Cancer Epidemiology. 2011;35(2):151-9.

95.   Parent ME, El-Zein M, Rousseau MC, Pintos J, Siemiatycki J. Night Work and the Risk of Cancer Among Men. American journal of epidemiology. 2012;176(9):751-9.

96.   Lin Y, Ueda J, Yagyu K, Kurosawa M, Tamakoshi A, Kikuchi S. A prospective cohort study of shift work and the risk of death from pancreatic cancer in Japanese men. Cancer causes & control : CCC. 2013;24(7):1357-61.

97.   Teschke K, Olshan AF, Daniels JL, De Roos AJ, Parks CG, Schulz M, et al. Occupational exposure assessment in case–control studies: opportunities for improvement. Occupational and environmental medicine. 2002;59:575-94.

98.   Siemiatycki J. Risk factors for cancer in the workplace. Boca Raton, FL: CRC Press; 1991.

99.   Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health. 1989;79:340-9.

100.   Greenland S. Multiple comparisons and association selection in general epidemiology. International journal of epidemiology. 2008;37:430–4.

101.   Rothman KJ. No Adjustments Are Needed for Multiple Comparisons. Epidemiology (Cambridge, Mass). 1990;1(1):43-6.

102.   Richardson L. Case control study methods: response rates, respondant characteristics and nonresponse bias. Montreal, Canada: McGill University; 1985.

103.   Szklo M, Nieto F. Epidemiology: Beyond the Basics. Third ed. Boston, MA: Jones & Bartlett Learning; 2014.

104.   McNamee R. Confounding and confounders. Occupational and environmental medicine. 2003;60:227-34.

105.   International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 100F. Coal-tar pitch. Lyon, France; 2012.

106.   Agency for Toxic Substances and Disease Registry. Toxicological Profile for Wood Creosote, Coal Tar Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles Atlanta, GA.2002 [Available from: http://www.atsdr.cdc.gov/toxprofiles/tp85-c6.pdf.

107.   Lamba AB, Ward MH, Weeks JL, Dosemeci M. Cancer mortality patterns among hairdressers and barbers in 24 US states, 1984 to 1995. Journal of Occupational and Environmental Medicine. 2001;43(3):250-8.

108.   Veyalkin I, Gerein V. Retrospective cohort study of cancer mortality at the Minsk leather tannery. Industrial health. 2006;44(1):69-74.

109.   Reul NK, Li W, Gallagher LG, Ray RM, Romano ME, Gao D, et al. Risk of Pancreatic Cancer in Female Textile Workers in Shanghai, China, Exposed to Metals, Solvents, Chemicals, and Endotoxin: Follow-Up to a Nested Case-Cohort Study. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine. 2016;58(2):195-9.

110.   Alguacil J, Porta M, Benavides FG, Malats N, Kogevinas M, Fernandez E, et al. Occupation and pancreatic cancer in Spain: a case-control study based on job titles. PANKRAS II Study Group. International journal of epidemiology. 2000;29(6):1004-13.

111.   Li K, Yu S. A nested case-control study on risk of pancreatic cancer among workers in the rubber industry. Pancreas. 2002;24(4):417-8.

112.   Brown LM, Moradi T, Gridley G, Plato N, Dosemeci M, Fraumeni JF. Exposures in the painting trades and paint manufacturing industry and risk of cancer among men and women in Sweden. Journal of Occupational and Environmental Medicine. 2002;44(3):258-64.

113.   Clary T, Ritz B. Pancreatic cancer mortality and organochlorine pesticide exposure in California, 1989-1996. American journal of industrial medicine. 2003;43(3):306-13.

114.   Steenland K, Woskie S. Cohort Mortality Study of Workers Exposed to Perfluorooctanoic Acid. American journal of epidemiology. 2012;176(10):909-17.

115.   Raleigh KK, Alexander BH, Olsen GW, Ramachandran G, Morey SZ, Church TR, et al. Mortality and cancer incidence in ammonium perfluorooctanoate production workers. Occupational and environmental medicine. 2014;71(7):500-6.

116.   Consonni D, Straif K, Symons JM, Tomenson JA, van Amelsvoort L, Sleeuwenhoek A, et al. Cancer Risk Among Tetrafluoroethylene Synthesis and Polymerization Workers. American journal of epidemiology. 2013;178(3):350-8.

117.   Kurumatani N, Natori Y, Mizutani R, Kumagai S, Haruta M, Miura H, et al. A historical cohort mortality study of workers exposed to asbestos in a refitting shipyard. Industrial health. 1999;37(1):9-17.

118.   Schwartz GG, Reis IM. Is cadmium a cause of human pancreatic cancer? Cancer Epidemiology Biomarkers & Prevention. 2000;9(2):139-45.

119.   Wong O, Harris F. Cancer mortality study of employees at lead battery plants and lead smelters, 1947–1995. American journal of industrial medicine. 2000;38(3):255-70.

120.   Marsh GM, Youk AO, Buchanich JM, Kant IJ, Swaen G. Mortality patterns among workers exposed to acrylamide: Updated follow up. Journal of Occupational and Environmental Medicine. 2007;49(1):82-95.

121.   Swaen GMH, Haidar S, Burns CJ, Bodner K, Parsons T, Collins JJ, et al. Mortality study update of acrylamide workers. Occupational and environmental medicine. 2007;64(6):396-401.

122.   Boffetta P, Dosemeci M, Gridley G, Bath H, Moradi T, Silverman D. Occupational exposure to diesel engine emissions and risk of cancer in Swedish men and women. Cancer Causes & Control. 2001;12(4):365-74.

123.   Kimbrough RD, Doemland ML, Mandel JS. A mortality update of male and female capacitor workers exposed to polychlorinated biphenyls. Journal of Occupational and Environmental Medicine. 2003;45(3):271-82.

124.   Ritz B, Zhao YX, Krishnadasan A, Kennedy N, Morgenstern H. Estimated effects of hydrazine exposure on cancer incidence and mortality in aerospace workers. Epidemiology (Cambridge, Mass). 2006;17(2):154-61.

125.   Wiebelt H, Becker N. Mortality in a cohort of toluene exposed employees (rotogravure printing plant workers). Journal of occupational and environmental medicine. 1999;41(12):1134-9.

126.   Rønneberg A, Haldorsen T, Romundstad P, Andersen A. Occupational exposure and cancer incidence among workers from an aluminum smelter in western Norway. Scandinavian journal of work, environment & health. 1999;25(3):207-14.

127.   Moulin J, Clavel T, Buclez B, Laffitte-Rigaud G. A mortality study among workers in a French aluminium reduction plant. International archives of occupational and environmental health. 2000;73(5):323-30.

128.   Spinelli JJ, Demers PA, Le ND, Friesen MD, Lorenzi MF, Fang R, et al. Cancer risk in aluminum reduction plant workers (Canada). Cancer Causes & Control. 2006;17(7):939-48.

129.   Colt JS, Stallones L, Cameron LL, Dosemeci M, Zahm SH. Proportionate mortality among US migrant and seasonal farmworkers in twenty-four states. American journal of industrial medicine. 2001;40(5):604-11.

130.   LeMasters GK, Genaidy AM, Succop P, Deddens J, Sobeih T, Barriera-Viruet H, et al. Cancer risk among firefighters: a review and meta-analysis of 32 studies. Journal of occupational and environmental medicine. 2006;48(11):1189-202.

131.   Amadeo B, Marchand JL, Moisan F, Donnadieu S, Gaelle C, Simone MP, et al. French firefighter mortality: analysis over a 30-year period. American journal of industrial medicine. 2015;58(4):437-43.

132.   Petralia SA, Dosemeci M, Adams EE, Zahm SH. Cancer mortality among women employed in health care occupations in 24 US States, 1984-1993. American journal of industrial medicine. 1999;36(1):159-65.

133.   Lin SY, Lin CL, Hsu WH, Wang IK, Chang CC, Huang CC, et al. A Comparison of Cancer Incidence among Physician Specialists and the General Population: A Taiwanese Cohort Study. Journal of Occupational Health. 2013;55(3):158-66.

134.   Koifman S, Malhao TA, de Oliveira GP, Camara VD, Koifman RJ, Meyer A. Cancer Mortality Among Brazilian Dentists. American journal of industrial medicine. 2014;57(11):1255-64.

135.   van Barneveld TA, Sasco AJ, van Leeuwen FE. A cohort study of cancer mortality among Biology Research Laboratory workers in the Netherlands. Cancer Causes & Control. 2004;15(1):55-66.

136.   Stern FB. Mortality among chrome leather tannery workers: An update. American journal of industrial medicine. 2003;44(2):197-206.

137.   Iaia TE, Bartoli D, Calzoni P, Comba P, De Santis M, Dini F, et al. A cohort mortality study of leather tanners in Tuscany, Italy. American journal of industrial medicine. 2006;49(6):452-9.

138.   Delzell E, Brown DA, Matthews R. Mortality Among Hourly Motor Vehicle Manufacturing Workers. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine. 2003;45:813-30.

139.   Rafnsson V. Incidence of cancer among bookbinders, printers, photoengravers, and typesetters. Occupational and environmental medicine. 2001;58(8):523-7.

140.   Band PR, Le ND, Fang R, Astrakianakis G, Bert J, Keefe A, et al. Cohort cancer incidence among pulp and paper mill workers in British Columbia. Scandinavian journal of work, environment & health. 2001;27(2):113-9.

141.   Battista G, Belli S, Comba P, Fiumalbi C, Grignoli M, Loi F, et al. Mortality due to asbestos-related causes among railway carriage construction and repair workers. Occupational Medicine-Oxford. 1999;49(8):536-9.

142.   Straif K, Weiland SK, Werner B, Chambless L, Mundt KA, Keil U. Workplace risk factors for cancer in the German rubber industry: part 2. Mortality from non-respiratory cancers. Occupational and environmental medicine. 1998;55(5):325-32.

143.   Saarni H, Pentti J, Pukkala E. Cancer at sea: a case-control seafarers study among male Finnish seafarers. Occupational and environmental medicine. 2002;59(9):613-9.

144.   Nichols L, Sorahan T. Cancer incidence and cancer mortality in a cohort of UK semiconductor workers, 1970-2002. Occupational Medicine-Oxford. 2005;55(8):625-30.

145.   Travier N, Gridley G, Blair A, Dosemeci M, Boffetta P. Cancer incidence among male Swedish veterinarians and other workers of the veterinary industry: a record-linkage study. Cancer Causes & Control. 2003;14(6):587-93.
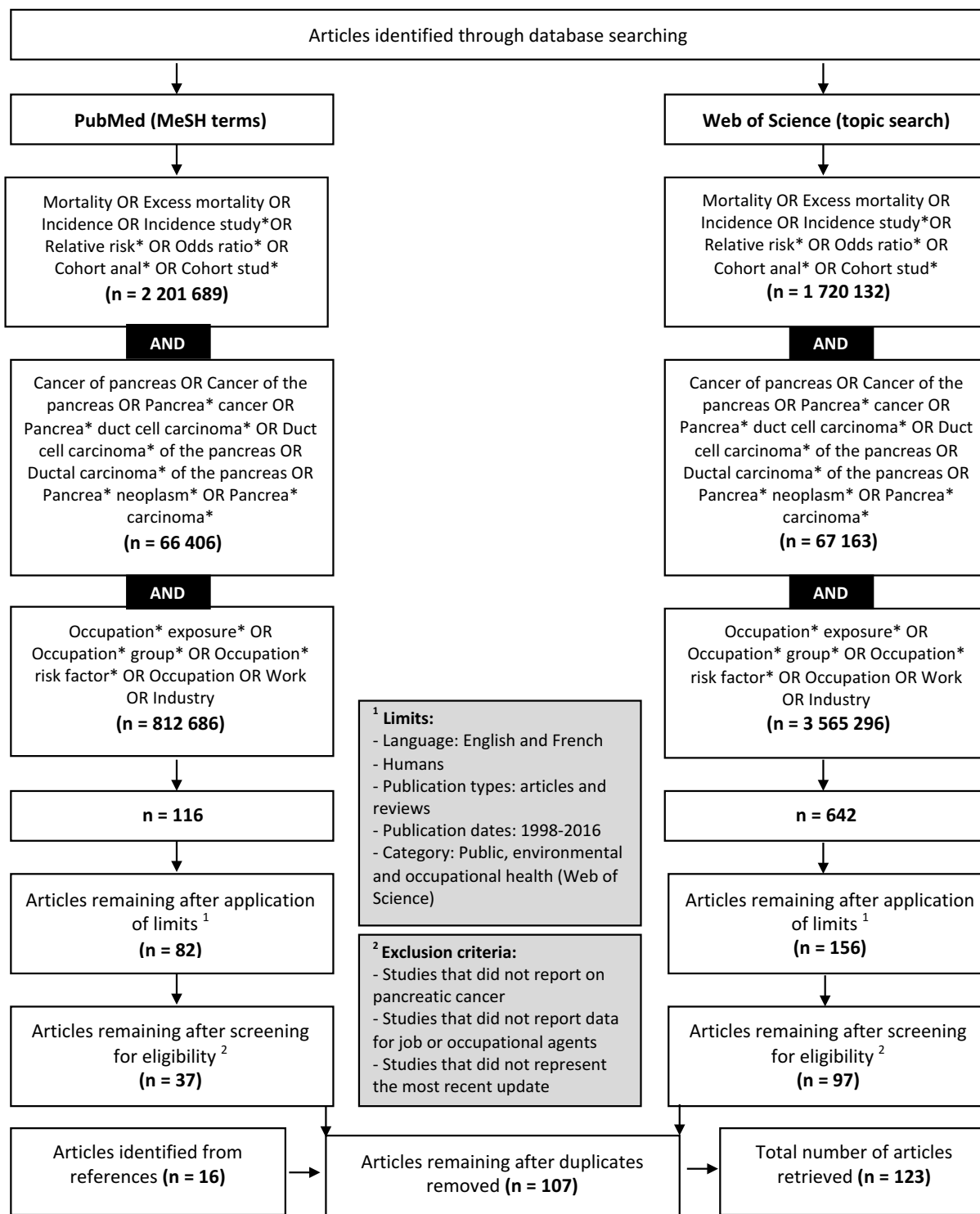
APPENDIX 1

Figure 1. Flowchart diagram outlining the database search strategy for the retrieval of research articles on occupational risk factors for pancreatic cancer.

APPENDIX 2

Table I. Summary of the associations between some non-occupational exposures and pancreatic cancer.

| | Direction of the association | | | | |
| | Positive | | | Negative | Null |
Strength of the evidence [1]	**High risk (RR ≥ 2.0)**	**Moderate risk (RR 1.5-1.9)**	**Low risk (RR 1-1.4)**	**Low protection (RR 0.5-0.9)**	
Strong	Chronic pancreatitis	Tobacco smoking Diabetes Hepatitis B	BMI High waist-to-hip ratio	Allergies	Coffee Tea Soft drinks Fish NSAIDS Statins
Moderate		Heavy alcohol intake H. pylori		Fruits High folate	Glycemic index/load
Poor		Hepatitis C	Sugar intake Red and processed meat	Vegetables	Environmental tobacco smoke

BMI, body-mass index; NSAIDs, non-steroidal anti-inflammatory drugs; RR, relative risk

[1] Reproduced from Maisonneuve and colleagues' grading of the evidence for the listed exposures (8). The authors defined "strong" evidence as based on more than one meta-analysis and confirmed in cohort studies or pooled studies; "moderate" evidence as based on either more than one meta-analysis or a single meta-analysis of cohort studies; and "poor" as evidence based on a single meta-analysis that was not exclusively based on cohort studies or if the results were discordant.

APPENDIX 3

Table II. Some studies of environmental exposures and pancreatic cancer risk.

Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Arsenic Lead Nickel Selenium	Amaral et al. 2012 (35)	Hospital-based case control (Spain)	Cases diagnosed at 5 participating hospitals 1992-1995, controls from the Spanish Bladder Cancer/EPICURO study 1998-2001 PC cases: 118, controls: 399	Concentrations in toenail specimens	$OR_{As} = 2.02$ (1.0-3.78) $OR_{Pb} = 6.26$ (2.71-14.47) $OR_{Se} = 0.27$ (0.12-0.59) $OR_{Ni} = 0.05$ (0.02-0.5)	Age, gender, regions, smoking
Arsenic	Garcia-Esquinas et al. 2013 (36)	Cohort — The Strong Heart Study (US)	3,935 men and women ages 45–75 from 13 American Indian communities PC deaths: 25	Urinary arsenic species	$HR_{\text{80th vs 20th percentile urinary arsenic concentration}} = 2.46$ (1.09-5.58)	Age, alcohol use, BMI, education, sex, state, smoking
Cadmium	Kriegel et al. 2006 (37)	Hospital-based case control (East Nile Delta region, Egypt)	Egyptian citizens diagnosed with PC at single participating hospital PC cases: 31, controls: 52	Serum cadmium	$OR = 1.12$ (1.04-1.23)	Age, occupation, sex, smoking
Cadmium	Chen et al. 2015 (31)	Meta-analysis	2 case-control studies 4 cohort studies	N/A	$MRR = 2.05$ (1.58-2.66)	N/A
Organochlorine pesticides	Clary et al. 2003 (113)	Cross-sectional (California, US)	Populations of three California counties PC deaths: 950 Non-cancer controls: 9,435	California Department of Pesticide Regulation Pesticide Use Reporting database used to assign exposure at ZIP code level	For duration of residence > 20 years $POR_{\text{1,3-d pesticide}} = 1.89$ (1.13-3.15)	Age at death, education, other pesticides, race, residence (urban vs. rural), year of death

BMI, body-mass index; CI, confidence interval; HR, hazard ratio; MRR, meta-risk ratio; OR, odds ratio; PC, pancreatic cancer; POR, prevalence odds ratio

APPENDIX 4

Table III. Occupational exposures and pancreatic cancer risk: summary of publications from 1998 to 2016.

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
BY AGENT							
Acids	APFO/PFOA	Steenland et al. 2012 (114)	Cohort (West Virginia, US)	5791 workers of DuPont chemical plant in Parkersburg; 67,294 male and 19,404 female workers of other DuPont plants (referent) PC deaths: 18	JEM	SMR = 1.04 (0.62-1.64) [vs. referent]	None
Acids	APFO/PFOA	Raleigh et al. 2014 (115)	Cohort (Minnesota, US)	Workers of two 3M Company plants; 4668 from Cottage Grove Plant (exposed) and 4359 from Saint Paul Plant (referent) PC cases: 10 PC deaths: 18	JEM	Incidence: $HR_{\text{highest exposure quartiles}} = 1.36$ (0.59-3.11) Mortality: $SMR_{\text{highest exposure quartile}} = 1.41$ (0.52-3.06) $HR_{\text{highest exposure quartile}} = 1.23$ (0.50-3.00)	Age, sex
Acids	TFE (APFO)	Consonni et al. 2013 (116)	Cohort — The TFE Multicenter Mortality Study (US and Europe)	5879 male workers from 6 PTFE production sites (4773 exposed) PC deaths: 13	JEM	$SMR_{\text{overall}} = 1.15$ (0.61-1.97) $SMR_{\text{high exposure}} = 1.47$ (0.54-3.21); P trend = 0.21 $SMR_{>20 \text{ y exposed}} = 1.16$ (0.14-4.21); P trend = 0.4	None

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Biological agents	Poultry	Johnson et al. 2010 (24)	Cohort (US)	20,132 workers employed in 11 poultry slaughtering/processing plants PC deaths: 27	Self-report (yes/no questions on individual plant activities)	$SMR_{overall}$ = 1.5 (0.8-2.3) $SMR_{slaughtering}$ = 1.1 (0.2-3.4)	None
Biological agents	Poultry	Felini et al. 2011 (25)	Case cohort (US)	Poultry and non-poultry workers from the United Food and Commercial Workers Union PC deaths: 23, controls: 1516	Proxy report (questionnaire)	**$OR_{slaughtering\ chickens}$ = 8.9 (2.7-29.3)** **$OR_{catching\ live\ chickens}$ = 3.6 (1.2-10.9)** **$OR_{slaughtering\ non-poultry}$ = 4.8 (1.5-16.6)**	Smoking
Dusts	Asbestos	Kurumatani et al. 1999 (117)	Cohort (Japan)	249 Japanese male laggers and boiler repairers in a refitting shipyard PC deaths: 4 (laggers)	Job title	**$SMR_{laggers,\ employed\ >12\ y}$ = 7.78 (2.07-25.19)**	None
Dusts	Asbestos	Ojajarvi et al. 2000 (26)	Meta-analysis of 23 chemical and physical agents	24 studies	N/A	MRR = 1.1 (0.9-1.5)	N/A
Dusts	Asbestos (among > 20 chemical agents and 4 physical agents)	Santibanez et al. 2010 (27)	Hospital-based case control (Spain)	Men and women aged 30–80 years hospitalized 1995–1999 in participant hospitals PC cases: 161, controls: 455	JEM (in-person interviews)	For ductal adenocarcinoma: **OR = 2.09 (1.05-4.13)**	Age, alcohol use, education, province, sex, smoking
Dusts	Asbestos (and 5 other agents)	Antwi et al. 2015 (28)	Hospital-based case control (US)	PC cases: 1892 Controls: 2316	Self-report (yes/no questions)	**OR = 1.54 (1.23-1.92)**	Age, BMI, education, diabetes, sex, smoking

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Dusts	Silica	Ojajarvi et al. 2000 (26)	Meta-analysis of 23 chemical and physical agents	3 studies	N/A	MRR = 1.4 (0.9-2.0)	N/A
Dusts	Silica	Birk et al. 2009 (29)	Cohort (Germany)	17,644 porcelain workers PC deaths: 33 men, 9 women	Job title	**SMR $_{men}$ = 1.71 (1.18-2.41)** SMR $_{women}$ = 0.72 (0.33-1.38)	None
Metals	Cadmium	Ojajarvi et al. 2000 (26)	Meta-analysis of 23 chemical and physical agents	2 studies	N/A	MRR = 0.7 (0.4-1.4)	N/A
Metals	Cadmium	Schwartz et al. 2000 (118)	Meta-analysis (Europe)	3 cohort studies	N/A	SMR = 166 (98–280)	N/A
Metals	Cadmium	Luckett et al. 2012 (38)	Population-based case control (South Louisiana, US)	Men and women > 20 years PC cases: 69, controls: 158	Self-report	OR = 1.69 (0.14-20.39)	Age, alcohol use, education, family history, race, sex, smoking
Metals	Chromium	Ojajarvi et al. 2000 (26)	Meta-analysis of 23 chemical and physical agents	9 studies	N/A	MRR = 1.4 (0.9-2.3)	N/A
Metals	Chromium (and 28 other chemical and physical agents)	Weiderpass et al. 2003 (33)	Cohort (Finland)	413,877 female workers in the industry and service sectors comprising 183 job titles PC cases: 1302	JEM	Medium-high exposure: **RR = 1.80 (1.04-3.12)** (significant associations for cadmium, lead, nickel and PAHs at low exposure levels)	Smoking (adjustment at job-title level)
Metals	Chromium (and 5 other agents)	Antwi et al. 2015 (28)	Hospital-based case control (US)	PC cases: 1892 Controls: 2316	Self-report (yes/no questions)	OR = 1.42 (0.89-2.26)	Age, BMI, education, diabetes, sex, smoking

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Metals	Lead	Ojajarvi et al. 2000 (26)	Meta-analysis of 23 chemical and physical agents	4 studies	N/A	MRR = 1.1 (0.8-1.5)	N/A
Metals	Lead	Wong et al. 2000 (119)	Cohort (US)	4518 male lead battery workers (10 plants) and 2300 male lead smelter workers (6 smelters) PC deaths: 41	Job title and some biological monitoring data	SMR = 92.6 (66.4-125.6)	None
Metals	Lead	Ilychova et al. 2012 (34)	Cohort (Moscow, Russia)	4525 workers from 27 printing plants PC deaths: 20	Job title, occupational history and industrial hygiene monitoring data	**SMR $_{employed > 10 y}$ = 1.81 (1.15-2.84) SMR $_{highest\ cumulative\ exposure}$ = 2.32 (1.46-3.68)**	None
Metals	Nickel	Ojajarvi et al. 2000 (26)	Meta-analysis of 23 chemical and physical agents	4 studies	N/A	**MRR = 1.9 (1.2-3.2)**	N/A
Metals	Nickel (and 5 other agents)	Antwi et al. 2015 (28)	Hospital-based case control (US)	PC cases: 1892 Controls: 2316	Self-report (yes/no questions)	OR $_{nickel}$ = 1.55 (0.95-2.52)	Age, BMI, education, diabetes, sex, smoking
Other chemicals	Acrylamide	Marsh et al. 2007 (120)	Cohort (US)	8508 male workers of three Cytec chemical manufacturing plants PC deaths: 54	Job title, occupational history and industrial hygiene monitoring data	SMR $_{overall}$ = 0.94 (0.7-1.22) RR $_{highest\ cumulative\ exposure}$ = 2.05 (0.84-5.02)	Smoking

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Other chemicals	Acrylamide	Swaen et al. 2007 (121)	Cohort (US)	696 workers of Dow Chemical acrylamide facilities PC deaths: 5	JEM	SMR = 222 (72.1-518.5)	None
Other chemicals	Dyes/inks	Felini et al. 2014 (25)	Case cohort (US)	Workers from the United Food and Commercial Workers Union PC deaths: 23, controls: 1516	Proxy report (questionnaire)	OR $_{\text{work where dyes made/handled}}$ = 7.5 (1.7-33.9)	Smoking
Other chemicals	N-nitrosamines	Fritschi et al. 2015 (60)	Population-based case control (Queensland, Australia)	PC cases: 504, controls: 643	Expert assessment	OR $_{\text{ever exposure}}$ = 0.85 (0.51-1.42); no exposure-response trend	Age, sex, smoking
PAHs	PAHs	Ojajarvi et al. 2000 (26)	Meta-analysis of 23 chemical and physical agents	4 studies	N/A	MRR = 1.5 (0.9-2.5)	N/A
PAHs	Bitumen fumes	Kauppinen et al. 2003 (52)	Cohort (Finland)	9643 road paving workers PC cases: 6	Job title, occupational history and industrial hygiene monitoring data	SIR $_{\text{men}}$ = 1.52 (0.56-3.31)	None
PAHs	Diesel exhaust	Ojajarvi et al. 2000 (26)	Meta-analysis of 23 chemical and physical agents	7 studies	N/A	MRR = 1.0 (0.9-1.2)	N/A

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
PAHs	Diesel exhaust	Boffetta et al. 2001 (122)	Record linkage (Sweden)	Members of the Swedish population who completed the 1960 census PC cases: 1859 men, 47 women	JEM	**SIR $_{men}$ = 1.05 (1.00-1.10)** SIR $_{women}$ = 1.09 (0.80-1.45); no exposure-response trend	Age, calendar period, residence (region), residence (rural vs. urban)
PAHs	Diesel exhaust	Boffetta et al. 2014 (55)	Meta-analysis	3 case-control studies 10 cohort studies	N/A	MRR = 0.9 (0.5-1.6) MRR = 1.0 (0.9-1.1)	N/A
Pesticides	Any pesticide	Cantor et al. 1999 (56)	Case-cohort (US)	Cohort of 9961 aerial pesticide applicators (exposed) and 9969 flight instructors (referent) PC cases: 22, controls: 8	Job title	**Mortality RR = 2.71 (1.4-5.3)** **RR $_{highest\ cumulative\ exposure}$ = 3.45**	None
Pesticides	22 agents 21 chemical agents, 4 physical agents & 2 other work-related factors	Alguacil et al. 2000 (58)	Hospital-based case control—PANKRAS II study (Spain)	Cases diagnosed at 5 participating hospitals 1992–1995 PC cases: 185, controls: 264	Expert assessment (22 agents) JEM (21 chemical agents, 4 physical agents & 2 other work-related factors)	**OR $_{pesticides}$ = 3.17 (1.09-9.18)** (expert assessment)	Age, alcohol use, hospital, sex, smoking
Pesticides	Fungicides, herbicides and insecticides	Ojajarvi et al. 2000 (26)	Meta-analysis of 23 chemical and physical agents	2 studies 10 studies 3 studies	N/A	MRR $_{fungicides}$ = 1.3 (0.4-3.8) MRR $_{herbicides}$ = 1.0 (0.8-1.3) MRR $_{insecticides}$ = 1.5 (0.6-3.7)	N/A

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Pesticides	Fungicides, herbicides and insecticides	Ji et al. 2001 (57)	Population-based case control (US)	Residents ages 30–79 from 3 US states covered by cancer registries PC cases: 485, controls: 2109	JEM	**OR $_{any\ pesticide,\ high\ exposure}$ = 1.3 (1.0-2.0); *P* trend = 0.01**	Age, alcohol use, exposure to other pesticides, income, race, sex, smoking, study area
Pesticides	Pesticides and natural fertilizers	Lo et al. 2007 (59)	Hospital-based case control (East-Nile Delta region, Egypt)	Incident cases from 2 major hospitals PC cases: 194, controls: 194	Self-report (in-person interview)	OR $_{pesticides}$ = 2.6 (0.97-7.2) OR $_{fertilizers}$ = 0.1 (0.2-0.4)	Age, residence, sex, smoking
Pesticides	Any pesticide (among > 20 chemical agents and 4 physical agents)	Santibanez et al. 2010 (27)	Hospital-based case control (Spain)	Men and women aged 30–80 years hospitalized 1995–1999 in participant hospitals PC cases: 161, controls: 455	JEM (in-person interviews)	For ductal adenocarcinoma: **OR = 2.16 (0.21-22.32)**	Age, alcohol use, education, province, sex, smoking
Pesticides	Pesticides (and 5 other agents)	Antwi et al. 2015 (28)	Hospital-based case control (US)	PC cases: 1892 Controls: 2316	Self-report (yes/no questions)	**OR = 1.21 (1.02-1.44)**	Age, BMI, education, diabetes, sex, smoking
Pesticides	Several classes of pesticides	Fritschi et al. 2015 (60)	Population-based case control (Queensland, Australia)	PC cases: 504, controls: 643	Expert assessment	OR $_{ever\ exposure,\ any\ pesticide}$ = 0.90 (0.61-1.33); no exposure-response trend	Age, sex
Pesticides	Organochlorines (DDE, HCB, PCBs, *t*-Nonachlor)	Hoppin et al. 2000 (63)	Population-based case-control study (San Francisco, US)	Residents aged 21–85 years of 6 San Francisco counties PC cases: 108, controls: 82	Serum measurements	**OR $_{total\ PCBs,\ highest\ concentration}$ = 4.2 (1.9-9.4); *P* trend < 0.001**	Age, race, sex
Pesticides	PCBs	Kimbrough et al. 2003 (123)	Cohort (New York, US)	7075 capacitor workers at 2 GE facilities PC deaths: 27	Job title	SMR $_{ever\ highly\ exposed}$ = 95 (25–242)	None

x

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Pesticides	DDT	Beard et al. 2003 (64)	Cohort (Australia)	394 exposed and 185 unexposed male outdoor workers PC deaths: 8	Job title and some biological monitoring data	< 3 years of employment: **SMR = 5.27 (1.09-15.40)** vs. the Australian male population **SIR = 7.00 (1.39-35.32)** vs. control group	None
Pesticides	DDT	Cocco et al. 2005 (65)	Cohort (Sardinia, Italy)	464 exposed DDT applicators, 1291 unexposed workers PC cases: 13, controls: 9	JEM	RR = 0.8 (0.4-1.8); no exposure-response trend	Age (at exit from follow-up and at start of exposure), ethnicity
Pesticides	24 different pesticides	Andreotti et al. 2009 (61)	Case-cohort—The Agricultural Health Study (US)	57,311 pesticide applicators PC cases: 64, controls: 52,721	Self-report (questionnaire)	**OR $_{pendimethalin, high\ exposure}$ = 3.0 (1.3-7.2)** **OR $_{EPTC, high\ exposure}$ = 2.56 (1.1-5.4)**	Age, diabetes, smoking
Pesticides	Acetochlor (herbicide)	Lerro et al. 2015 (62)	Cohort — The Agricultural Health Study (US)	33,484 male pesticide applicators PC cases: 62	Self-report (telephone interview)	RR $_{ever\ exposure}$ = 2.36 (0.98-5.65)—significant at $p < 0.1$; no exposure-response trend	Age, alcohol use, applicator type (private or commercial), BMI, correlated pesticide use, education, family history of cancer, race, smoking, state, use of enclosed cab

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Physical agents	Electromagnetic fields	Ji et al. 1999 (39)	Population-based case control (Shanghai, China)	Incident cases aged 30–74 years diagnosed 1990–1993 identified through the Shanghai Cancer Registry PC cases: 135, controls: 125	JEM	Men: $OR_{high\ intensity\ exposure} = 3.3\ (1.4-7.9)$; P trend = 0.05 $OR_{high\ probability\ exposure} = 2.6\ (1.2-5.4)$; P trend = 0.05	Age, education, income, other occupations, smoking
Physical agents	Electromagnetic fields	Ojajarvi et al. 2000 (26)	Meta-analysis of 23 chemical and physical agents	5 studies	N/A	MRR = 1.1 (0.8-1.4)	N/A
Physical agents	Electromagnetic fields (and 28 other chemical and physical agents)	Weiderpass et al. 2003 (33)	Cohort (Finland)	413,877 female workers in the industry and service sectors comprising 183 job titles PC cases: 1302	JEM	Medium-high exposure: $RR_{low\ frequency\ EMF} = 1.82\ (1.18-2.81)$	Smoking (adjustment at job-title level)
Physical agents	Ionizing radiation	Sont et al. 2001	Cohort (Canada)	191,333 workers monitored by the NDR PC cases: 76	Individual recorded dosimetry data used to calculate cumulative dose	SIR = 0.75 (90% CI: 0.62-0.91) Excess RR/Sv = 6.9 (90% CI: < 0-27.1)	None
Physical agents	Ionizing radiation	Zielinski et al. 2005 (70)	Cohort (Canada)	42,175 dental workers monitored by the NDR PC cases: 16 PC deaths: 13	Individual recorded dosimetry data used to calculate cumulative dose	SIR = 1.15 (90% CI: 0.62-1.74) SMR = 0.99 (90% CI: 0.59-1.58)	None
Physical agents	Ionizing radiation	Cardis et al. 2007 (71)	Cohort (International)	600,000 nuclear workers from 15 countries PC deaths: 272	Individual recorded dosimetry data used to calculate cumulative dose	Excess RR/Sv = 2.10 (90% CI: 0.59-6.77)	Age, duration of employment, facility, SES, sex

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Physical agents	Ionizing radiation	Rogel et al. 2009 (72)	Cohort (France)	22,393 nuclear workers of the French electricity company monitored for exposure to radiation PC deaths: 25	Radiation monitoring data linked to personnel data	SMR = 1.18 (0.82-1.65)	None
Physical agents	Ionizing radiation (among > 20 chemical agents and 4 physical agents)	Santibanez et al. 2010 (27)	Hospital-based case control (Spain)	Men and women aged 30–80 years hospitalized 1995–1999 in participant hospitals PC cases: 161, controls: 455	JEM (in-person interviews)	For ductal adenocarcinoma: **OR = 15.19 (2.12-109.15)**	Age, alcohol use, education, province, sex, smoking
Solvents	Solvents (in addition to metals, dyes, inks, resins, lubricants, pesticides, endotoxin)	Reul et al. 2016 (109)	Case cohort (Shanghai, China)	267,400 female textile workers from 502 factories PC cases: 481, controls: 3191	JEM	HR $_{exposure > 20\ y}$ = 1.51 (0.99-2.30); ***P* trend = 0.004**	Age, smoking
Solvents	Aliphatic and alicyclic hydrocarbons	Ojajarvi et al. 2000 (26)	Meta-analysis of 23 chemical and physical agents	20 studies	N/A	MRR = 1.3 (0.8-2.0)	N/A
Solvents	Benzene	Antwi et al. 2015 (28)	Hospital-based case control (US)	PC cases: 1892 Controls: 2316	Self-report (yes/no questions)	**OR = 1.70 (1.23-2.35)**	Age, BMI, education, diabetes, sex, smoking
Solvents	CHCs	Ojajarvi et al. 2000 (26)	Meta-analysis of 23 chemical and physical agents	20 studies	N/A	**MRR = 1.4 (1.0-1.8)**	N/A

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Solvents	CHCs	Ojajarvi et al. 2001 (74)	Meta-analysis	5 studies 1 study 4 studies 5 studies 5 studies 2 studies 1 study	N/A	$MRR_{trichloroethylene}$ = 1.24 (0.79-1.97) $RR_{tetrachloroethylene}$ = 3.08 (0.63-8.99) $MRR_{methylene\ chloride}$ = 1.42 (0.80-2.53) $MRR_{vinyl\ chloride}$ = 1.17 (0.71-1.91) MRR_{PCBs} = 1.37 (0.56-3.31) $MRR_{carbon\ tetrachloride}$ = 0.9 (0.2-2.6) **$RR_{chlorhydrin}$ = 4.92 (1.58-11.4)**	N/A
Solvents	CHCs	Ojajarvi et al. 2007 (41)	Meta-analysis (Asia, Europe, North America)		JEM	**MRR = 2.21 (1.31-3.68)**	N/A
Solvents	CHCs (among > 20 chemical agents and 4 physical agents)	Santibanez et al. 2010 (27)	Hospital-based case control (Spain)	Men and women aged 30–80 years hospitalized 1995–1999 in participant hospitals PC cases: 161, controls: 455	JEM (in-person interviews)	$OR_{high\ exposure}$ = 1.99 (0.62-6.42) For ductal adenocarcinoma: **$OR_{high\ exposure}$ = 4.11 (1.11-15.23)**	Age, alcohol use, education, province, sex, smoking
Solvents	CHCs (and 5 other agents)	Antwi et al. 2015 (28)	Hospital-based case control (US)	PC cases: 1892 Controls: 2316	Self-report (yes/no questions)	**OR = 1.63 (1.32—**	Age, BMI, education, diabetes, sex, smoking
Solvents	Formaldehyde	Ojajarvi et al. 2000 (26)	Meta-analysis of 23 chemical and physical agents	5 studies	N/A	MRR = 0.8 (0.5-1.0)	N/A

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Solvents	Formaldehyde	Collins et al. 2001 (80)	Meta-analysis	8 cohort studies, 2 case-control studies, 4 PMR studies	N/A	$MRR_{industrial\ workers}$ = 0.9 (0.8-1.7) **$MRR_{embalmers}$ = 1.3 (1.0-1.6) $MRR_{pathologists}$ = 1.3 (1.0-1.7)**	N/A
Solvents	Formaldehyde	Hauptmann et al. 2004 (81)	Cohort (US)	25,619 workers in formaldehyde industries PC deaths: 13	Job title, occupational history and industrial hygiene monitoring data	$RR_{highest\ cumulative\ exposure}$ = 0.74	Pay category
Solvents	Formaldehyde	Pira et al. 2014 (82)	Cohort (Piedmont, Italy)	2750 laminated plastic workers PC deaths: 4	Job-title and occupational history	SMR = 48.3 (13.1-123.7)	None
Solvents	Hydrazine	Ritz et al. 2006 (124)	Cohort (US)	Aerospace workers: 6004 mortality cohort; 5048 incidence cohort PC cases: 21 PC deaths: 39	JEM	Incidence: $RR_{high\ exposure,\ 20-year\ lag}$ = 2.38 (0.48-11.9) Mortality: $RR_{high\ exposure,\ 20-year\ lag}$ = 2.02 (0.53-7.61)	Age, other exposures, pay type, SES, time since employment
Solvents	Metalworking fluids, TCE	Ritz et al. 1999 (90)	Cohort (Ohio, US)	3527 white male workers of a uranium processing facility PC deaths: 18	JEM	SMR = 1.20 (0.71-1.89) $RR_{MWF,\ >10\ y}$ = 0.78 (0.16-3.84) $RR_{TCE,\ >10\ y}$ = 0.57 (0.12-2.85)	Pay type, radiation dose, time since hire
Solvents	Metalworking fluids	Kazerouni et al. 2000 (91)	Cohort (US)	11,383 male manufacturers in an automobile plant PC deaths: 49	Job-title and occupational history	SMR = 1.07 (0.79-1.42); no exposure-response trend	None

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Solvents	Metalworking fluids	Eisen et al. 2001 (88)	Cohort (Michigan, US)	46,399 automobile manufacturing workers PC deaths: 169	Job title	**SMR $_{white\ men}$ = 1.44 (1.11-1.83)** RR $_{straight;\ soluble;\ synthetic}$ = 0.8 (0.58-1.12); 1.03 (0.86-1.23); 0.99 (0.49-1.06)	Age, calendar year at risk, decade of hire, plant, race, sex
Solvents	Metalworking fluids	Yassi et al. 2003 (89)	Cohort (Canada)	2222 male workers in a transformer manufacturing plant PC cases: 168 PC deaths: 261	Job title	**SMR $_{overall}$ = 3.56 (1.90-6.09) SMR $_{transformer\ assembly}$ = 7.48 (1.50-21.8) SIR $_{overall}$ = 2.68 (1.29-4.94) SIR $_{transformer\ assembly}$ = 7.22 (1.45-21.1)**	None
Solvents	Metalworking fluids	Friesen et al. 2012 (92)	Cohort — The United Autoworkers-General Motors cohort (Michigan, US)	4825 female autoworkers PC deaths: 22	Job-title and occupational history	SMR = 1.45 (0.89-2.14)	None
Solvents	Methylene chloride	Liu et al. 2013 (75)	Meta-analysis (US, UK)	3 cohort studies, 1 case-control study	N/A	MRR = 0.97 (0.93-1.01)	N/A
Solvents	Styrene	Collins et al. 2013 (84)	Cohort (US)	15,826 workers from 30 reinforced plastic industry facilities PC deaths: 63	Job title, occupational history, expert assessment and industrial hygiene monitoring data	SMR = 0.96 (0.73-1.22); P trend = 0.274	None

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Solvents	Styrene	Coggon et al. 2015 (85)	Cohort (England)	7970 workers from 8 glass-reinforced plastic industry companies PC deaths: 48	Job-title and occupational history	$SMR_{overall} = 1.13$ (0.83-1.50) $SMR_{> background exposure} = 0.98$ (0.64-1.42)	None
Solvents	Styrene	Ruder et al. 2016 (86)	Cohort (Washington, US)	1678 boat builders from 2 plants PC deaths: 10	Job title, occupational history and industrial hygiene monitoring data	$SMR_{overall} = 1.08$ (0.52-1.98) $SMR_{high exposure} = 1.33$ (0.27-3.90)	None
Solvents	Toluene	Wiebelt et al. 1999 (125)	Cohort (Germany)	6830 male workers from 11 rotogravure printing plants PC deaths: 5	Job title, occupational history and industrial hygiene monitoring data	SMR = 94.3 (26.9-261.3)	None
BY OCCUPATION/INDUSTRY							
Aluminum production	CTPVs/PAHs	Ronneberg et al. 1999 (126)	Cohort (Norway)	5908 male aluminum smelter workers (2888 production workers) PC cases: 12 (among production workers)	JEM	$SIR_{production workers} = 103$ (53–179); P trend = 0.13	None
Aluminum production	CTPVs/PAHs	Moulin et al. 2000 (127)	Cohort (France)	2133 workers from 11 plants of the Aluminum Pechiney company PC deaths: 5	Job title and occupational history	SMR = 1.10 (0.36-2.57)	None

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Aluminum production	CTPVs/PAHs	Romundstad et al. 2000 (46)	Cohort (Norway)	5627 male aluminum smelter workers PC cases: 13	JEM	$SIR_{work > 3 y}$ = 1.13 (0.60-1.94) **$RR_{high exposure, 10 y lag}$ = 6.38 (1.33-30.6); *P* trend > 0.016**	None
Aluminum production	CTPVs/PAHs	Romundstad et al. 2000 (47)	Cohort (Norway)	11,103 male aluminum smelter workers PC cases: 46	JEM	SIR = 0.9 (0.7-1.2) **$RR_{high exposure, 20 y lag}$ = 2.8 (1.1-7.1); *P* trend = 0.03**	Age, calendar period
Aluminum production	CTPVs/PAHs	Carta et al. 2004 (48)	Cohort (Sardinia, Italy)	1152 male aluminum smelter workers PC deaths: 6	Job title, occupational history and industrial hygiene monitoring data (including biological samples)	**SMR = 2.41 (1.11-5.23) $SMR_{anodes factory}$ = 5.0 (2.07-12.08) $OR_{anodes factory}$ =4.53 (p=0.013)** (anodes factory = highest exposure group)	Smoking
Aluminum production	CTPVs/PAHs	Spinelli et al. 2006 (128)	Cohort (British Columbia, Canada)	6423 male aluminum smelter workers PC deaths: 23	JEM (for benzo[a]pyrene and benzene soluble material)	SMR = 1.22 (0.78-1.84) SIR = 1.25 (0.79-1.87)	Smoking
Aluminum production	CTPVs/PAHs	Gibbs et al. 2007 (49)	Cohort (Quebec, Canada)	5977 male aluminum smelter workers of three plants PC deaths: 63	Job title and occupational history	$SMR_{overall}$ = 108.1 (83.2-138.5) **$SMR_{plant C}$ = 387.8 (142.3-844.0)**; *P* trend > 0.2	None
Aluminum production	CTPVs/PAHs	Gibbs et al. 2007 (50)	Cohort (Quebec, Canada)	1421 aluminum smelter workers PC cases: 11	Job title and occupational history	**SIR = 259 (129.3-463.4)**; no exposure-response trend	None

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Aerospace industry	Mineral oils, TCE	Zhao et al. 2005 (93)	Cohort (US)	5048 aerospace workers PC cases: 21	JEM	$RR_{\text{mineral oils, high exposure}} = 0.51$ (0.06-4.07) $RR_{\text{TCE, high exposure}} = 0.28$ (0.04-2.14)	Age, SES, time since employment
Asphalt industry	Bitumen fumes	Kauppinen et al. 2003 (52)	Cohort (Finland)	5676 male workers in road paving companies PC deaths: 6 (bitumen work), 9 (construction work)	JEM	$SMR_{\text{ever bitumen worker}} = 2.39$ (0.88-5.21) **$SMR_{\text{construction worker}} = 2.35$ (1.08-4.47)**	None
Dry cleaning	CHC	Ojajarvi et al. 2001 (74)	Meta-analysis	8 studies	N/A	**MRR = 1.4 (1.1-2.4)**	N/A
Dry cleaning	PCE	Ruder et al. 2001 (76)	Cohort (US)	625 workers in shops using PCE (PCE-only); 1083 workers in shops using PCE and/or other solvents (PCE-plus) PC deaths: 3 (PCE-only); 15 (PCE-plus)	Job title and occupational history	$SMR_{\text{PCE-only}} = 0.80$ (0.17-2.35) **$SMR_{\text{PCE-plus}} = 1.89$ (1.06-3.11)**	None
Dry cleaning	Tetrachloroethylene	Lynge et al. 2006 (77)	Case cohort (Denmark, Finland, Norway, Sweden)	46,798 laundry and dry cleaning workers from the 1970 censuses PC cases: 229, controls: 891	Job-title and self-report (questionnaire and telephone interview)	RR = 1.27 (0.90-1.80)	None
Farming	Pesticides and fertilizers	Cerhan et al. 1998 (66)	Mortality study (Iowa, US)	White male farmers > 20 years PC deaths: 278	Job title (from death certificate)	**$PMR_{> 65 \text{ y}} = 1.18$ (1.04-1.34)**	None

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Farming	Diesel exhaust, dusts, fertilizers, pesticides	Lee et al. 2002 (67)	Mortality study (US)	222,459 crop farmers and 44,339 livestock farmers from 26 US states PC deaths: 1791 (crop), 465 (livestock)	Job title (from death certificate)	PMR $_{crop\ farmers}$ = 98 **PMR $_{livestock\ farmers}$ = 112**	None
Farming	Diesel exhaust, dusts, fertilizers, pesticides	Kriegel et al. 2006 (37)	Hospital-based case control (East Nile Delta region, Egypt)	Egyptian citizens diagnosed with PC at single participating hospital PC cases: 3, controls: 52	Self-report (in-person interview)	**OR = 3.25 (1.03-11.64)**	Age, serum cadmium level, sex, smoking
Farmworking	Diesel exhaust, dusts, fertilizers, pesticides, poor living conditions	Colt et al. 2001 (129)	Mortality study (US)	Farmworkers from 24 US states PC deaths: 220	Job title (from death certificate)	PMR = 97 (84–110)	None
Firefighting	Various	LeMasters et al. 2006 (130)	Meta-analysis	13 studies	N/A	MRR = 1.10 (0.91-1.34)	N/A
Firefighting	Various	Amadeo et al. 2015 (131)	Cohort (France)	11,577 professional male firefighters PC deaths: 42	Job title	SMR = 1.27 (0.92-1.72)	None
Hairdressers & barbers	Various chemicals including hair dyes	Lamba et al. 2001 (107)	Mortality study (US)	38,721 hairdressers and barbers > 20 years of age in 24 US states PC deaths: 480 (312 white women)	Job title (from death certificate)	**MOR $_{hairdressers,\ white\ women}$ = 1.24 (1.11-1.39)**	None

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Healthcare	Biological agents, chemotherapy drugs, radiation, solvents	Petralia et al. 1999 (132)	Mortality study (US)	Female healthcare workers from 24 US states PC deaths: 13 (radiological technicians)	Job title (from death certificate)	**MOR $_{radiological\ technician}$ = 1.7 (1.0-2.9)**	None
Healthcare	Biological agents, chemotherapy drugs, radiation, solvents	Lin et al. 2013 (133)	Cohort (Taiwan)	22,309 physician specialists and 89,236 non-physicians (referent cohort, frequency matched by age and sex) PC cases = 82	Job title	HR = 0.88 (0.51-1.52)	Age, comorbidities
Healthcare	Biological agents, chemotherapy drugs, radiation, solvents	Koifman et al. 2014 (134)	Mortality study (Brazil)	Dentists aged 20–79 years PC deaths: 40 (males 50–79 years)	Job title	Men aged 50–79 years: **MOR = 2.66 (1.90-3.60) PMR = 1.76 (1.18-2.39)**	None
Laboratory (biology)	Biological agents, chemotherapy drugs, radiation, solvents	Barneveld et al. 2004 (135)	Cohort (Netherlands)	7307 laboratory research workers PC deaths: 5 men, 5 women	Job title	SMR men = 0.7 (0.2-1.6) SMR women = 1.7 (0.6-4.0)	None
Leather tanning	Various	Stern et al. 2003 (136)	Cohort (US)	9352 production workers from two leather tanneries PC deaths: 27	Job-title and occupational history	SMR $_{overall}$ = 90 (59–131)	None
Leather tanning	Various	Iaia et al. 2006 (137)	Cohort (Italy)	4874 workers from 92 factories PC deaths: 2 (finishers)	Job title	SMR $_{finishers}$ = 1.2 (21.3-378.6)	None

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Leather tanning	Various	Veyalkin et al. 2006 (108)	Mortality study (Belarus)	3500 workers of the Minsk Leather Tannery PC deaths: 8 women, 5 men	Job title	**PMR $_{women}$ = 363 (156–716)** PMR $_{men}$ = 195 (60–430)	None
Metal degreasing	CHC	Ojajarvi et al. 2001 (74)	Meta-analysis	6 studies	N/A	**MRR = 2.0 (1.2-3.6)**	N/A
Motor vehicle manufacture	Various	Delzell et al. 2003 (138)	Cohort (US)	198,245 workers of Ford Motor Company	Job title	SMR = 97 (89–105)	None
Painting trades	Pigments, resins, solvents	Brown et al. 2002 (112)	Cohort (Sweden)	5741 men employed in paint and varnish plants PC cases: 30	Job title (from census)	**SIR = 1.7 (1.1-2.4)**	None
Pipefitting/plumbi ngwelding	Metal fumes	Luckett et al. 2012 (38)	Population-based case control (South Louisiana, US)	Men and women > 20 years PC cases: 69, controls: 158	Job title (in-person interviews)	**OR = 5.88 (1.33-26.01)**	Age, alcohol use, education, family history, race, sex, smoking
Printing industry	Lead, mineral oils, pigments, resins, solvents	Rafnsson 2001 (139)	Cohort (Iceland)	1332 men and 426 women employed in the printing industry PC cases: 5	Job title	SIR $_{men}$ = 0.83 (0.17-2.43) SIR $_{women}$ = 2.54 (0.29-9.16)	None
Printing industry	Inks/pigments, lead, mineral oils, solvents	Kvam et al. 2005 (42)	Cohort (Norway)	10,459 workers in the printing industry PC cases: 74	Job title	**SIR = 1.42 (1.12-1.79)**	None
Pulp and paper mill industry	Arsenic, CHC, formaldehyde, sulfuric acid mist	Band et al. 2001 (140)	Cohort (British Columbia, Canada)	28,278 pulp and paper workers PC cases: 49	Job title	SIR = 1.00 (0.78-1.27) **SIR $_{sulfite\ process\ workers}$ = 1.77 (1.19-2.55)**	None

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Railway carriage construction	Asbestos	Battista et al. 1999 (141)	Cohort (Italy)	734 male workers PC cases: 6	Job title	SMR = 224 (98–443)	None
Rubber industry	Nitrosamines, solvents, talc powder	Straif et al. 1998 (142)	Cohort (Germany)	11,633 male workers in the German rubber industry PC deaths: 22	Job title	$SMR_{\text{work area I; II; III}}$ = 86 (35–178); 74 (34–140); 68 (25–149)	None
Rubber industry	Nitrosamines, solvents, talc powder	Li et al. 2002 (111)	Case-cohort (Shanghai, China)	1598 workers in the rubber industry PC deaths: 9, controls: 36	Job-title and occupational history	$OR_{\text{tire curing}}$ = **9.28 (1.00-86.1)**	Alcohol use, SES, smoking
Seafarers	Various	Saarni et al. 2002 (143)	Case cohort (Finland)	30,940 male seafarers PC cases: 58, controls: 174	Job title	$OR_{\text{deck officers, ≥ 1 month exposure}}$ = **2.00 (1.02-3.93)** $OR_{\text{deck officers, ≥ 3 y exposure}}$ = 1.30 (0.62-2.76) $OR_{\text{engine officers, ≥ 1 month exposure}}$ = **0.32 (0.13-0.80)** $OR_{\text{engine officers, ≥ 3 y exposure}}$ = **0.27 (0.09-0.81)**	None
Semiconductor manufacture	Various	Nichols et al. 2005 (144)	Cohort (West Midlands, UK)	1807 workers in a semiconductor manufacturing facility		SMR_{women} = 195 (89–370) SIR_{women} = **226 (108–415)**	None

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Several occupational categories	Usual occupation	Ji et al. 1999 (39)	Population-based case control (Shanghai, China)	Incident cases aged 30–74 years diagnosed 1990–1993 identified through the Shanghai Cancer Registry PC cases: 451, controls: 1552	Job title	Men: $OR_{printer} = 5.2$ (1.1-25) $OR_{toolmaker} = 3.2$ (1.4-7.1) $OR_{electrical\ worker} = 6.2$ (2.4-16.4) $OR_{electrician} = 7.5$ (2.6-21.8) $OR_{plumber/welder} = 3.0$ (1.2-7.5) $OR_{construction\ worker} = 2.6$ (1.1-6.3)	Age, education, income, other occupations, smoking
Several occupational categories	Jobs in Spain's National Classification of Occupations with at least 4 exposed subjects	Alguacil et al. 2000 (110)	Hospital-based case control—PANKRAS II study (Spain)	Incident cases diagnosed at 5 participating hospitals 1992–1995 PC cases: 185, controls: 264	Job title	Men: $OR_{engineering\ science\ technicians,\ men} = 20.2$ (1.8-228) Women: $OR_{textile\ workers} = 11.5$ (1.0-135)	Age, alcohol use, coffee consumption, hospital, smoking
Several occupational categories	Jobs in the Nordic Classification of Occupations	Alguacil et al. 2003 (40)	Record linkage (Sweden)	1.8 million men and 1.1 million women aged 25–64 years PC cases: 6563 (adenocarcinoma only)	Job title	Men: $RR_{travel\ agent} = 1.55$ (1.15-2.08) $RR_{metal\ workers} = 1.94$ (1.12-3.34) $RR_{docker/freight\ handler} = 1.61$ (1.11-2.33) Women: $RR_{driver} = 2.50$ (1.24-5.07) $RR_{electronic\ related} = 1.72$ (1.15-2.57) $RR_{steward} = 5.17$ (2.31-11.6)	Age, geographical category, period, town size

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Several occupational categories	Industry and occupation groups	Zhang et al. 2005 (54)	Population-based case control (Iowa, US)	Cases diagnosed 1985–1987 identified through the State Health Registry of Iowa (all histologically confirmed) PC cases: 376, controls: 2434	Self-report (questionnaire and telephone interview)	Men: **OR $_{\text{chemical industry} > 10\,y}$ = 4.7 (1.5-14.3)** **OR $_{\text{railroad transport} > 10\,y}$ = 5.1 (2.3-11.5)** **OR $_{\text{railroad operators} > 10\,y}$ = 5.1 (2.3-11.5)** Women: **OR $_{\text{furniture stores} > 10\,y}$ = 5.1 (1.1-27.3)** OR $_{\text{textile sewing machine operators} > 10\,y}$ = 5.6 (1.0-31.4)	Age, family history, fruit intake, physical activity, red meat intake, smoking
Several occupational categories	53 occupational groups of the Nordic Classification of Occupations	Ji et al. 2006 (53)	Record linkage (Sweden)	3.3 million men, 2.8 million women	Job title	Men: **SIR $_{\text{sales agents}}$ = 1.11 (1.03-1.20)** **SIR $_{\text{shop managers/assistants}}$ = 1.21 (1.06-1.36)** Women: **SIR $_{\text{drivers}}$ = 1.42 (1.01-1.89)** SIR $_{\text{cooks/stewards}}$ = 1.13 (1.00-1.27)	None
Several occupational categories	28 job titles	Ojajarvi et al. 2007 (41)	Meta-analysis (Asia, Europe, North America)	7 studies 6 studies	Job title	**MRR $_{\text{laundry/dry cleaners}}$ = 1.41 (1.13-1.76)** **MRR $_{\text{metal-plating workers}}$ = 2.04 (1.17-3.55)**	N/A

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Several occupational categories	Occupations with at least 10 exposed subjects (5 if previously reported as a possible risk factor)	Santibanez et al. 2010 (27)	Hospital-based case control (Spain)	Spanish men and women aged 30–80 years hospitalized 1995–1999 in any 9 participant hospitals PC cases: 161, controls: 455	Job title (in-person interviews)	For ductal adenocarcinoma in men: **OR building finishers, related trades = 3.58 (1.03-12.44) OR miners, shotfirers, stone cutters, carvers = 8.14 (1.55-42.68) OR machinery/electrical workers = 3.61 (1.24-10.47)**	Age, alcohol use, education, province, sex, smoking
Veterinary medicine	Pesticides, radiation, zoonotic viruses	Travier et al. 2003 (145)	Cohort (Sweden)	1178 male veterinarians or workers in the veterinary industry PC cases: 8	Job title	**RR = 2.13 (1.01-4.47)** [vs. male population group with highest income/education]	Age, calendar period, geographic region, urban setting

OTHER OCCUPATIONAL FACTORS

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Occupational physical activity	Higher occupational physical activity	Parent et al. 2011 (94)	Population-based case-control study (Montreal, Canada)	Cases diagnosed in 18 Montreal hospitals among men aged 35–70 years (histologically confirmed) PC cases: 116, controls: 512	Expert assessment	OR = 0.81 (0.24-2.72)	Age, alcohol use, ancestry, ß- carotene, BMI, coffee consumption, education, family income, respondent status, smoking
Occupational physical activity	Overall occupational physical activity	Behrens et al. 2015 (17)	Meta-analysis (Asia, Europe, North America)	6 cohort studies, 5 case-control studies	N/A	**RR cohort = 0.86 (0.76-0.98)** RR case control = 0.97 (0.73-1.30)	N/A

Exposure category	Exposures	Author, year (reference)	Study design (location)	Study population	Exposure assessment	Results (95% CI)	Control variables
Light at night	Night work	Parent et al. 2012 (95)	Population-based case-control study (Montreal, Canada)	Cases diagnosed in 18 Montreal hospitals among men aged 35–70 years (histologically confirmed) PC cases: 94, controls: 512	Expert assessment	**OR ever = 2.27 (1.24-4.15_**	Age, alcohol use, ancestry, ß- carotene, BMI, coffee consumption, education, family income, respondent status, smoking
Light at night	Shift and night work	Lin et al. 2013 (96)	Cohort — The JACC study (Japan)	22,224 men aged 40–65 years working full time or self-employed PC deaths: 127	Self-report (questionnaire)	RR nighttime work = 0.61 (0.22-1.60) RR rotating shift work = 0.83 (0.43-1.60)	Age, alcohol use, BMI, history of diabetes, perceived stress, sleep time, smoking

APFO, ammonium perfluorooctanoate; BMI, body-mass index; CHC, chlorinated hydrocarbons; CI, confidence interval; CTPVs, coal tar pitch volatiles; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; FINJEM, Finish Job-Exposure Matrix; HCB, hexachlorobenzene; HR, hazard ratio; JEM, job-exposure matrix; MOR, mortality odds ratio; MRR, meta-risk ratio; MWF, metalworking fluids; NDR, National Dose Registry; OR, odds ratio; PAH, polycyclic aromatic hydrocarbons; PC, pancreatic cancer; PCBs, polychlorinatedbiphenyls; PCE, perchloroethylene; PMR, proportionate mortality ratio; PTFE, polytetrafluoroethylene; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TCE, trichloroethylene; TFE, tetrafluoroethylene

APPENDIX 5

List of industrial agents included in the Montreal Multisite cancer study (1979-1985).

1.	Abrasives dust	40.	Chromium dust
2.	Inorganic insulation dust	41.	Iron dust
3.	Soil dust	42.	Iron oxides
4.	Metallic dust	43.	Nickel dust
5.	Chrysotile asbestos	44.	Copper dust
6.	Amphibole asbestos	45.	Zinc dust
7.	Cristalline silica	46.	Zinc oxide
8.	Portland cement	47.	Cadmium dust
9.	Glass dust	48.	Lead dust
10.	Glass fibers	49.	Lead oxides
11.	Industrial talc	50.	Basic lead carbonate
12.	Brick dust	51.	Lead chromate
13.	Clay dust	52.	Organic dyes and pigments
14.	Concrete dust	53.	DDT
15.	Refractory brick dust	54.	Cotton dust
16.	Bronze dust	55.	Wool fibers
17.	Brass dust	56.	Silk fibers
18.	Stainless steel dust	57.	Wood dust
19.	Mild steel dust	58.	Grain dust
20.	Inorganic pigments	59.	Flour dust
21.	Mineral wool fibers	60.	Fur dust
22.	Extenders	61.	Flax fibers
23.	Aluminum alloy dyst	62.	Cork dust
24.	Ashes	63.	Hair dust
25.	Mica	64.	Starch dust
26.	Cosmetic talc	65.	Sugar dust
27.	Borates	66.	Rosin
28.	Sodium carbonate	67.	Genuine felt dust
29.	Sodium hydrosulphite	68.	Leather dust
30.	Sodium silicate	69.	Tobacco dust
31.	Alumina	70.	Natural rubber
32.	Alum	71.	Tannic acid
33.	Silicon carbide	72.	Synthetic fibers
34.	Sulfur	73.	Plastic dust
35.	Calcium oxide	74.	Rayon fibers
36.	Calcium sulphate	75.	Acrylic fibers
37.	Calcium carbide	76.	Polyester fibers
38.	Calcium carbonate	77.	Nylon fibers
39.	Titanium dioxide	78.	Acetate fibers

79. Cellulose acetate
80. Cellulose nitrate
81. Polyethylene
82. Polypropylene
83. Polystyrene
84. Polyvinyl chloride
85. Polyvinyl acetate
86. Polyamides
87. Poly-acrylates
88. Alkyds
89. Epoxies
90. Phenol-formaldehyde
91. Urea-formaldehyde
92. Melamine-formaldehyde
93. Polyurethanes
94. Polyesters
95. Styrene-butadiene rubber
96. Polychloroprene
97. Treated textile fibers
98. Coal dust
99. Carbon black
100. Cellulose
101. Soot from any source
102. Coke dust
103. Rubber dust
104. Graphite dust
105. Charcoal dust
106. Hydrogen
107. Carbon monoxide
108. Hydrogen cyanide
109. Ammonia
110. Nitrogen oxides
111. Ozone
112. Hydrogen fluoride
113. Sulphur dioxide
114. Hydrogen sulphide
115. Chlorine
116. Hydrogen chloride
117. Chlorine dioxide
118. Natural gas
119. Methane
120. Propane
121. Formaldehyde
122. Ethylene oxide
123. Ethylene
124. Acetylene
125. Butadiene
126. Vinyl chloride
127. Phosgene
128. Anaesthetic gases
129. Spray gases
130. Coal gas
131. Gas welding fumes
132. Arc welding fumes
133. Soldering fumes
134. Metal oxide fumes
135. Magnesium fumes
136. Aluminum fumes
137. Calcium oxide fumes
138. Titanium dioxide fumes
139. Chromium fumes
140. Manganese fumes
141. Iron fumes
142. Nickel fumes
143. Copper fumes
144. Zinc fumes
145. Silver fumes
146. Cadmium fumes
147. Tin fumes
148. Gold fumes
149. Lead fumes
150. Other pyrolysis fumes
151. Cooking fumes
152. Leaded engine emissions
153. Coal combustion products
154. Diesel engine emissions (any)
155. Liquid fuel combustion products
156. Wood combustion products
157. Natural gas combustion products
158. Jet fuel engine emissions
159. Propane engine emissions
160. Plastics pyrolysis products
161. Rubber pyrolysis products
162. Propane combustion products
163. Coke combustion products
164. Strong inorganic acid mist
165. Alkali, caustic solutions
166. Javel water

167. Plating solutions
168. Nitric acid
169. Hydrogen peroxide
170. Phosphoric acid
171. Sulfuric acid
172. Mercury
173. Paraffin
174. Silicone oils and greases
175. Methanol
176. Ethanol
177. Ethylene glycol
178. Isopropanol
179. Glycerine
180. Hexamethylene tetramine
181. Acetic acid
182. Formic acid
183. Diethyl ether
184. Nitroglycerine
185. RDX
186. Carbon tetrachloride
187. Chloroform
188. Methylene chloride
189. 1,1,1-trichlorethane
190. Carbon disulphide
191. Acrylonitrile
192. Trichloroethylene
193. Perchloroethylene
194. Methyl methacrylate
195. Acetone
196. Benzene
197. Toluene
198. Xylene
199. Styrene
200. Phenol
201. Trinitrotoluene
202. Animal, vegetable glues
203. Turpentine
204. Linseed oil
205. Camphor
206. Synthetic adhesives
207. Organic solvents
208. Waxes, polishes
209. Leaded gasoline
210. Kerosene

211. Diesel oil (light)
212. Heating oil
213. Mineral spirits post 1970
214. Crude oil
215. Lubricating oils and greases (mineral-based)
216. Cutting fluids
217. Asphalt
218. Coal tar and pitch
219. Creosote
220. Hydraulic fluid
221. Other mineral oils
222. Jet fuel (JP5, Jet A, Jet A1)
223. Aviation gasoline
224. Mineral spirits pre 1970
225. Polychlorinated biphenyls or PCBs
226. Cutting fluids pre-1955 (straight, mineral-based)
227. Cutting fluids post-1955 (straight, mineral-based)
228. Other paints, varnishes
229. Wood varnishes, stains
230. Inks
231. Metal coatings
232. Cyanides
233. Fluorides
234. Chromium (VI)
235. Hypochlorites
236. Nitrates
237. Beryllium
238. Magnesium
239. Aluminum
240. Titanium
241. Vanadium
242. Chromium
243. Manganese
244. Iron
245. Cobalt
246. Nickel
247. Copper
248. Zinc
249. Arsenic
250. Selenium
251. Silver
252. Cadmium

APPENDIX 6

List of industry groups included in the Montreal Multisite cancer study (1979-1985).

1. Forestry (including Logging)
2. Fishing and Trapping
3. Metal Mines
4. Mineral Fuels Industry
5. Asbestos Mines
6. Quarries, Sand Pits and Other Non-metal Mines
7. Services Incidental to Mining
8. Meat, Poultry and Fish Product Industries
9. Fruit and Vegetable Processing Industry
10. Dairy Product Industry
11. Flour, Feed and Bakery Product Industry
12. Miscellaneous Food Industry
13. Beverage Industry
14. Tobacco Products Industries
15. Rubber Product Industries
16. Plastic Product Industries
17. Leather Tanneries
18. Leather Goods Manuf.
19. Textile Industries
20. Clothing Industry
21. Fur Goods Industry
22. Wood Industries
23. Veneer and Plywood Mills
24. Wood Prods.
25. Household Furniture Manufacturing Industries
26. Office and Miscellaneous Furniture Manufacturing Industries
27. Pulp and Paper Mills
28. Asphalt Roofing Manuf. Industries
29. Paper Converting Industries
30. Commercial Printing and Publishing Industries
31. Platemaking, Typesetting and Trade Bindery Industries
32. Iron and Steel Industries
33. Smelting and Refining
34. Aluminium, Copper and Other Alloys Industries
35. Metal Fabricating and Machinery Industries
36. Aircraft and Aircraft Parts Manufacturing Industries
37. Transportation Equipment Industries (Except Aircraft)
38. Electrical and Electronic Products Manufacturing Industries
39. Non-Metallic Mineral Products Industries
40. Petroleum and Coal Products Industries
41. Chemical and Chemical Products Industries (Except Paint and Varnish)
42. Paint and Varnish Manuf. Industries
43. Miscellaneous Manuf. Industries
44. Jewellery and Silverware Industries
45. Construction Industry
46. Air Transport
47. Railway Transport
48. Water Transport
49. Truck and Bus Transport, and Taxicab Operations
50. Highway, Bridges, and Pipeline Transportation and Maintenance
51. Grain Elevators
52. Other Storage and Warehousing
53. Communications
54. Electrical Power, Gas and Water Utilities
55. Wholesale Trade
56. Wholesalers of Coal and Coke
57. Wholesalers of Petroleum Products
58. Retail Trades (Excl. Service Station)
59. Service Station, Motor Vehicle Dealers and Repairs
60. Jewellery and Watch Stores and Repair Shops
61. Finance, Insurance and Real Estate Industries
62. Education and Related Services
63. Vocational Centres and Trade Schools
64. Health Services
65. Welfare, and Religious Services
66. Amusement and Recreation Services
67. Services to Business Management
68. Shoe Repair Shops
69. Barber and Beauty Shops
70. Laundries, Cleaners and Pressers
71. Miscellaneous Personal Services
72. Accommodation and Food Services
73. Equipment Rentals, Photographic Services and Repairs
74. Defence Services
75. Federal, Provincial and Local Administration
76. Unspecified or Undefined
77. Forestry (including Logging)

APPENDIX 7

List of occupation groups included in the Montreal Multisite cancer study (1979-1985).

1. ADMINISTRATION MANAGEMENT AND RELATED OCCUPATIONS
2. Production Management Occupations
3. Management Occupations Construction Operations
4. PHYSICAL SCIENCE ENGINEERING AND RELATEDFIELDS
5. Chemists
6. Physical Sciences Technologists and Technicians
7. SOCIAL SCIENCES LAW LIBRARY RELIGION AND RELTD. OCCUPATIONS
8. SCHOOL COLLEGES AND UNIVERSITY TEACHING OCCUPATIONS
9. Community College and Vocational School Teachers
10. OCCUPATIONS IN MEDICINE AND HEALTH
11. Nursing Therapy and Related Assisting Occupations
12. OCCUPATIONS IN PERFORMING PHOTOGRAPHING AND COMMERCIAL ARTS
13. OCCUPATIONS IN SPORTS AND RECREATION
14. CLERICAL AND RELATED OCCUPATIONS
15. Material Recording Scheduling and Distributing Occupations
16. OCCUPATIONS IN SALES AND SERVICES
17. Service Station Attendants
18. PROTECTIVE SERVICE OCCUPATIONS
19. Fire Fighting Occupations
20. FOOD AND BEVERAGE PREPARATION AND RELATED OCCUPATIONS
21. Supervisors Food and Beverage Preparation. Chefs and Cooks
22. OCCUPATIONS IN LODGING AND OTHER ACCOMMODATION
23. PERSONAL SERVICE OCCUPATIONS
24. Barbers Hairdressers and Related Occupations
25. APPAREL AND FURNISHINGS SERVICE OCCUPATIONS
26. OTHER SERVICE OCCUPATIONS
27. Janitors Charworkers and Cleaners
28. FARMING HORTICULTURAL AND ANIMAL HUSBANDRY OCCUPATIONS
29. Nursery and Related Workers
30. FISHING HUNTIN TRAPPING AND RELATED OCCUPATIONS
31. FORESTRY AND LOGGING OCCUPATIONS
32. MINING QUARRYING AND GAS FIELD OCCUPATIONS
33. MINERAL ORE TREATING OCCUPATIONS
34. METAL PROCESSING AND RELATED OCCUPATIONS
35. Metal Smelting Converting and Refining Furnacemen
36. Moulding Coremaking and Metal Casting Occupations
37. Plating Metal Spraying and Related Occupations
38. CLAY GLASS AND STONE PROCESSING FORMING AND RELATED OCCUPATIONS
39. CHEMICALS PETROLEUM RUBBER PLASTIC AND RELATED MATERIAL PROCESSING OCCUPATIONS
40. FOOD BEVERAGE AND RELATED PROCESSING OCCUPATIONS
41. Baking Confectionery Making and related occupations
42. Slaughtering and Meat Cutting Canning Curing and Packing Occupations
43. WOOD PROCESSING OCCUPATIONS EXCEPT PAPER PULP
44. PULP AND PAPERMAKING AND RELATED OCCUPATIONS

APPENDIX 8

Definitions of exposures selected for this analysis of the Montreal Multisite cancer study (1979–1985).

Antimony: comprises antimony (Sb) dust, antimony fumes, dust from antimony-containing alloys and ores and all other antimony-containing substances. Antimony itself is a lustrous, silvery blue-white, extremely brittle metal. When alloyed with other metals, it increases hardness, lowers melting points and reduces shrinkage upon freezing.

Brass dust: dust generated when objects made of brass are cut, abraded, machined, polished, etc. Brasses are the most widely used alloys of copper. They are fundamentally binary alloys of copper with zinc but often their properties are modified by the addition of other elements in small amounts. Brasses are stronger than copper and are used in structural applications. Uses include bullet jackets, imitation gold jewelry, plumbing hardware, pipes, radiator cases and condenses tubing.

Chlorinated alkanes: saturated hydrocarbons in which at least one hydrogen atom is replaced by a chlorine atom. This replacement increases many desirable properties, such as specific gravity and boiling point, and reduces flammability. These materials (e.g., methylene chloride, chloroform, carbon tetrachloride) are used as solvents for fats, oils, for metal degreasing, for dry cleaning of textiles, as refrigerants, in insecticides, and in fire extinguishers.

Chlorinated alkenes: unsaturated hydrocarbons in which one or more hydrogen atoms are replaced with chlorine atoms. These relatively nonflammable, organic compounds are used in dry cleaning of textiles and in metal degreasing. Examples are trichloroethylene, tetrachloroethylene and vinyl chloride.

Cleaning agents: materials which have cleansing action such as soap. Their main function is to aid water in the cleaning process. They may be simple sulfonated fatty acids or complex synthetic materials. Does not include organic solvents.

Coal combustion products: a mixture of gases and particulates generated when coal is used as a heat or energy source. Includes variable amounts of particulates such as carbon, silica, alumina and iron oxides. Coal combustion has been widespread in certain industries and was also widely used for domestic purposes until the 1950s.

Fluorides: includes exposure to all fluorides (e.g., sodium aluminum fluoride, also called cryolite, used as a flux in the production of aluminum, in the fabrication of special glasses, porcelain and in insecticides). Some welding electrode coatings contain a calcium carbonate-calcium fluoride system; this is thermally degraded during welding to silicon hexafluoride which gives rise to hydrogen fluoride in the presence of water. Sodium, potassium and calcium fluorides are also present in the welding environment.

Hydrogen fluoride: anhydrous hydrogen fluoride is a colourless gas prepared by the action of sulfuric acid on calcium fluoride. It is strongly corrosive and irritating. Aqueous solutions and salts of hydrofluoric acid are used in the production of fluorides and plastics, in frosting and etching glass, in polishing crystals, in enamelling and galvanizing iron, in working silk, in analytical chemistry, and to increase the porosity of ceramics.

Hypochlorites: includes both sodium and calcium hypochlorites. These compounds decompose easily in water and are used as a source of chlorine for cleaning, bleaching, and sanitizing. A water solution of sodium hypochlorite known as javel water is used extensively in the laundry industry. These bleaching powders have also been used in the textile and paper pulp industries.

Javel water: a clear solution containing sodium hypochlorite and sodium chloride with a strong irritating odour which is known by several trade names such and Javex ®, Chlorosol ®, and Clorox ®. It is widely used as a household bleach and disinfectant and as a bleaching agent in the textile industry.

Nickel: comprises nickel (Ni) dust and nickel fumes, dust from nickel containing-alloys and ores and all other nickel containing substances. Uses include plating and as a catalyst in hydrogenation of organic compounds.

Nitric acid: a reddish fuming liquid usually marketed in aqueous solutions. The main uses of nitric acid are in the production of fertilizers and explosives. It has also been used in metal degreasing, electroplating, and as a reagent in chemical laboratories.

Polycyclic aromatic hydrocarbons from any source: a group of chemicals made up of three or more benzene rings interlinked in various arrangements. They are naturally present in fossil fuels or can be formed by thermal decomposition of any organic material containing carbon and hydrogen.

Plastic dust: dust produced when a plastic (of any polymer) material is cut, ground or abraded. The main constituents are polymer resins; colour pigments, filler pigments, anti-UV agents, plasticizers, fungicides, fire-retardants, stabilizers and anti-static agents.

Sulfuric acid: an oily, highly corrosive liquid made by burning sulfur to the dioxide, oxidizing to the trioxide and reacting with steam. Produced industrially for over 200 years, this is an important raw material in the manufacture of fertilizers, rayon, and soap and is also commonly used in chemistry laboratories and in the pharmaceutical industry. It has also been used in the pickling and cleaning of metals, as an electrolyte in batteries, and in the purification of petroleum products.

Soot: a black carbonaceous substance formed by the combustion of coal, wood, oil or other fuel. In addition to carbon and PAHs, it may contain other mineral constituents as well as trace amounts of metals (e.g., lead, vanadium, barium, chromium). The composition of soot varies according to the fuel and the completeness of the combustion.

Synthetic adhesives: includes all adhesives based on synthetic resins and rubbers, such as formaldehyde, epoxy resins, polyvinyl acetate resins and hot melts. Many of these adhesives contain organic solvents. Adhesives are used in many industries, particularly in the furniture and shoe industries.

Tin fumes: fumes generated during high temperature processes involving tin and tin (Sn)-containing alloys or ores. Tin melts at a relatively low temperature. It is used extensively in solder alloys.

Waxes/polishes: includes waxes and polishes for floors, automobiles, leather, and furniture. These may contain a variety of substances of animal and vegetable origin such as fatty acids in combination with higher alcohols, petroleum distillates (kerosene, mineral spirits, paraffin waxes), abrasives, and perfumes.

Reference: Siemiatycki J. Risk factors for cancer in the workplace. Boca Raton, FL: CRC Press; 1991. (Definitions reproduced with minor modifications.)